Drug Class Review

Targeted Immune Modulators

Final Update 3 Evidence Tables

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The Agency for Healthcare Research and
Quality has not yet seen or approved this report

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The literature on this topic is scanned periodically

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

TABLE OF CONTENTS

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Alonso-Ruiz et al.**[1] **Year: 2008** **Country:** Multinational
FUNDING:	Authors declare that they have no competing interests; no external funding reported
DESIGN:	**Study design:** Systematic review & meta-analysis **Number of patients:** 7,098
AIMS OF REVIEW:	To analyze available evidence on the efficacy and safety of anti-TNFα drugs (INF, ETA and ADA) for treating RA.
STUDIES INCLUDED IN META-ANALYSIS	13 trials (7,098 patients) ADA (5 trials) Weinblatt (ARMADA) 2003; van de Putte 2004; Furst (STAR) 2003; Keystone 2004; Breedveld (PREMIER) 2006 ETA (4 trials) Moreland 1999; Weinblatt 1999; Bathon 2000; van der Heijde (TEMPO) 2006; INF (4 trials) Lipsky 2000; St. Clair 2004; Quinn 2005; Westhovens 2006
TIME PERIOD COVERED:	Up to October 2006
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs of INF, ETA or ADA for treatment of RA; trial duration ≥ 6 months with efficacy measured by ACR response; trials were excluded if they either used administration routes other than recommended or included no treatment arm with recommended doses. Only information published in the trial reports was assessed.
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients had to meet ACR criteria for diagnosis of RA

Authors: Alonso-Ruiz et al. **Year: 2008**	
CHARACTERISTICS OF INTERVENTIONS:	ADA 10-40 mg/wk, ETA 20-50 mg/wk, or INF 7.5 -20mg/wk; compared with and/or MTX
MAIN RESULTS:	• Global comparison of ACR20 efficacy of any dose of any anti-TNFα drug with any control treatment showed a combined effect of 1.81 (95% CI 1.43–2.29) with an NNT of 6 (5–7). • Combined effects were 1.89 (1.30–2.75) for ADA, 1.71 (1.11–2.63) for ETA and 1.82 (1.19–2.77) for INF. • ACR50 efficacy showed a combined effect of 2.46 (95% CI 1.75-3.45) • ACR70 showed combined effect of 2.77 (95% CI 1.85-4.15) • Analysis of this set of 13 trials provided evidence of relevant and statistically significant heterogeneity (Q = 157.7; $P < 0.001$; I^2 92%). • ACR20 effect of anti-TNF in MTX-naive patients: 1.10 (0.96-1.26) • ACR20 effect of ant-TNF in patients with previous insufficient response to MTX: 2.32 (1.99-2.72); NNT of 4 (3-5)
ADVERSE EVENTS:	• No significant overall difference between experimental and control groups in withdrawals due to adverse events: pooled RR = 1.25 (0.65-2.39) • ETA-treated patients less likely to withdraw from AEs than controls • INF- and ADA-treated patients more likely to withdraw from AEs than controls • More adverse events in anti-TNF patients: RR 1.02 (1.00–1.04); $P = 0.021$) • INF patients showed a higher frequency of serious adverse events ($P = 0.048$) and infections ($P = 0.004$), but the combined estimates for all three anti-TNFα drugs and safety outcomes were not significant. • No significant increases in risk detected in anti-TN patients in severe infections, malignancies and deaths vs. controls
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes; Trials were searched in scientific journals and congress conference proceedings. Information from the MEDLINE, EMBASE and Cochrane Library databases up to October 2006 was checked using a high-sensitivity strategy. The computerized search was completed with a manual search of reference lists.
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: An, et al.**[2] **Year: 2010** **Country: China** **Quality rating:** Fair
FUNDING:	
DESIGN & SIZE:	**Study design:** SR **Number of patients:** 2,701 **Trials:** 4
OBJECTIVE OF REVIEW:	To evaluate the effect of adding tocilizumab to disease-modifying antirheumatic drug (DMARD) therapy for the treatment of rheumatoid arthritis (RA).
ELIGIBILITY CRITERIA:	RCTs (blinded and unblinded) that included patients of any age with RA and evaluated the efficacy and safety of tocilizumab in addition to DMARD therapy for RA.
STUDIES INCLUDED IN REVIEW:	Efficacy & safety: Emery, 2008 Genovese, 2008 Maini, 2006 Smolen, 2008
LITERATURE SEARCH DATES:	PubMed up to August 2009; Cochrane Register up to Issue 2, 2009; Embase 1980 to August 2009
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	All were multi-center, double-blind RCTs and were performed in adult patients with RA. Two trials included patients who experienced an inadequate response to MTX. One trial included patients with moderate to severe active RA who showed a failure to respond or who were intolerant to one or more TNF antagonists treated with MTX for >12 weeks. Tocilizumab (or placebo) was administered every 4 weeks, and dose was either 4 or 8 mg/kg plus MTX and folate. Study duration ranged from 16 to 24 weeks, and number enrolled ranged from 359 to 1,220.

Authors: An, et al. **Year: 2010**	
DATA SYNTHESIS METHODS:	Meta-analysis (random effects model)
MAIN RESULTS: (RESULTS IN SUBGROUPS)	**Tocilizumab 8mg/kg vs. placebo:** ACR20: RR (95% CI)=2.53 (1.89, 3.39) ACR50: RR (95% CI)=3.75 (2.37, 5.95) ACR70: RR (95% CI)=6.02 (2.76, 13.09) DAS28 remission: RR (95% CI)=10.17 (5.20, 19.91) **Tocilizumab 4mg/kg vs. placebo:** ACR20: RR (95% CI)=1.96 (1.40, 2.73) ACR50: RR (95% CI)=2.45 (1.25, 4.79) ACR70: RR (95% CI)=2.55 (0.60, 10.84) DAS28 remission: RR (95% CI)=6.54 (1.58, 27.11) **Tocilizumab 8mg/kg vs. tocilizumab 4mg/kg:** ACR20: RR (95% CI)=1.30 (1.08, 1.58) ACR50: RR (95% CI)=1.47 (1.21, 1.79) ACR70: RR (95% CI)=2.11 (1.49, 3.00) DAS28 remission: RR (95% CI)=2.83 (1.42, 5.64)
ADVERSE EVENTS:	Adverse events: **Tocilizumab 8mg/kg vs. placebo:** RR (95% CI)=1.12 (1.03, 1.20) **Tocilizumab 4mg/kg vs. placebo:** RR (95% CI)=1.08 (1.00, 1.17) **Tocilizumab 8mg/kg vs. tocilizumab 4mg/kg:** RR (95% CI)=0.99 (0.90, 1.09) Serious adverse events: **Tocilizumab 8mg/kg vs. placebo:** RR (95% CI)=1.18 (0.69, 2.01) **Tocilizumab 4mg/kg vs. placebo:** RR (95% CI)=0.78 (0.51, 1.17) **Tocilizumab 8mg/kg vs. tocilizumab 4mg/kg:** RR (95% CI)=1.20 (0.64, 2.24)
LIMITATIONS OF PRIMARY STUDIES	Only 4 trials included some inherent heterogeneity in study and patient characteristics.

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Bao et al.**[3] **Year: 2011** **Study name: Secondary failure to treatment with recombinant human IL-1 receptor antagonist in Chinese patients with rheumatoid arthritis** **Country:** China **Quality rating: fair**	
FUNDING:	This study was supported in part by the grants from National Natural Science Foundation of China and Shanghai Natural Science Foundation.	
RESEARCH OBJECTIVE:	The aim of the study is to assess the efficacy of anakrinra plus MTX in patients with active rheumatoid arthritis refractory to MTX therapy.	
DESIGN & SIZE:	**Study design:** placebo controlled trials **Setting:** Shanghai hospital, China **Number screened: 54** **Number eligible: 54** **Number enrolled: 54** **Run-in/Wash-out period:** none	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Anakrina (+MTX)** 80mg 24 weeks 42	**Placebo with concurrent MTX** 3:1 ratio 24 weeks 12
INCLUSION CRITERIA:	Eligible patients were 18-65 years of age, fulfilled the revised 1987 American Rheumatism Association criteria for the classification of RA, and had active disease despite consecutive treatment with MTX at a stable dosage of 7.5-25 mg per week for at least 12 weeks before enrollment.	
EXCLUSION CRITERIA:		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Patients were allowed to take stable dosage of non-steroidal anti-inflammatory drugs or oral corticosteroids (<10 mg/day of prednisone or equivalent). Except MTX, other disease modifying-rheumatic drugs were discontinued for at least 4 weeks before enrollment.	

Authors: Bao et al. **Year: 2011**			
POPULATION CHARACTERISTICS:	**Anakrina (+MTX)**	**Placebo with concurrent MTX**	
Mean age (years):	45	45	
Sex (% female):	79	83	
Ethnicity:	NR	NR	
Class naïve:			
Other germane population qualities:			
• **Tender joint count**	11.4 (+/-6.5)	10.4 (+/-7.1)	
• **Swollen joint count**	7.8 (+/-4.5)	6.1 (+/-4.0)	
• **Mean disease duration**			
• **DMARD use (%)**			
• **MTX use (%)**			
• **Corticosteroids use (%)**	38	58	
• **DAS score**	DAS28: 5.5 (+/-1.3)	DAS28: 5.2 (+/-1.0)	
• **HAQ score**	0.6 (+/-0.7)	0.7 (+/-0.6)	
RESULTS:	**Primary Outcome Measures:** An at least 20% improvement at 24 weeks, as defined by ACR criteria (ACR 20) After 24 weeks, more patients achieved clinical benefits as determined by the ACR20 improvement treated with anakrina plus MTX compared with MTX alone (64% vs. 17%, P=0.004) **Secondary Outcome Measures:** In the anakrina group, an ACR50 response was observed in 38% and an ACR70 response in 17%. None of the patients treated with MTX alone achieved ACR50 or ACR70 improvement. A significant increase in mean DAS28 from baseline was found in the non-responders to anakrina compared with placebo (0.83 +/- 1.38 vs. -1.28 +/- 0.78, P<0.001)		

Authors: Bao et al. **Year: 2011**			
METHOD OF ADVERSE EVENTS REPORTING:	**Not reported**		
ADVERSE EVENTS (%):	**Drug 1**	**Drug 2**	**Drug 3**
Overall adverse effects reported: • Infections • URTI • abnormal LFT • herpes simplex • pneumonia	**Not reported**	**Not reported**	
ATTRITION (*overall*):	**Overall attrition:** 8 **Attrition differential high:** no		
ATTRITION (*treatment specific*):	**Anakrina (+MTX)**	**Placebo with concurrent MTX**	
Attrition overall:	5	1	
Attrition due to adverse events:	2	0	

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Bathon et al.,[4] Genovese et al.,[5,6] and Kosinski et al.[7]** **Year: 2000, 2002 and 2005** **Country:** US		
FUNDING:	Immunex Corporation		
RESEARCH OBJECTIVE:	To compare etanercept and methrotrexate in patients with early RA		
DESIGN:	**Study design:** RCT **Setting:** Clinics **Sample size:** 632		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**MTX** 20mg/week 12 months 217	**ETA10** 10 mg 2x week 12 months 208	**ETA25** 25 mg 2x week 12 months 207
INCLUSION CRITERIA:	At least 18 years of age; RA < 3 years; positive serum test for RF or at least 3 bone erosions evident on radiographs of the hands, wrists, or feet; at least 10 swollen joints and at least 12 tender or painful joints; erythrocyte sedimentation rate of at least 28 mm per hour; a serum CRP concentration of at least 2.0 mg per deciliter, or morning stiffness that lasted at least 45 minutes		
EXCLUSION CRITERIA:	Prior treatment with MTX; no other important concurrent illnesses		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable doses of NSAIDs and prednisone (≤ 10 mg daily)		

Authors: Bathon et al., Genovese et al., and Kosinski et al. **Year: 2000, 2002 and 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Early RA (mean disease duration 1 year)		
	MTX	**ETA 10mg**	**ETA 25mg**
Mean age (years):	49	50	51
Sex (% female):	75	75	74
Ethnicity (% white):	88	84	86
Other germane population qualities:			
• TJC	30	31	31
• SJC	24	24	24
• DMARD use (%)	46	25	23
• MTX use (%)	N/A	N/A	N/A
• Corticosteroids use (%)	41	42	39
• Total Sharp score	12.9	11.2	12.4
• Mean disease duration (mo)	12	11	12
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR-N/20/50/70; radiographic progression - Sharp score **Secondary Outcome Measures:** CRP **Timing of assessments:** Base line, 2 weeks, 1, 6, 8, 10, and 12 months		

Authors: Bathon et al., Genovese et al., and Kosinski et al. **Year: 2000 and 2002**	
RESULTS:	**Health Outcome Measures:** • Up to 6 months significantly more patients on ETA 25mg than on MTX achieved ACR50 and ACR70 responses ($P < 0.05$); thereafter no significant difference existed between ETA 25mg and MTX. **Intermediate Outcome Measures:** • At 12 months no significant differences existed in ACR 20 response rates: 72% ETA 25mg vs. 65% MTX ($P = 0.16$). • Compared to MTX, ETA acted more quickly to decrease symptoms and slow joint damage in patients with early active RA. The area under the curve was significantly greater for ETA 25mg throughout the study ($P < 0.05$) • At 12 months there was less joint erosion in the ETA 25mg than in the MTX group; mean increase in Sharp score ETA 25mg 0.47 vs. MTX 1.03 ($P = 0.002$). **24 months open-label extension:** • Significantly more patients on ETA 25 mg than on MTX achieved ACR 20 response at 24 months (72% vs. 59%; $P = 0.005$) • No significant differences for ACR50 (49% vs. 42%) and ACR 70 (29% vs. 24%) responses. • Significantly more patients on ETA 25mg than on MTX had a HAQ improvement of at least 0.5 units (55% vs. 37%; $P < 0.001$)

Authors: Bathon et al., Genovese et al., and Kosinski et al. **Year: 2000, 2002 and 2005**			
Significant differences in adverse events:	Yes - number of infections per patient year in both ETA10mg and 25mg 1.5 vs. MTX 1.9 events per patient-year $P = 0.006$ **24 months open-label extension:** • No significant differences in sever adverse events between MTX and ETA **5 year extension** Observed number of malignancies were within expected rates of the general population; lymphoma, however, was increased: SIR: 3.3		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 19% (118) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**MTX**	**ETA10**	**ETA25**
Loss to follow-up:	45(21%)	42(20%)	31(15%)
Withdrawals due to adverse events:	24(11%)	12(6%)	11(5%)
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Blumenauer et al.**[8] **Year: 2002** **Country:** US
FUNDING:	Institute of Population Health, Canada and other sources listed on the CMSG scope
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 529
AIMS OF REVIEW:	To assess the efficacy and safety of infliximab for the treatment of RA.
STUDIES INCLUDED IN META-ANALYSIS	Lipsky PE et al., 2000, Maini RN et al., 1998, and Maini RN et al. 1999
TIME PERIOD COVERED:	1966- March 2002
CHARACTERISTICS OF INCLUDED STUDIES:	RCT or controlled trials comparing INF and MTX to MTX alone or comparing INF alone to placebo; at least 6 months study duration; patients could also be taking other DMARDs or corticosteroids provided they were on stable doses and were randomly allocated to treatment with INF or to treatment without INF
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients were 16 years of age or older; met the ACR 1987 revised criteria for RA; Had evidence of active disease as demonstrated by at least two of the following symptoms: TJC, SJC, early morning stiffness greater than 30 minutes, and acute phase reactants.

Authors: Blumenauer et al. **Year:** 2002 **Country:** US	
CHARACTERISTICS OF INTERVENTIONS:	Treatment with INF (3mg/kg every 4 weeks and 10mg/kg every 4 weeks) and MTX versus MTX or INF (3mg/kg every 4 weeks and 10mg/kg every 4 weeks) alone versus placebo; minimum trial duration of 6 months.
MAIN RESULTS:	• **ACR 20** response was significantly improved in all INF doses compared to control at 6 months: INF 3mg/kg/8 weeks: 53% vs. 20% (controls); NNT: 3.03 INF 3mg/kg/4 weeks: 49% vs. 19% (controls); NNT: 3.33 INF 10mg/kg/8 weeks: 53% vs. 20% (controls); NNT: 3.13 INF 10mg/kg/4 weeks: 55% vs. 19% (controls); NNT: 2.78 • **ACR 50** response was significantly improved in all INF doses compared to control at 6 months: INF 3mg/kg/8 weeks: 26% vs. 5% (controls); NNT: 4.76 INF 3mg/kg/4 weeks: 32% vs. 4% (controls); NNT: 3.57 INF 10mg/kg/8 weeks: 30% vs. 5% (controls); NNT: 4 INF 10mg/kg/4 weeks: 28% vs. 4% (controls); NNT: 4.17 • **ACR 70** response was significantly improved in all INF doses compared to control at 6 months: INF 3mg/kg/8 weeks: 8% vs. 0% (controls); NNT: 12.5 INF 3mg/kg/4 weeks: 10% vs. 0% (controls); NNT: 10 INF 10mg/kg/8 weeks: 17% vs. 0% (controls); NNT: 5.88 INF 10mg/kg/4 weeks: 11% vs. 0% (controls); NNT: 9.09 • **ACR 20** response was significantly improved in all INF doses compared to control at 12 months INF 3mg/kg/8 weeks: 42% vs. 17% (controls); NNT: 4 INF 3mg/kg/4 weeks: 48% vs. 17% (controls); NNT: 3.23 INF 10mg/kg/8 weeks: 59% vs. 17% (controls); NNT: 2.38 INF 10mg/kg/4 weeks: 59% vs. 17% (controls); NNT: 2.38 Significantly more patients in the control groups withdrew than in the INF groups, RR 0.42; 95% CI 0.31-0.56

Authors: Blumenauer et al. **Year:** 2002 **Country:** US	
ADVERSE EVENTS:	• Withdrawals due to adverse events were not statistically significantly different between groups: RR 0.96; 95% CI 0.43-2.14 • 6 months, infections requiring antibiotics 31% of INF patients versus 21% of controls (not statistically different) • At 12 months, serious adverse events (WHO definition) were statistically different between INF and placebo for any dose. RR: 0.8;95% CI: 0.5 – 1.29; serious infections were not statistically different, RR 0.76; 95% CI 0.33-1.73
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Chen et al.**[9] **Year: 2009** **Study name:** **Country:** Taiwan **Quality rating:** Fair	
FUNDING:	NR	
RESEARCH OBJECTIVE:	To compare the efficacy and safety of adalimumab plus methotrexate (MTX) and MTX alone in Taiwanese patients with active RA.	
DESIGN & SIZE:	**Study design:** RCT **Setting:** Taichung Veterans General Hospital in Taiwan **Number screened:** NR **Number eligible:** NR **Number enrolled:** 47 **Run-in/Wash-out period:** 4 week washout from DMARDS other than MTX	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Drug 1** Adalimumab 40mg (+MTX) 12 weeks 35	**Drug 2** Placebo (+MTX) 12 weeks 12
INCLUSION CRITERIA:	Fulfill 1987 American College of Rheumatology criteria for RA, RA >1year, receiving a stable dose of MTX 10-15mg weekly	
EXCLUSION CRITERIA:	Previous use of TNF-α, alkylating agents such as chlorambucil or cyclophosphamide, investigational biological agents including anti-CD4 antibody, other investigational agents within 30 days, live vaccine within 3 months prior to study, clinically active TB or radiographic evidence of old pulmonary TB, renal or hepatic impairment, platelet count <150,000/mm^3, WBCs<3000 cells/mm^3, history of alcohol or drug abuse, positive serology for HIV antibody, hepatitis B surface antigen, or hepatitis C antibody, history of collagen-vascular disease, central nervous system demyelinating disorders, significant medical disease such as uncompensated congestive heart failure, concomitant use of hydroxychloroquine, sulfasalazine, azathioprine, cyclophosphamide, minocycline, or mycophenolate mofetil.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs, oral corticosteroids, MTX, and aspirin were allowed as long as the dose was maintained throughout the study.	

Authors: Chen et al. **Year: 2009**		
POPULATION CHARACTERISTICS:	**Drug 1** Adalimumab + MTX	**Drug 2** Placebo + MTX
Mean age (years):	53.0	53.0
Sex (% female):	74.3%	91.7%
Ethnicity:	Not Reported	Not Reported
Class naïve:	100%	100%
Other germane population qualities:		
• **Tender joint count**	32.5	37.2
• **Swollen joint count**	21.9	24.1
• **Mean disease duration**	6.2 yrs	8.3 yrs
• **DMARD use (%)**		
• **MTX use (%)**	100%	100%
• **Corticosteroids use (%)**		
• **DAS28 score**	6.41±0.33	6.54±0.42
• **HAQ score, Disability Index**	1.7	1.8
• **RF-Positive**	85.7%	91.7%
• **CRP**	2.0	2.4
RESULTS:	**Primary Outcome Measures:** Reduction in tender and swollen joint counts of 20% (ACR20), as determined by the ACR criteria in week 12; ACR20: Drug 1: 54.3%; Drug 2: 33.3% (p=0.318) **Secondary Outcome Measures:** Reduction in tender and swollen joint counts of 50% (ACR50), and 70% (ACR70) as determined by the ACR criteria in week 12; change from baseline in the individual components of the ACR response at week 12, and change from baseline in presence/absence and duration of morning stiffness at week 12; ACR50: Drug 1: 34.3%; Drug 2: 16.7% (p=0.302); ACR70: Drug 1: 14.3%; Drug 2: 0% (p=0.309); Tender joint count change from baseline: Drug 1: 13.9; Drug 2: 9.4 (p>0.05); Swollen joint count change from baseline: Drug 1: 12.6; Drug 2: 5.6 (p<0.05); VAS: Drug 1: 18.4; Drug 2: +1.3 (p<0.05); Patient's GA: Drug 1: 18.0; Drug 2: 4.7 (p<0.05); Physician's GA: Drug 1: 40.3; Drug 2: 26.1 (p>0.05); Disability index, HAQ: Drug 1: 0.6; Drug 2: 0.2 (p<0.05); CRP: 0.6; Drug 2: 0.1 (p>0.05)	

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Authors: Chen et al. **Year: 2009**		
METHOD OF ADVERSE EVENTS REPORTING:	**Not Specified**	
ADVERSE EVENTS (%):	**Drug 1**	**Drug 2**
Overall adverse effects reported:	80.0%	91.7%
• infections		
• URTI	37.1%	33.3%
• abnormal LFT	14.3%	0%
• herpes simplex	8.6%	0%
• pneumonia	2.9%	0%
• tb	2.9%	0%
• ISR	2.9%	0%
• Sinusitis	2.9%	0%
• Urinary Tract Infection	0%	8.3%
ATTRITION (*overall*):	**Overall attrition:** Not Reported **Attrition differential high:** Not Reported	
ATTRITION (*treatment specific*):	**Drug 1**	**Drug 2**
Attrition overall:	Not Reported	Not Reported
Attrition due to adverse events:	8.6%	0%

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Cohen et al.**[10] **and Keystone et al.**[11,12] **Year: 2005, 2008, 2009** **Country:** Multinational (US, Europe, Canada, Israel) **Trial Name:** REFLEX	
FUNDING:	Hoffmann-La Roche, Biogen Idec, and Genentech.	
RESEARCH OBJECTIVE:	efficacy and safety of treatment with RIT plus MTX in patients with active RA who had an inadequate response to anti–tumor necrosis factor (anti-TNF)	
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 520	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**RIT +MTX** 2 infusions of 1,000 mg days 1 and 15 24 weeks 311	**Placebo +MTX** N/A 24 weeks 209
INCLUSION CRITERIA:	adult patients, active RA and an inadequate response to 1 or more anti-TNF agents (INF (≥3 mg/kg; at least 4 infusions)), ADA (40 mg every other week for ≥3 months), or ETA (25 mg twice weekly for ≥3 months), or intolerant to at least 1administration of these agents + MTX (10–25 mg/week) for at least 12 weeks.	
EXCLUSION CRITERIA:	rheumatic autoimmune disease other than RA (except secondary Sjögren's syndrome), significant systemic involvement secondary to RA (vasculitis, pulmonary fibrosis, or Felty's syndrome), or ACR functional class IV disease.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	glucocorticoids (≤10 mg/day of prednisone or equivalent)	

Authors: Cohen et al. and Keystone et al. **Year: 2005, 2008, 2009**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** moderate-refractory	
	RIT +MTX	**Placebo +MTX**
Mean age (years):	52.2 ± 12.2	52.8 ± 12.6
Sex (% female):	251 (81)	169 (81)
Ethnicity:	NR	NR
Other germane population qualities:		
• Active joint count	NR	NR
• Swollen joint count	22.9	23.4
• Mean disease duration	11.7	12.1
• DMARD use (%)	2.6 +- 1.8	2.4 +- 1.8
• Weekly dose of MTX	16.4 +- 8.8	16.7+- 9.9
• Corticosteroids use (%)	200 (65)	127 (61)
• DAS score	6.9	6.8
• HAQ DI score	1.86 +- 0.58	1.91 +- 0.54
• VAS-pain	64.08 +- 22.28	64.46 +- 21.32
• FACIT-F	30.40 +- 10.75	30.24 +- 11.75
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 response at week 24, physician's global assessment of disease activity; patient's global assessment of disease activity, patient's assessment of pain, patient's assessment of physical function, and either the CRP level or the ESR **Secondary Outcome Measures:** ACR50 and ACR70, DAS28, EULAR response criteria, swollen joint count, tender joint count, patient's and physician's global assessments of disease activity, patient's assessment of pain, HAQ DI, the CRP level, and the ESR, Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score, the Short Form 36 (SF-36), Genant-modified Sharp radiographic score **Timing of assessments:** at screening, on day 1, and every 4 weeks through week 24. After week 24, up to 18 months posttreatment.	
RESULTS:	**Health Outcome Measures:** • proportion of patients ACR20 response at 24 weeks rituximab 51% versus placebo 18% • proportion of patients ACR50 response at 24 weeks rituximab 27% versus placebo 5% • proportion of patients ACR70 response at 24 weeks rituximab 12% versus placebo 1% Mean changes from baseline in individual parameters of the ACR improvement criteria at week 24:	

	• Swollen joint count RIT -10.4 + - 13.0 vs. placebo -2.6 + - 10.4 • Tender joint count RIT -14.4 + - 17.7 vs. placebo -2.7 + - 15.5 • Patient's global assessment of disease activity, mm (0–100-mm VAS) RIT -26.0 + -30.0 vs. placebo -5.3 +- 22.9 • Physician's global assessment of disease activity, mm (0–100-mm VAS) RIT -29.5 + - 27.4 vs. placebo -6.2 + - 27.1 • Health Assessment Questionnaire Disability Index RIT -0.4 + - 0.6 vs. placebo -0.1 + - 0.5 • Patient's assessment of pain, mm (0–100-mm VAS) RIT -23.4 + - 29.4 vs. placebo -2.5 + - 23.3 **Unadjusted mean changes (baseline to week 24) in patient-reported outcomes** SF-36 PCS RIT + MTX 6.64 +- 8.74 versus placebo 1.48 +- 7.32 **(*P* < 0.0001).** SF-36 MCS RIT + MTX 5.32 +- 12.41 versus placebo 2.25 +- 12.23 **(*P* = 0.0269)** VAS-pain RIT + MTX -23.37 +- 29.35 versus placebo -2.50 +- 23.30 FACIT-F RIT + MTX -9.14 +- 11.31 versus placebo -0.54 +- 9.84 HAQ DI RIT + MTX -0.44 +- 0.60 versus placebo -0.07 +- 0.45

Authors: Cohen et al. and Keystone et al. **Year: 2005, 2008, 2009**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Severe adverse event	**RIT +MTX** 261 (85%) - 55 (18)		**Placebo+MTX** 183 (88%) - 49 (23)
Significant differences in adverse events:	UTI RIT 3% vs. placebo 8% nausea RIT 7% vs. placebo 2%		
ANALYSIS:	**ITT:** Yes, but 21 excluded **Post randomization exclusions:** Yes, 3		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 29% **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*):	**RIT +MTX**	**Placebo+MTX**	**Placebo**
Loss to follow-up:	18%	46%	50%
Withdrawals due to adverse events:	3%	<1%	0
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: De Filippis et al.**[13] **Year: 2006** **Country:** Italy	
FUNDING:	None reported	
RESEARCH OBJECTIVE:	Comparison of INF and ETA	
DESIGN:	**Study design:** Open label randomized trial **Setting:** Rheumatology clinic **Sample size:** 32	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg 2x a week 52 weeks 16	**INF** 3 mg/kg 0,2,6 wks then every 2 months 52 weeks 16
INCLUSION CRITERIA:	Ages 20-60, met 1987 ACR criteria; symptom duration more than 2 yrs; active disease; not responding to DMARDS for more than 6 months including stable dose of MTX	
EXCLUSION CRITERIA:	Early onset disease; hospitalization in last 6 months for important medical problems or infections; hepatic or renal failure; positive ANA; heart failure; positive TBC; more than 10 mg of prednisone	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Cox-2 or NSAIDS, MTX	

Authors: De Fillipis **Year: 2006**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe	
	ETA	**INF**
Mean age (years):	44.7	46.79
Sex (% female):	NR	NR
Ethnicity:	NR	NR
Other germane population qualities:		
• Tender joint count	22.4	20.93
• Swollen joint count	16.87	14.73
• Mean disease duration	NR	NR
• DMARD use (%)	100	100
• MTX use (%)	NR	NR
• Corticosteroids use (%)	NR	NR
• DAS score	1.89	1.67
• HAQ score		
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20/50/70 **Secondary Outcome Measures:** HAQ **Timing of assessments:** Baseline weeks 14, 22 and 54	
RESULTS:	**Health Outcome Measures: INF vs. ETA** • HAQ 14 wks -14.08 vs. -12.7 *P* = NS 22 wks -16.2 vs. -17.5 *P* = NS 54 wks -21.6 vs.-32.3 *P* = NS • ACR responders 14 wks 74.4% vs. 54.4% 22 wks 60% vs. 60% 54 wks 60% vs. 74.4% • Most data reported in graphs	

Authors: De Fillipis **Year: 2006**		
ADVERSE EVENTS: **Overall adverse effects reported:**	**ETA** NR	**INF** NR
Significant differences in adverse events:	None reported	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes – 2, 1 from each group	
ARE GROUPS COMPARABLE AT BASELINE:	Yes	
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes	
STATISTICAL ANALYIS ADEQUATE:	No	
ATTRITION (*overall*):	**Overall attrition:** 2- 6% **Attrition differential high:** No	
ATTRITION (*treatment specific*):	**ETA**	**INF**
Attrition overall:	1	1
Attrition due to adverse events:	0	0
QUALITY RATING:	**Fair**	

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Devine et al.[14]** **Year: 2011** **Country: United States** **Quality rating: Fair**
FUNDING:	NR
DESIGN & SIZE:	**Study design:** Systematic Review **Number of patients: 11,589 in the 6-month model and 6,051 in the 12-month model** **Trials: 33**
OBJECTIVE OF REVIEW:	**To compare the efficacy of biologic DMARDs versus placebo with or without MTX, in treating rheumatoid arthritis**
ELIGIBILITY CRITERIA:	Clinical trials of the 9 biologic DMARDs approved in the U.S. for treating moderate to-severe rheumatoid arthritis. Published in English, human subjects, adults, and RCTs. RCTs of biologic DMARDs with or without MTX or other nonbiologic DMARDs, compared with placebo with or without MTX or other nonbiologic DMARDs. Included studies in which patients could have failed MTX therapy and had not yet received biologic therapies. Included studies in which patients had not been unsuccessfully treated with biologics, but a minimum washout period of 8 weeks before study enrollment was required. Excluded studies: Patients who had previously failed or had an inadequate response to biologics, involved dosage titration or rotation during the study, follow-up < 22 weeks, or did not report ACR50.
STUDIES INCLUDED IN REVIEW:	Kremer 2006, Kremer 2003, Rau 2002, Weinblatt 2003 (ARMADA), Furst 2003(STAR), Keystone 2004, van de Putte 2004, Bresnihan 1998, Cohen 2002, Cohen 2004, Smolen 2009 (RAPID 2), Fleischmann 2009 (FAST4WARD), Moreland 1999, Weinblatt 1999, Bathon 2000, Klareskog 2004, Keystone 2009 (GO-FORWARD), Maini 1999, Lipsky 2000, Westhovens 2006 (START), Edwards 2004, Genovese 2008, Nishimoto 2009 (SATORI), Jones 1020 (AMBITION), Smolen 2008 (OPTION), Westhovens 2009, Breedveld 2006 (PREMIER), Keystone 2008, Emery 2008 (COMET), St. Clair 2004
LITERATURE SEARCH DATES:	January 1990–July 2010
INCLUDED STUDIES:	**Studies Included in 6-Month Model**

Study Interventions	**Mean Age**	**M Disease Duration**	**Mean Baseline HAQ**	**# of Patients**	**ACR50 (%)**
Kremer 2006 Placebo + MTX Abatacept 2 mg/kg q 4 wks + MTX	55	9.3	1.0	119	12

	Abatacept 10 mg/kg q 4 wks + MTX				105 115	23 37
	Kremer 2003 Placebo + MTX Abatacept 10 mg/kg q 4 wks + MTX	51	8.7	1.7	 219 433	 16.8 39.9
	Rau 2002 & Weinblatt 3003 Placebo + MTX Adalimumab 20 mg q o wk + MTX Adalimumab 40 mg q o wk + MTX Adalimumab 60 mg q o wk + MTX	56	12.3	1.6	 62 69 67 73	 8 32 55 43
	Furst 2003 (STAR) Placebo + standard therapy Adalimumab 40 mg q o wk + standard therapy	55	10	4	 318 318	 11 29
	Keystone 2004 Placebo + MTX Adalimumab 20 mg q o wk + MTX Adalimumab 40 mg q o wk + MTX	57	11	1.5	 200 212 207	 10 41 39
	Van de Putte 2004 Placebo Adalimumab 20 mg q o wk Adalimumab 20 mg q wk Adalimumab 40 mg q o wk Adalimumab 40 mg q wk	53	10.9	1.9	 110 106 112 113 103	 8 19 21 22 35
	Bresnihan 1998 Placebo Anakinra 30 mg q.d. Anakinra 75 mg q.d. Anakinra 150 mg q.d.	53	4	1.5	 121 119 116 116	 8 17 11 19
	Cohen 2002 Placebo + MTX Anakinra 0.04 mg/kg q.d. + MTX Anakinra 0.1 mg/kg q.d. + MTX Anakinra 0.4 mg/kg q.d. + MTX Anakinra 1.0 mg/kg q.d. + MTX Anakinra 2.0 mg/kg q.d. + MTX	53	7.5	1.4	 74 63 74 77 59	 4 13 20 11 24

					72	17
	Cohen 2004 Placebo + MTX Anakinra 100 mg q.d. + MTX	57	10.7	1.3	 251 250	 8 17
	Smolen 2009 (OPTION) Placebo + MTX Certolizumab 200 mg q o wk + MTX Certolizumab 400 mg q o wk + MTX	52	6.2	1.6	 127 246 246	 3 33 33
	Fleischmann 2009 (FAST4WARD) Placebo Certolizumab 400 mg q 4 wks	54	10.1	1.5	 109 111	 4 23
	Moreland 1999 Placebo Etanercept 10 mg twice/wk Etanercept 25 mg twice/wk	52	12	1.7	 80 76 78	 5 24 40
	Weinblatt 1999 (ARMADA) Placebo + MTX Etanercept 25 mg twice/wk + MTX	50	13	1.5	 30 59	 3 39
	Bathon 2000 Placebo + MTX Etanercept 10 mg twice/wk Etanercept 25 mg twice/wk	50	1	1.4	 217 208 207	 31 33 39
	Klareskog 2004 Placebo + MTX Etanercept 25 mg twice/wk + MTX Etanercept 25 mg twice/wk	53	6.6	1.8	 228 231 223	 40 58 41
	Keystone 2009 (GO-FORWARD) Placebo + MTX Golimumab 100 mg q 4 wks + placebo Golimumab 50 mg q 4 wks + MTX Golimumab 100 mg q 4 wks + MTX	51	6	1.4	 133 133 89 89	 14 20 37 33
	Maini 1999 & Lipsky 2000 Placebo + MTX Infliximab 3 mg/kg q 8 wks + MTX Infliximab 3 mg/kg q 4 wks + MTX	53	10.6	1.7	 88 86 86	 9 22 30

	Infliximab 10 mg/kg q 8 wks + MTX Infliximab 10 mg/kg q 4 wks + MTX				87 81	40 35
	Westhovens 2006 MTX Infliximab 3 mg/kg q 4 wks + MTX Infliximab 10 mg/kg q 8 wks + MTX	52	7.8	1.5	 363 360 361	 10 32 35
	Edwards 2004 Placebo + MTX Rituximab 1000 mg q 2 wks Rituximab 1000 mg q 2 wks + cyclophosphamide 750 mg q 2 wks Rituximab 1000 mg q 2 wks + MTX	54	10.6	NA	 40 40 41 40	 13 33 41 43
	Genovese 2008 Placebo + synthetic DMARD Tocilizumab 8 mg/kg q 4 wks + synthetic DMARD	53	10	1.5	 413 803	 9 38
	Nishimoto 2009 (SATORI) Placebo + MTX Tocilizumab 8 mg/kg q 4 wks + synthetic DMARD	51.6	8.6	NA	 64 61	 11 49
	Jones 1020 (AMBITION) MTX Tocilizumab 8 mg/kg q 4 wks	50.4	6.3	1.6	 294 286	 34 44
	Smolen 2008 (RAPID 2) Placebo + MTX Tocilizumab 4 mg/kg q 4 wks + MTX Tocilizumab 8 mg/kg q 4 wks + MTX	51	8	1.6	 204 214 205	 11 31 44
	Studies Included in 12-Month Model					
	Study Interventions	**Mean Age**	**Mean Disease Duration**	**Mean Baseline HAQ Score**	**# of Patients**	**ACR50 (%)**
	Kremer 2006 Placebo + MTX Abatacept 2 mg/kg q 4 wks + MTX Abatacept 10 mg/kg q 4 wks + MTX	55	9.3	1.0	 119 105 115	 20 22 42

	Westhovens 2009 Placebo + MTX Abatacept 10 mg/kg q 4 wks + MTX	50	6.5	1.7	 253 256	 42 57
	Breedveld 2006 MTX Adalimumab 40 mg q o wk Adalimumab 40 mg q o wk + MTX	52	0.7	1.5	 257 274 268	 46 41 62
	Keystone 2004 Placebo + MTX Adalimumab 20 mg q o wk + MTX Adalimumab 40 mg q o wk + MTX	57	11	1.5	 200 212 207	 10 38 42
	Keystone 2008 Placebo + MTX Certolizumab 200 mg q 2 wks + MTX Certolizumab 400 mg q 2 wks + MTX	51	6.2	1.7	 199 393 390	 8 37 40
	Klareskog 2004 Placebo + MTX Etanercept 25 mg twice/wk + MTX Etanercept 25 mg twice/wk	53	6.6	1.8	 228 231 223	 43 69 48
	Emery 2008 (COMET) MTX Etanercept 50 mg once/wk + MTX	51.4	9	1.7	 263 265	 49 71
	Maini 1999 & Lipsky 2000 Placebo + MTX Infliximab 3 mg/kg q 8 wks + MTX Infliximab 3 mg/kg q 4 wks + MTX Infliximab 10 mg/kg q 8 wks + MTX Infliximab 10 mg/kg q 4 wks + MTX	53	10.6	1.7	 88 86 86 87 81	 8 21 34 39 38
	St. Claire 2004 MTX Infliximab 3 mg/kg q 8 wks + MTX Infliximab 6 mg/kg q 8 wks + MTX	50	0.9	1.5	 282 359 363	 32 46 50
	Edwards 2004 Placebo + MTX Rituximab 1000 mg q 2 wks	54	10.6	NA	 40 40	 5 15

	Rituximab 1000 mg q 2 wks + cyclophosphamide 750 mg q 2 wks Rituximab 1000 mg q 2 wks + MTX				41 40	27 35

Authors: Devine et al. **Year: 2011**			
DATA SYNTHESIS METHODS:	Two random-effects logistic regression models (6-month model & 12-month model)		
MAIN RESULTS: (RESULTS IN SUBGROUPS)	**Drug**	**Median Log OR**	**95% Credible interval**
	6-month model		
	Certolizumab	0.44	1.83–3.59
	Tocilizumab	0.19	1.31–2.07
	Rituximab	0.59	0.55–2.85
	Infliximab	0.27	1.03–2.10
	Etanercept	0.25	1.00–2.00
	Adalimumab	0.22	0.94–1.83
	Golimumab	0.38	0.64–2.14
	Abatacept	0.27	0.61–1.68
	Anakinra	0.28	0.47–1.58
	MTX	0.19	0.39–1.17
	Baseline disease duration	0.04	< 0.01–0.18
	Baseline HAQ score	0.53	–1.49–0.63
	Variance	0.02	< 0.01–0.28
	12-month model		
	Certolizumab	2.02	1.16–2.83
	Rituximab	1.95	0.47–4.00
	Adalimumab	1.37	0.83–1.89
	Infliximab	1.36	0.80–1.99
	Etanercept	0.86	0.28–1.43
	Abatacept	0.63	0.08–1.24
	MTX	0.84	0.42–1.26
	Baseline disease duration	0.10	< 0.01–0.17
	Baseline HAQ score	0.46	–1.11–1.89
	Variance	0.02	< 0.01–0.88
	Estimates for the 6-Month and 12-Month Models by Therapeutic Class		
	6-month model		
	Rituximab	1.70	0.56–3.00
	Tocilizumab	1.70	1.29–2.15

	TNF - α antagonists	1.56	1.31–1.86
	Abatacept	1.15	0.53–1.76
	Anakinra	0.99	0.43–1.64
	MTX	0.88	0.46–1.28
	12-month model		
	Rituximab	2.02	0.39–4.31
	TNF - α antagonists	1.29	0.92–1.73
	Abatacept	0.59	–0.26–1.36
	MTX		0.38–1.46
	Pairwise Comparisons Between Biologic DMARDs and MTX (MTX), 6-month model Only significant difference between Certolizumab and MTX (log OR 1.8, 99.9% Crib 0.6–3) **Pairwise Comparisons Between Biologic DMARDs and MTX, 12-month model** None significant **Pairwise Comparisons of Biologics by Therapeutic Class, 6-month model** Pairwise comparisons between MTX and three of five classes (rituximab, tocilizumab, and TNF-α antagonists) were significant. **Pairwise Comparisons of Biologics by Therapeutic Class, 12-month model** None significant		
ADVERSE EVENTS:	NR		
LIMITATIONS OF PRIMARY STUDIES	NR		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Edwards et al.[15] and Strand et al.[16]** **Year: 2004 and 2006** **Country:** Multinational			
FUNDING:	Roche			
RESEARCH OBJECTIVE:	To confirm the role of B cells in RA by evaluating the effect of RIT in patients with active RA.			
DESIGN:	**Study design:** RCT, double-blind **Setting:** Multicenter (26 rheumatology centers) **Sample size:** 161			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**MTX** ≥ 10 mg/wk up to 2 yrs 40	**RIT** 1000 mg days 1 and 15 up to 2 yrs 40	**RIT + Cyclophosphamide** 1000 mg days 1 and 15 + 750 mg days 3 and 17 up to 2 yrs 41	**RIT + MTX** 1000 mg days 1 and 15 + ≥ 10 mg/wk up to 2 yrs 40
INCLUSION CRITERIA:	Age ≥ 21 years; fulfillment of revised 1987 American Rheumatism Association criteria; active disease (defined as ≥ 8 swollen & 8 tender joints and at least 2 of the following: a serum CRP level ≥ 15mg/l, ESR ≥ 28mm/hr, or morning stiffness lasting longer than 45 minutes) despite treatment with ≥ 10mg of MTX per week; RF ≥ 20 IU per ml.; failed at least 1 DMARD.			
EXCLUSION CRITERIA:	Autoimmune disorder other than RA (except concurrent Srjogen's); American Rheumatism Association functional class IV disease; active rheumatoid vasculitis; a history of systemic diseases associated with arthritis; chronic fatigue syndrome; serious & uncontrolled coexisting diseases; active infection; a history of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms; primary of secondary immunodeficiency; or a history of cancer (except basal cell carcinoma of the skin that had been excised).			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDS at stable doses or corticosteroids at doses ≤ 12.5 mg per day of prednisolone (or the equivalent); all groups, including control, also received a 17-day course of treatment with corticosteroids and a single 10mg dose of leucovorin.			

Authors: Edwards et al. and Strand et al. **Year: 2004 and 2006**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** "highly active" (mean disease duration 10.5 years)			
	MTX	**RIT**	**RIT + Cyclophosphamide**	**RIT + MTX**
Mean age (years):	54	54	53	54
Sex (% female):	80	73	83	75
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• TJC	32	34	33	32
• SJC	19	21	19	23
• Mean disease duration	11	9	10	12
• DMARD use (no.)	2.6+/- 1.3	2.5+/-1.6	2.6+/-1.4	2.5+/-1.4
• DAS score	6.9	6.8	6.9	6.8
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR50 response at week 24. **Secondary Outcome Measures:** ACR20 & ACR70 responses; change in DAS; response according to EULAR **Timing of assessments:** Clinical assessments at baseline and at weeks 12, 16, 20, & 24; lab assessments at screening (3 weeks before baseline), on days 1, 3, 15, 17, and at weeks 4, 8, 12, 16, 20, and 24.			
RESULTS:	**Health Outcome Measures:** at 24 weeks n (%) MTX vs. RIT vs. RIT + CTX + RIT + MTX ACR20 15 (38) vs. 26 (65)* vs. 31 (76)** vs. 29 (73)** ACR50 5 (13) vs. 13 (33) vs. 17 (41)** vs. 17 (43)** ACR70 2 (5) vs. 6 (15) vs. 6 (15) vs. 9 (23)* *$P < 0.05$, **$P < 0.01$ • %patients with improved HAQ-DI at 26 weeks 45 vs. 68 vs. 59 vs. 63 At week 24, mean change from baseline in DAS score showed significant improvement over MTX alone in all RIT groups ($P \leq 0.002$): -1.3 +/- 1.2 (MTX), -2.2 +/- 1.4 (RIT), -2.6 +/- 1.5 (RIT + CYP), -2.6 +/- 1.3 (RIT + MTX) • At 24 weeks, 20-24% RIT groups had a good EULAR response; MTX group (5%) ($P \leq 0.004$). • Moderate or good EULAR response (P value for comparison with MTX group) 50% (MTX), 85% (RIT; $P = 0.002$), 85% (RIT + CYP; $P = 0.001$), 83% (RIT + MTX; $P = 0.004$) **Intermediate Outcome Measures:** • RIT treatment was associated with a large, rapid, & sustained decrease in RF levels; conversely, treatment with MTX alone resulted in modest decreases that returned to baseline by week 24.			

Authors: Edwards et al. and Strand et al. **Year: 2004 and 2006**				
ADVERSE EVENTS:	**MTX**	**RIT**	**RIT + Cyclophosphamide**	**RIT + MTX**
Overall adverse effects reported:	80%	80%	73%	85%
• Hypotension	18	30	29	18
• RA exacerbation	40	15	15	5
• Hypertension	15	15	7	25
• Nasopharyngitis	15	10	5	10
• Arthralgia	8	8	2	10
• Rash	3	10	10	3
• Back pain	5	10	7	0
• Cough	0	13	2	5
• Pruritis	0	10	10	0
• Nausea	3	5	10	0
• Dyspnea	0	10	0	0
Significant differences in adverse events:	NR			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No			
ADEQUATE RANDOMIZATION:	Method not described			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	Yes			
ATTRITION (*overall*):	**Overall loss to follow-up:** 6.2% at 24 weeks (37.8% at 48 weeks) **Loss to follow-up differential high:** No			
ATTRITION (*treatment specific*):	**MTX**	**RIT**	**RIT + Cyclophosphamide**	**RIT + MTX**
Loss to follow-up (24 weeks):	7.5%	5%	7.3%	2.5%
Withdrawals due to adverse events:	1	2	2	1
QUALITY RATING:	**Fair**			

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Emery et al.**[17] **Year: 2006** **Country:** Multinational		
FUNDING:	Roche		
RESEARCH OBJECTIVE:	To examine the safety & efficacy of different rituximab doses plus methotrexate, with or without gkucocorticoids, in patients with active RA resistant to DMARDs.		
DESIGN:	**Study design:** RCT, double blind, placebo-controlled **Setting:** Multicenter, outpatient **Sample size:** 465		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**RIT/placebo** N/A Days 1 and 15; 24 weeks 149	**RIT 500mg** Two 500mg infusions Days 1 and 15; 24 weeks 124	**RIT 1,000mg** Two 1,000mg infusions Days 1 and 15; 24 weeks 192
INCLUSION CRITERIA:	Outpatients between 18 & 80 years old; ≥ 6 month history of moderate to severe RA (diagnosed according to ACR) despite ongoing with MTX (10-25 mg/week) for at least 12 weeks before randomization, with stable dosage during the last 4 weeks; active disease defined as swollen and TJC ≥ 8 and either an ESR ≥ 28mm/hour or a CRP level ≥ 1.5 mg/dl; failed prior treatment with 1-5 DMARDs; patients on glucocorticoids included if oral dosage stable > 4 weeks or parenteral / intraarticular dosage given > 4 weeks before screening.		
EXCLUSION CRITERIA:	Significant systemic involvement secondary to RA; evidence of significant other illnesses, recurrent infections, or lab abnormalities; history of severe allergic / anaphylactic reactions to humanized or murine monoclonal antibodies; previous treatment with RIT or any lymphocyte-depleting therapies.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs, if the dosage had been stable at least 2 weeks prior to entry		

Authors: Emery et al.
Year: 2006

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: moderate to severe (mean disease duration 10.4 years)

	RIT/placebo	RIT 500mg	RIT 1,000mg
Mean age (years):	51.1	51.4	51.1
Sex (% female):	80	83	80
Ethnicity (% white):	NR	NR	NR
Other germane population qualities:			
• TJC	35	33	32
• SJC	21	22	22
• Mean disease duration (years)	9.3	11.1	10.8
• DMARD use (mean no.)	2.2	2.5	2.5
• DAS score	6.8	6.8	6.7
• HAQ score	1.7	1.8	3.0

OUTCOME ASSESSMENT:

Primary Outcome Measures: ACR20 response
Secondary Outcome Measures: ACR50, ACR70, DAS28, and EULAR responses; fatigue measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale; HAQ-DI
Timing of assessments: Week 24, otherwise NR

RESULTS:

Health Outcome Measures: The primary ITT efficacy population was 367 RF-positive patients.

- The proportion of these patients achieving ACR20 response was significantly greater in both RIT groups compared to placebo ($P < 0.0001$): 55% of RIT 500mg group, 54% of RIT 1000mg group, and 28% of placebo group. No statistically significant difference in the odds of achieving ACR20 response between the 2 RIT groups (OR 0.93, $P = 0.768$)
- Compared to placebo, a greater proportion of patients in either RIT group achieved ACR50 response (both $P \leq 0.001$) and an ACR70 response ($P = 0.029$ for 500mg; $P \leq 0.001$ for 100mg)
- Changes in DAS28 at week 24 reflected ACR response findings.
- Compared with placebo, moderate or good EULAR responses occurred in more RIT-treated patients ($P < 0.0001$ in both groups)
- Changes in mean HAQ-DI scores = -0.43 (RIT 500mg), -0.49 (1,000mg), and -0.16 (placebo)
- Percent improvement in FACIT-F = 20% (RIT 500mg), 28% (RIT 1000mg), and 4% (placebo)

Intermediate Outcome Measures:

- Treatment with RIT led to nearly complete depletion of peripheral B cells, sustained at 24 weeks.
- Antibodies to the test agent were detectable in 0.7% (placebo), 4.2% (RIT 500mg), 2.7% (1,000mg).

Authors: Emery et al. **Year: 2006**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Severe events • RA exacerbation • Headache • Nausea • Upper respiratory infection • Nasopharyngitis • Arthralgia • Diarrhea • Fatigue • Hypertension • Rigors • Dizziness • Serious infections	**RIT/placebo** 70 18 30 13 9 6 5 3 5 5 3 2 4 1	**RIT 500mg** 81 17 17 11 6 8 6 4 6 4 4 4 3 1	**RIT 1,000mg** 85 18 14 11 10 6 5 6 3 4 6 7 5 2
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (13)		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 18.1% **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**RIT/placebo** 35% NR	**RIT 500mg** 9% NR	**RIT 1,000mg** 14% NR
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Emery et al.[18]** **Year: 2010** **Study name: Study Evaluating Rituximab's Efficacy in MTC iNadequate rEsponders (SERENE)** **Country: Multinational (11 countries)** **Quality rating: Fair**		
FUNDING:	Hoffmann-La Roche, Genentech, Biogen Idec		
RESEARCH OBJECTIVE:	To study the efficacy and safety of RTX 2 x 500 mg and 2 x 1000 mg with MTX in active RA patients who had inadequate response to MTX and no prior biologic treatment		
DESIGN & SIZE:	**Study design:** Placebo-controlled RCTs **Setting:** Multicenter (102 centers) **Number screened: NR** **Number randomized: 511** **Run-in/Wash-out period: 2 wk wash-out for all DMARDs**		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo + MTX** MTX 10-25 mg/wk 24 wks 172	**RTX: 2 x 500 mg + MTX** RTX: 500 mg IV infusion on days 1 and 15 + MTX: 10-25 mg/wk 24 wks 167	**RTX: 2 x 1000 mg + MTX** RTX: 1000 mg IV infusion on days 1 and 15 + MTX: 10-25 mg/wk 24 wks 170
INCLUSION CRITERIA:	• Treatment resistant to 10-25 mg MTX/wk for 12 wks or more • 18-80 yrs old • RA according to ACR (SJC and TJC of both at least 8) • CRP at least 0.6 mg/dl or ESR at least 28 mm/h) for 6 mos or more • Absolute neutrophil count of 1500 mcg/mcl or more • Hemoglobin of 8 g/dl or more • IgM of 40 mg/dl or more • IgG of 500 mg/dl or more		
EXCLUSION CRITERIA:	• Previous treatment with a biologic		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	• Oral corticosteroids (≤10 mg/day prednisolone or equivalent) • Non-steroidal anti-inflammatory drugs		

Authors: Emery et al. **Year: 2010**			
POPULATION CHARACTERISTICS:	**Placebo + MTX**	**RTX: 2 x 500 mg + MTX**	**RTX: 2 x 1000 mg + MTX**
Mean age (years):	52.16	51.91	51.30
Sex (% female):	85.5	79.6	81.2
Ethnicity (% Caucasian):	82.6	80.2	80.6
Class naïve:			
Other germane population qualities:			
• **Tender joint count**	30.2	27.1	28.7
• **Swollen joint count**	20.9	18.6	19.5
• **Mean disease duration (yrs)**	7.48	7.10	6.61
• **DMARD use (%)**	NR	NR	NR
• **MTX use (%)**	NR	NR	NR
• **Corticosteroids use (%)**	47.7	47.9	39.4
• **DAS28-ESR score**	6.54	6.40	6.49
• **DAS28-CRP score**	5.95	5.81	5.86
RESULTS:	**Primary Outcome Measures:** At week 24, ACR 20/50/70 response rates and DAS28 scores were statistically significantly greater with rituximab + methotrexate than with methotrexate + placebo **Secondary Outcome Measures:** Higher proportions of patients receiving rituximab + MTX achieved EULAR responses, LDA, and remission than placebo + MTX Higher proportions of patients receiving rituximab + MTX also achieved MCIDs for HAQ and SF-36 subscales		

Authors: Emery et al. **Year: 2010**			
METHOD OF ADVERSE EVENTS REPORTING:	**Adverse events and serious adverse events were recorded throughout the study and rates were calculated. Rates of infections and serious infections per 100 patient-years were calculated.**		
ADVERSE EVENTS (%):	**Placebo + MTX**	**RTX: 2 x 500 mg + MTX**	**RTX: 2 x 1000 mg + MTX**
Overall adverse effects reported:			
• Infections (reported at 24 wks)	43	41	36
• URTI	NR	NR	NR
• abnormal LFT	NR	NR	NR
• herpes simplex	NR	NR	NR
• pneumonia	NR	NR	NR
• tb	NR	NR	NR
• ISR	NR	NR	NR
ATTRITION (*overall*):	**Overall attrition:** 5% **Attrition differential high:**		
ATTRITION (*treatment specific*):	**Placebo + MTX**	**RTX: 2 x 500 mg + MTX**	**RTX: 2 x 1000 mg + MTX**
Attrition overall (%)l:	7.6	3.6	3.5
Attrition due to adverse events (%):	1.2	1.2	1.8

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Finckh et al.**[19] **Year: 2006** **Country:** Switzerland		
FUNDING:	Swiss Health Authorities; Swiss Academy for Medical Sciences; Abbott; Essex; Wyeth; Aventis; Bristol-Mayers; Mepha; Merck; Novartis; Roche; Swiss National Science Foundation; Geneva University Hospital; Kirkland Scholars Fellowship; NIH; Grant Number: P60-AR-47782; Kirkland Scholars Fellowship; NIH; Grant Number: AR-047605; NIH; Grant Number: AR-47782; Kirkland Scholar Award; Lupus Clinical Trials Consortium; Faculty of Medicine, Northwestern University, Chicago, Illinois		
RESEARCH OBJECTIVE:	To compare the effectiveness of DMARDs + infliximab vs. DMARDs + etanercept vs. etanercept in preventing progressive joint damage, in a population-based cohort.		
DESIGN:	**Study design:** Observational (prospective and retrospective) **Setting:** Swiss Clinical Quality Management System **Sample size:** 372		
INTERVENTION: **Dose (median mg/week):** **Duration (years):** **Sample size:**	**ETA** 50 1.76 110	**ETA + DMARD** 50 1.73 130	**INF + DMARD** 3.3 mg/kg every 8 wks 1.63 132
INCLUSION CRITERIA:	Patients with RA; anti-TNF treatment > 10 months.		
EXCLUSION CRITERIA:	Did not have complete serial radiographs of the hands and feet; previous treatment failure with other anti-TNF agents; interruption in therapy within 10 months of treatment initiation because of side effects or treatment ineffectiveness.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes, at physicians discretion		

<table>
<tr><td colspan="4">Authors: Finckh et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes but ETA group seems a little more severe
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>ETA</u></td><td><u>ETA + DMARD</u></td><td><u>INF + DMARD</u></td></tr>
<tr><td>Mean age (years):</td><td>53.6</td><td>54.4</td><td>53.2</td></tr>
<tr><td>Sex (% female):</td><td>79</td><td>74</td><td>82</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• TJC</td><td>6</td><td>4</td><td>3</td></tr>
<tr><td>• SJC</td><td>8</td><td>7.5</td><td>8</td></tr>
<tr><td>• Median disease duration</td><td>10.9</td><td>9.0</td><td>10.6</td></tr>
<tr><td>• DMARD use (%)</td><td>0</td><td>100</td><td>100</td></tr>
<tr><td>• MTX use (%)</td><td>0</td><td>70</td><td>92</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>29</td><td>36</td><td>35</td></tr>
<tr><td>• DAS score</td><td>4.7</td><td>4.3</td><td>4.3</td></tr>
<tr><td>• HAQ score</td><td>1.46</td><td>1.29</td><td>1.40</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Radiographic disease progression with Ratingen score (JSN; assessed prospectively)
Secondary Outcome Measures: Cartilage destruction, via progressive narrowing of the joint space width (assessed retrospectively)
Timing of assessments: < 4 months before therapy started and < 4months after treatment cessation.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No statistically significant differences between groups in functional disability measured with the HAQ (data NR).
Intermediate Outcome Measures:
• Progression of erosions: No significant differences between INF + DMARDs and ETA + DMARDs (Data NR; P = 0.07).
• Joint space narrowing (JSN): INF plus DMARDs was statistically significantly better than ETA plus DMARDs (data NR; P = 0.02). No difference, however, was obvious when comparison was limited to INF + MTX and ETA + MTX (data NR; P = NR)
• INF + DMARDs was significantly more effective than ETA in all outcome measures (data NR).</td></tr>
</table>

Authors: Finckh et al. **Year: 2006**			
ADVERSE EVENTS:	**ETA** NR	**ETA + DMARD** NR	**INF + DMARD** NR
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 14% **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A		
QUALITY RATING:	**N/A**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Geborek et al.**[20] **Year: 2002** **Country:** Sweden		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To assess the efficacy and safety of etanercept, infliximab, and leflunomide in a population-based setting		
DESIGN:	**Study design:** Non-randomized, open-label trial **Setting:** Primary care clinics; university clinic **Sample size:** 369 (33 patients tried two different treatments and one tried all three; 404 treatments)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** Varied 12 months 166	**INF** Varied 12 months 135	**Leflunomide** Varied 12 months 103
INCLUSION CRITERIA:	Diagnosis of RA according to the clinical judgment of the treating doctor. All patients included were required to have failed to respond to or not tolerated at least two DMARDs, including MTX. The patients were selected on the basis of current disease activity and/or unacceptable steroid requirement as judged by the treating doctor, but had different backgrounds concerning previous treatment, concomitant diseases, and functional impairment and disability		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

Authors: Geborek et al. **Year: 2002**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR **Disease severity:** Mild-moderate-severe (mean disease duration 14.5 years)		
	ETA	**INF**	**Leflunomide**
Mean age (years):	54.0	55.4	61.3
Sex (% female):	78	79	82
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• Mean disease duration	14.9	14.1	14.9
• DMARD use (%)	NR	NR	NR
• MTX use (%)	NR	NR	NR
• Corticosteroids use (%)	83	81	73
• DAS score	5.8	5.6	5.4
• HAQ score	1.55	1.47	1.46
• CRP	43.7	44.4	37.7
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR 20/50/70 **Secondary Outcome Measures:** DAS28 **Timing of assessments:** At months 0, 3 ,6, 12 and then every 3 or 6 months		
RESULTS:	**Health Outcome Measures:** • The ETA and INF performed significantly better than leflunomide • ACR 20-ETA significantly better than INF at three months ($P < 0.02$) and six months ($P < 0.05$) • ETA and INF significant decreases in prednisolone use after 2 weeks ($P < 0.001$) • ETA had a significantly higher ACR response rate than INF at 3 and 6 months (data NR; $P < 0.02$; $P < 0.05$) • ETA had a significantly higher ACR50 response rate at 3 months (data NR; $P < 0.05$) • Response rates of ETA and INF as monotherapies were not significantly better than MTX monotherapy		

Authors: Gerborek et al. **Year: 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Fatal • Life threatening • Serious • Moderate • Mild • Not graded	**ETA** 120 3 0 15 36 61 5	**INF** 107 0 3 11 34 59 0	**Leflunomide** 55 0 0 4 20 22 9
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ARE GROUPS COMPARABLE AT BASELINE:	Yes		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	No, outcome assessors not blinded		
STATISTICAL ANALYSIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A		
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Genovese et al.**[21] **Year: 2004** **Country:** US		
FUNDING:	Amgen, Inc., Thousand Oaks, CA		
RESEARCH OBJECTIVE:	To determine the potential for additive or synergistic effects of combination therapy with the selective anti-TNF-α agent etanercept and the anti-IL1 agent anakinra.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter, specialty clinic **Sample size:** 242		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg *twice* per week 24 weeks 80	**½ ETA + AKA** 25 mg *once* per week; 100 mg/day 24 weeks 81	**ETA + AKA** 25 mg *twice* per week; 100 mg/day 24 weeks 81
INCLUSION CRITERIA:	Age 18 or greater; greater than 6-month history of RA diagnosed by ACR criteria; 6+ swollen joints; 9+ tender/painful joints; at least 2 of: morning stiffness lasting 45 or more minutes, serum CRP of ≥ 1.5 mg/dl, or ESR ≥28 mm/hr; and, received MTX for at least 16 weeks, with a stable dose in the range of 10-25 mg/week for at least 8 weeks.		
EXCLUSION CRITERIA:	Any DMARD other than MTX within the past 4 weeks; treatment with AKA or any protein-based TNF-alpha inhibitor; received any intraarticular or systemic corticosteroid injections within past 4 weeks; or, had a recent history of significant infection or other important concurrent illness.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Continued treatment with stable doses of MTX and other stable medications, such as corticosteroids.		

Authors: Genovese, et al.
Year: 2004

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes, but there is a slight overall trend to more severe disease in full ETA + AKA group.
Disease severity: Moderate

	ETA	½ ETA + AKA	ETA + AKA
Mean age (years):	54.4	53.8	55.7
Sex (% female):	82.5	71.6	77.8
Ethnicity (% white race):	86.3	77.8	75.3
Other germane population qualities:			
• TJC	31.0	31.0	35.9
• SJC	21.4	19.8	23.4
• MTX use (%)	100	100	100
• Corticosteroids use (%)	48.8	54.3	44.4
• HAQ score	1.5	1.5	1.6

OUTCOME ASSESSMENT:

Primary Outcome Measures: ACR50 at week 24.
Secondary Outcome Measures: ACR20 and ACR70 at week 24; sustained ACR20 response ("response for at least 4 monthly measurements, not necessarily consecutive, with 1 occurring at month 6"); good or moderate EULAR response at week 24; improvement in the ACR core criteria components; duration of morning stiffness; the DAS; and the SF-36; plasma AKA and ETA concentrations and anti-AKA and anti-ETA antibody concentrations.
Timing of assessments: Baseline and weeks 2, 4, 8, 12, 16, 20, and 24; plasma concentrations at weeks 4, 12, and 24; antibody concentrations at weeks 12 and 24.

RESULTS:

Health Outcome Measures (ETA v. ½ ETA + AKA v. ETA + AKA), measure (95% CI):

- At week 24 there were no significant differences in outcomes between the treatment groups
  ACR50 at week 24: 41% v. 39% v. 31% (*P* = 0.914, by 1-tailed t-test)
  - OR (ETA + AKA v. ETA alone) 0.64 (90% CI: 0.37 to 1.09)
  - Sensitivity analysis yielded similar results.
- **ACR20 at week 24:**
  - 68% v. 51% v. 62% Only significant difference is between ETA alone and the ½ ETA + AKA group (*P* = 0.037).
- ACR70 at week 24: 21% v. 24% v. 14% (*P*-value NR)
- Sustained ACR20 response: between 43% and 54% of subjects in each group (specifics NR).
- EULAR response at week 24: 79% v. 66% v. 73% (*P*-value NR)
- Mean % reduction in DAS: 39% v. 41% v. 40% (*P*-value NR)

Authors: Genovese et al. **Year: 2004**			
ADVERSE EVENTS:	**ETA**	**½ ETA + AKA**	**ETA + AKA**
Overall adverse effects reported, %:	90.0	95.1	93.8
• Infections	40.0	37.0	46.9
• URTI	20.0	11.1	13.6
• ISR	40.0	67.9	70.4
• Any serious adverse event	2.5	4.9	14.8
• Serious infection	0.0	3.7	7.4
Significant differences in adverse events:	Patients receiving ETA (any dosage) + AKA experienced more ISRs and serious adverse events than patients receiving ETA alone. *P*-values NR.		
ANALYSIS:	**ITT:** YES **Post randomization exclusions:** 2		
ADEQUATE RANDOMIZATION:	**YES**		
ADEQUATE ALLOCATION CONCEALMENT:	Unknown		
BLINDING OF OUTCOME ASSESSORS:	YES		
ATTRITION (*overall*):	**Overall loss to follow-up:** 15.7% **Loss to follow-up differential high:** 15% between ETA alone and ½ ETA + AKA		
ATTRITION (*treatment specific*):	**ETA**	**½ ETA + AKA**	**ETA + AKA**
Loss to follow-up:	7%	22%	20%
Withdrawals due to adverse events:	0%	8.6%	7.4%
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Hetland et al.**[22] **Year: 2010** **Study name:** DANBIO Registry **Country:** Denmark **Quality rating: Good**		
FUNDING:	Unrestricted grants from Abbott, Wyeth, and Schering-Plough (since 2004), Bristol-Myers Squibb, and Roche (since 2006), and UCB-Nordic (since 2007). The Danish Regions provided financial support for the activities related to quality improvement of biologic treatment. Dr. Hetland's work was supported by a grant from the Danish Rheumatism Association and by the Margarethe Astrid Hedvig Schaufuss Legat.		
RESEARCH OBJECTIVE:	To compare tumor necrosis factor inhibitors directly regarding the rates of treatment response, remission, and the drug survival rate in patients with rheumatoid arthritis (RA), and to identify clinical prognostic factors for response.		
DESIGN & SIZE:	**Study design:** Observational, registry **Setting:** Multicenter, outpatient **Number screened: 8074** **Number eligible: 2326** **Number enrolled: 2326** **Run-in/Wash-out period: No**		
INTERVENTION: **Dose:** **Duration (median):** **Sample size:**	**Adalimumab** 40 mg every 2 weeks 20 months 675	**Etanercept** 45 mg every week 21 months 517	**Infliximab** 229 mg every 7 weeks 16 months 1134
INCLUSION CRITERIA:	Since October 2000, Danish rheumatologists have monitored and reported details of TNF inhibitor therapy for patients with RA to the DANBIO registry.		
EXCLUSION CRITERIA:	Prior treatment with TNF inhibitor		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

Authors: Hetland et al. **Year: 2010**			
POPULATION CHARACTERISTICS:	**Adalimumab**	**Etanercept**	**Infliximab**
Mean age (years):	56	58	57
Sex (% female):	75	72	73
Ethnicity:	NR	NR	NR
Class naïve:	100%	100%	100%
Other germane population qualities:			
• **DMARD use (%)**	NR	NR	NR
• **MTX use (%)**	70	61	87
• **Corticosteroids use (%)**	40	43	50
• **DAS 28 score (mean)**	5.3	5.4	5.4
RESULTS:	**Primary Outcome Measures:** at 6 months ACR70 response 19% adalimumab, 17% etanercept, and 11% infliximab **Secondary Outcome Measures:** at 6 months EULAR good response adalimumab 41%, etanercept 34%, and infliximab 27%, DAS28 remission, adalimumab 26%, etanercept 21%, and infliximab 17% CDAI remission adalimumab 15%, etanercept 10%, and infliximab 8%, Adherence - At 48 months, the unadjusted drug adherence rates: for adalimumab, 52% (95% CI 46–57%); etanercept, 56% (95% CI 51–62%); infliximab, 41% (95% CI 37–44%) ($P < 0.0001$, by log rank test). These are the Lundex adjusted results which include all patients, crude responses are only completers at 6 months.		

Authors: Hetland et al. **Year: 2010**			
METHOD OF ADVERSE EVENTS REPORTING:	NR		
ADVERSE EVENTS (%):	**Adalimumab**	**Etanercept**	**Infliximab**
Overall adverse effects reported: • infections • URTI • abnormal LFT • herpes simplex • pneumonia • tb • ISR • • •	NR	NR	NR
ATTRITION (*overall*):	**Overall attrition:** 449 (23.9%) at 6 months **Attrition differential high:** NR		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**Overall at 6 months** 449 38%		

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Hyrich et al.**[23] **Year: 2006** **Country:** Great Britain					
FUNDING:	British Society for Rheumatology Biologics Register					
RESEARCH OBJECTIVE:	Compare outcome at 6 months in unselected "real-world" patients with RA treated with etanercept or infliximab as either monotherapy, or cotherapy with methotrexate or another DMARD					
DESIGN:	**Study design:** Prospective cohort study **Setting:** Multi-clinic **Sample size:** 2711					
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg 2x wk 6 months 763	**ETA+DMARD** Not specified 6 months 245	**ETA+MTX** Not specified 6 months 250	**INF** 3mg/kg wks 0,2,6 then every 8wks 6 months 128	**INF+DMARD** Not specified 6 months 121	**INF+MTX** Not specified 6 months 1204
INCLUSION CRITERIA:	16 years and older; starting either ETA or INF as their first biologic drug; 1987 ACR criteria for RA.					
EXCLUSION CRITERIA:	None reported					
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes					

Authors: Hyrich et al.
Year: 2006

POPULATION CHARACTERISTICS:

Groups similar at baseline:
Disease severity: Mild-moderate-severe (mean disease duration 14.6 years)

	ETA	ETA+DMARD	ETA+MTX	INF	INF+DMARD	INF+MTX
Mean age (years):	58	55	54	59	58	55
Sex (% female):	80	79	76	79	74	77
Ethnicity:	NR	NR	NR	NR	NR	NR
Other germane population qualities:						
• Mean disease duration	16	15	13	16	14	14
• Corticosteroids use (%)	54	51	44	69	59	48
• DAS score	6.8	6.6	6.6	6.8	6.8	6.7
• HAQ score	2.2	2.1	2.1	2.1	2.1	2.2

OUTCOME ASSESSMENT:

Primary Outcome Measures: EULAR response

Secondary Outcome Measures: mean improvement in the DAS28

Timing of assessments: monthly

RESULTS:

Health Outcome Measures:

EULAR response at 6 months

- ETA+MTX had an increased EULAR response compared to ETA (OR 2.0, 95% CI 1.5-2.7) or ETA+DMARD vs. ETA (OR 1.2, 95% CI 0.9-1.6)
- EULAR response rates numerically greater for ETA than for INF at 6 months (64% vs. 53%)
- A better EULAR response in both the MTX (OR 1.35 [95% CI 0.92-2.00]) and DMARD (OR 1.26 [95% CI 0.75-2.13]) subgroups as compared with the INF monotherapy

DAS28 at 6 months

- ETA 4.8 $\pm$ 1.4; ETA+MTX 4.3 $\pm$ 1.5; ETA+DMARD 4.6 $\pm$ 1.5
- INF 5.0 $\pm$ 1.6; INF+MTX 4.6 $\pm$ 1.6; INF+DMARD 4.9 $\pm$ 1.6

Authors: Hyrich et al. **Year:2006**						
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	NR					
Significant differences in adverse events:	NR					
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A					
ARE GROUPS COMPARABLE AT BASELINE:	Yes					
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes					
STATISTICAL ANALYIS ADEQUATE:	Yes					
ATTRITION (*overall*):	**Overall loss to follow-up:** 21% **Loss to follow-up differential high:**					
ATTRITION (*treatment specific*):	**ETA**	**ETA+DMARD**	**ETA+MTX**	**INF**	**INF+DMARD**	**INF+MTX**
Loss to follow-up (%):	22	19	16	30	22	21
Withdrawals due to adverse events (%):	11	9	7	16	12	10
QUALITY RATING:	**Fair**					

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Jobanputra et al.**[24] **Year:** 2002 **Country:** Multinational
FUNDING:	Health Technology Assessment Programme (UK)
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 1692 (ETA: 1062, INF: 630)
AIMS OF REVIEW:	To examine evidence for the clinical effectiveness of etanercept and infliximab in adult RA patients.
STUDIES INCLUDED IN META-ANALYSIS	• ***ETA studies (6 total studies):*** Bathon, et al. (2000: ERA Trial)); Mathias, et al. (2000); Moreland, et al. (1996); Moreland, et al. (1997); Moreland, et al. (1998: ETA v. placebo, 26wks); Weinblatt, et al. (1999); Wojdula, et al. (2000: ETA European Investigators Network) • ***INF studies (4 total studies):*** Antoni, et al. (2000); Elliot, et al. (1994); Lipsky, et al. (2000); Maini, et al. (1998); Maini, et al. (1999); Kavanaugh, et al. (2000: ATTRACT); Kavanaugh, et al. (2000: additional placebo-controlled study of INF);
TIME PERIOD COVERED:	1994-2001
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized placebo-controlled (except 1) trials of TNF-alpha antagonists in patients with highly active RA; the exception compared ETA with MTX.
CHARACTERISTICS OF INCLUDED POPULATIONS:	Mean ages ranged from 48 to 55 years; duration of disease >7 years in vast majority of patients; majority had failed at least one DMARD and some were taking MTX up to trial start; majority of patients were taking low-dose steroids.

Authors: Jobanputra et al. **Year:** 2002 **Country:** International	
CHARACTERISTICS OF INTERVENTIONS:	INF 1, 3 or 10 mg/kg intravenously every 4 to 8 weeks versus placebo ETA 10 or 25 mg subcutaneously one to two times per week versus placebo
MAIN RESULTS:	• Pooled estimates at 6 months presented significantly greater improvements for TNF-alpha antagonist than placebo on all outcome measures (95% CI) ▪ ACR20: RR 3.09 (2.29 to 4.18); RD 0.37 (0.28 to 0.45); NNT 2.7 ▪ ACR50: RR 6.72 (3.57 to 12.68); RD 0.26 (0.21 to 0.30); NNT 3.8 ▪ ACR70: RR 11.97 (2.94 to 48.69); RD 0.12 (0.09 to 0.15); NNT 8.3 ▪ HAQ: -0.37 (-0.77 to 0.03) ; Patient Global Assessment: -1.9 (-2.9 to -0.4) ▪ SJC: -8.1 (-14.5 to -1.7) ETA v. placebo at Trial End (4 weeks to 1 year): ▪ ACR20: RR 4.29 (3.12 to 5.88); RD 0.44 (0.39 to 0.49); NNT 2.3 INF v. placebo at Trial End (4 weeks to 1 year): ▪ ACR20: RR 3.55 (2.33 to 5.41); RD 0.37 (0.25 to 0.48); NNT 2.7 NOTE: Data specific to ETA and INF at 6 months (or any other specific time point) NR.
ADVERSE EVENTS:	The frequency of serious adverse events was low and comparable to those experienced in the placebo groups. INF: ▪ The ATTRACT study followed patients to one year and reported 62% v. 26% INF v. placebo developing ANA during the study ($P = 0.002$) and 10% v. 0% developed anti-DNA antibodies ($P = 0.013$); 5% of patients receiving INF developed a malignancy versus 0% in the placebo group. ▪ Total deaths: 1% v. 3% INF v. placebo group in the ATTRACT study. ETA: ▪ ISRs occurred more frequently in patients receiving ETA: 46% v. 13 % ($P < 0.05$), 42% v. 7% ($P < 0.001$), 23% v. 1% ($P < 0.001$), and 34% v. 7% (P-value NR) for the 4 studies > 3 months in duration ▪ URTIs: 31% v. 16%, which correspond to 0.98 and 0.93 events/patient year. (Moreland, et al.); 23% v. 27% (European ETA Investigators Network); P-values NR ▪ Total deaths: 3 in combined ETA groups and 0 in combined placebo groups.
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	YES
STANDARD METHOD OF APPRAISAL OF STUDIES:	YES
QUALITY RATING:	**Good**

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Keystone et al.,[25] Kavanaugh et al.,[26] Strand et al.[27] RAPID 1 (Rheumatoid Arthritis Prevention of Structural Damage 1)** **Year: 2008** **Country:** Multinational		
FUNDING:	UCB Inc		
RESEARCH OBJECTIVE:	Efficacy and safety of 2 dosage regimens of certolizumab pegol as adjunctive therapy to MTX in patients with active RA with an inadequate response to MTX therapy alone.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 982		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 52 weeks w/early escape at 16 weeks 199	**CZP 200** 200 mg 52 weeks 393	**CZP 400** 400 mg 52 weeks 390
INCLUSION CRITERIA:	at least 18 years; diagnosis of RA, 6 months prior to screening but <15 years.; required to have received MTX for 6 months, with a stable dosage of 10 mg/week for 2 months prior to baseline.		
EXCLUSION CRITERIA:	Diagnoses of any other inflammatory arthritis or a secondary noninflammatory arthritis that could have interfered with our evaluation of the effects of certolizumab pegol on RA; history of TB or a chest radiograph showing active or latent TB; positive findings on a purified protein derivative (PPD) skin test were excluded, unless the PPD positivity was associated with previous vaccination with BCG (PPD positive by local standard); at a high risk of infection; a history of malignancy, demyelinating disease, blood dyscrasias, or severe, progressive, and/or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease; received any biologic therapy within 6 months (or had received ETA and/or ANA within 3 months) of baseline and/or any previous biologic therapy that resulted in a severe hypersensitivity or anaphylactic reaction were excluded, as were patients who had previously failed to respond to treatment with an anti-TNF agent.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids (≤10 mg/day of prednisone or equivalent, with a stable dosage NSAIDs/cox- 2 inhibitors, and analgesics		
Authors: Keystone et al. **Year: 2008**			
POPULATION	**Groups similar at baseline:** Yes		

CHARACTERISTICS:	Disease severity: Mild-moderate-severe		
	Placebo	**CZP 200**	**CZP 400**
Mean age (years):	52.2	51.4	52.4
Sex (% female):	83.9	82.4	83.6
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• Tender joint count	28.8	30.8	31.1
• Swollen joint count	21.2	21.7	21.5
• Mean disease duration	6.2	6.1	6.2
• DMARD use (# used)	1.4	1.3	1.3
• MTX use (%)	100	100	100
• Corticosteroids use (%)	NR	NR	NR
• DAS score	7.0	6.9	6.9
• HAQ score	1.7	1.7	1.7
• Employed (%)	38.3	45.4	39.5
• Productivity in workplace (employed patients only)	N = 69	N = 162	N = 139
o Work days missed due to arthritis (mean per month)	4.6	3.1	4.5
o Days with work productivity reduced by ≥50% due to arthritis (mean per month; not including days missed)	6.2	7.2	7.5
o Rate of arthritis interference with productivity (mean; 0-10 scale)	5.5	5.2	5.1
• Productivity at home			
o Household work days missed due to arthritis	8.8	7.6	8.2
o Days with household work productivity reduced ≥50% due to arthritis (mean per month)	10.5	10.2	10.5
o Days with family, social,			

<table>
<tr><td>or leisure activities missed due to arthritis (mean per month)
o Days with outside help hired due to arthritis (mean per month)
o Rate of arthritis interference with household work productivity (mean, 0-10 scale)</td><td>6.8

6.2

6.4</td><td>6.2

5.1

6.1</td><td>5.6

5.4

6.1</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ACR20 and mean change in modified TSS, work and home productivity measures (WPS-RA (Work Productivity Survey – Rheumatoid Arthritis)
Secondary Outcome Measures: HAQ DI, ACR50 and 70
Timing of assessments: Baseline, weeks 1, 2, 4, 6, 8, 10, 12, 14, 16 then every 4 weeks until week 52 or withdrawal</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
<table>
<tr><td>Measure</td><td>Placebo</td><td>CZP 200</td><td>CZP 400</td></tr>
<tr><td>ACR20 at 52 wks</td><td>13.6%</td><td>58.8% (P < 0.001 vs. placebo)</td><td>60.8% (P < 0.001 vs. placebo)</td></tr>
<tr><td>ACR50 at 52 wks</td><td>7.6%</td><td>37.1% (P < 0.001 vs. placebo)</td><td>39.9% (P < 0.001 vs. placebo)</td></tr>
<tr><td>ACR70 at 52 wks</td><td>3.0%</td><td>21.4% (P < 0.001 vs. placebo)</td><td>20.6% (P < 0.001 vs. placebo)</td></tr>
<tr><td>HAQ DI change from baseline at 12 weeks</td><td>-8.2</td><td>-30.4 (P < 0.001 vs. placebo)</td><td>-27.6 (P < 0.001 vs. placebo)</td></tr>
<tr><td>SF-36 physical component scale at 12 weeks (Change from baseline)</td><td>0.7</td><td>5.8 (P < 0.001 vs. placebo)</td><td>6.4 (P < 0.001 vs. placebo)</td></tr>
<tr><td>SF-36 mental component scale at 12 weeks (Change from baseline)</td><td>2.0</td><td>5.6 (P < 0.001 vs. placebo)</td><td>5.5 (P < 0.001 vs. placebo)</td></tr>
</table></td></tr>
</table>

	Productivity in the workplace (employed patients only) at 52 wks	N = 69	N = 162	N = 139
	Work days per month missed (mean) at 52 wks	4.5	1.0 ($P \leq 0.05$ vs. placebo)	1.4 ($P \leq 0.05$ vs. placebo)
	Days per month with work productivity reduced ≥50% (mean) at 52 wks	4.4	2.1 ($P \leq 0.05$ vs. placebo)	21.1 ($P \leq 0.05$ vs. placebo)
	Monthly rate of RA interference with work productivity (mean, 0-10 scale) at 52 wks	5.2	2.4 ($P \leq 0.05$ vs. placebo)	2.4 ($P \leq 0.05$ vs. placebo)
	Household work days missed per month (mean) at 52 wks	7.2	2.4 ($P \leq 0.05$ vs. placebo)	2.8 ($P \leq 0.05$ vs. placebo)
	Days with household work productivity reduced ≥50% per month (mean) at 52 wks	7.3	4.2 ($P \leq 0.05$ vs. placebo)	3.8 ($P \leq 0.05$ vs. placebo)
	Days with outside help hired per month (mean) at 52 wks	4.0	1.9 ($P \leq 0.05$ vs. placebo)	1.7 ($P \leq 0.05$ vs. placebo)
	Rate of interference with household work productivity per month (mean, scale 0-10) at 52 wks	5.6	3.3 ($P \leq 0.05$ vs. placebo)	3.1 ($P \leq 0.05$ vs. placebo)

Authors: Keystone et al. Kavanaugh et al., Strand et al. **Year: 2008, 2009**			
ADVERSE EVENTS incidence/100 pys:	**Placebo**	**CZP 200**	**CZP 400**
Overall adverse effects reported:	125.9	96.6	94.5
• infections	56.9	56.4	56.2
• Serious infections	2.2	14.8	15.2
• Headache	12	7.3	5.7
• Hypertension	2.2	8.2	10.2
• Back pain	2.2	5.6	6.4
• Malignancy	1.1	2.3	1.3
• Urinary tract infection	14.2	7.6	10.5
• Nasopharyngitis	3.3	6.9	9.5
• URTI	5.5	7.9	6.7
Significant differences in adverse events:	see headaches and hypertension		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** None		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 58% **Attrition differential high:** Yes		
ATTRITION (*treatment specific*):	**Placebo**	**CZP 200**	**CZP 400**
Attrition overall (16 weeks for lack of efficacy):	78.4% (62.8%)	35.1% (21.1%)	29.7% (17.4%)
Attrition due to adverse events:	1.5%	4.3%	5.7%
QUALITY RATING:	**Fair for first 12 weeks of data**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Kievit** et al.[28] **Year: 2008** **Country:** The Netherlands		
FUNDING:	Dutch National Health Insurance Board and the Dutch affiliations of Wyeth Pharmaceuticals, Abbott Pharmaceuticals and Roche Pharmaceuticals enabled the data collection for the DREAM cohort.		
RESEARCH OBJECTIVE:	To evaluate the effects of ADA, ETA and INF on disease activity, functional ability and quality of life and the medication costs in a naturalistic design		
DESIGN:	**Study design:** prospective cohort study **Setting:** The Netherlands RA Register (DREAM) **Sample size:** 707		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA** 40 mg per 2 weeks N/A 267	**ETA** 25 mg twice weekly N/A 289	**INF** 3 mg/kg every 8 weeks after a loading dose 151
INCLUSION CRITERIA:	DAS28 > 3.2 and failed on at least two DMARDs including MTX at an optimal dose of 25 mg/week.		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	a DMARD, corticosteroids or other treatment		

<table>
<tr><td colspan="4">Authors: Kievit et al.
Year: 2008</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline:
Disease severity: Moderate</td></tr>
<tr><td></td><td><u>ADA,</u> 40 mg per 2 weeks</td><td><u>ETA,</u> 25 mg twice weekly</td><td><u>INF,</u> 3 mg/kg every 8 weeks</td></tr>
<tr><td>Mean age (years):</td><td>55.1 (12.6)</td><td>54.6 (14.2)</td><td>57.8 (13.4)</td></tr>
<tr><td>Sex (% female):</td><td>70.0%</td><td>68.9%</td><td>70.2%</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Tender joint count</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Swollen joint count</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Mean disease duration</td><td>7.7</td><td>6.0</td><td>7.7</td></tr>
<tr><td>• DMARD use (%)</td><td>87%</td><td>78%</td><td>85%</td></tr>
<tr><td>• MTX use (%)</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>41%</td><td>57%</td><td>48%</td></tr>
<tr><td>• DAS score</td><td>5.3 (1.3)</td><td>5.5 (1.2)</td><td>5.2 (1.3)</td></tr>
<tr><td>• HAQ score</td><td>1.3 (0.7)</td><td>1.4 (0.7)</td><td>1.4 (0.7)</td></tr>
<tr><td>• RF</td><td>81.0%</td><td>71.1%</td><td>77.7%</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures:
course of the DAS28 over the 12 months follow-up.

Secondary Outcome Measures: HAQ, EQ-5D, SF-36

Timing of assessments: every 3 months</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Decrease in DAS28: ADA -1.8 (1.5) vs. ETA -1.8 (1.4) vs. INF -1.2 (1.4)

Intermediate Outcome Measures:
• SF-36 PCS “ADA and ETA patients improved after baseline and the course over 12 months was significantly better (P = 0.001) than the course of INF patients”
• HAQ: ADA -0.42 (0.6) vs. ETA -0.35 (0.6) vs. INF -0.26 (0.5)</td></tr>
</table>

Authors: Kievit et al. **Year: 2008**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**ADA,** 40 mg per 2 weeks NR	**ETA,** 25 mg twice weekly NR	**INF,** 3 mg/kg every 8 weeks NR
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** N/A (22.8% patients in database not included)		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall attrition:** 4.7% **Attrition differential high:** N/A		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**ADA,** 40 mg per 2 weeks	**ETA,** 25 mg twice weekly	**INF,** 3 mg/kg every 8 weeks
QUALITY RATING:	**Good**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Klareskog et al.[29] and van der Heijde et al.[30-32]** **Study name:** TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) **Year: 2004, 2006, 2007** **Country:** Multinational (Europe)		
FUNDING:	Wyeth Research		
RESEARCH OBJECTIVE:	To compare safety, efficacy and patient reported outcomes of the combination of ETA and MTX with the monotherapies in patients with RA who had failed previous DMARD treatment.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 682		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**MTX** 20 mg per week 52 weeks (2 yrs) (3 yrs) 228	**ETA** 25 mg twice per week 52 weeks (2 yrs) (3 yrs) 223	**MTX + ETA** Same MTX + ETA doses 52 weeks (2 yrs) (3 yrs) 231
INCLUSION CRITERIA:	Aged 18 years or older; disease duration of 6 months to 20 years; active, adult-onset RA (ACR functional class I-III), defined as 10 or more swollen and 12 or more painful joints and at least one of: ESR $\geq$ 28 mm/h, plasma CRP $\geq$ 20 mg/L, or morning stiffness for $\geq$ 45 minutes; less than satisfactory response at the discretion of the investigator, to at least one DMARD other than MTX.		
EXCLUSION CRITERIA:	Previous treatment with MTX if patient experienced clinically toxic side effects or had no response; treatment with MTX within 6 months; previous treatment with ETA or other TNF antagonist; previous treatment with immunosuppressive drugs within 6 months of screening; use of any investigational drug or biological agent within 3 months of screening; any other DMARD or corticosteroid injection within 4 months of the baseline visit; and presence of relevant comorbidity, including active infections.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Folic acid 5 mg twice per week; NSAIDs		

Authors: Klareskog et al. and van der Heijde et al. **Year: 2004 and 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe (mean disease duration 6.6 years)		
	MTX	**ETA**	**Combination**
Mean age (years):	53.0	53.2	52.5
Sex (% female):	79	77	74
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• Disease duration, years	6.8	6.3	6.8
• RF positive, %	71	75	76
• Corticosteroid use, %	64	57	62
• Total Sharp score, median	26.8	21.8	21.8
• Number of tender joints	33.1	35.0	34.2
• Number of swollen joints	22.6	23.0	22.1
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Efficacy: ACR-N AUC over the first 24 weeks; radiographic: change from baseline in total joint damage score (modified total Sharp score) over 52 weeks; EQ5D-Vas; HAQ. **Secondary Outcome Measures:** ACR20, ACR50, ACR70 responses; DAS, remission (DAS < 1.6); and HAQ **Timing of assessments:** Baseline, 24 weeks, and 53 weeks and 100 weeks for primary and secondary end points; unspecified frequency of "patient visits throughout the study" for assessment of vital signs, blood work, and adverse events.		

Authors: Klareskog et al. and van der Heijde et al. Year: 2004 and 2006	

RESULTS:	**Health Outcome Measures: (combination vs. ETA v. MTX) (95% CI)**
	• Overall, combination treatment achieved significantly better results on most outcome measures than ETA and MTX, separately
	• ACR-N AUC at 24 weeks was significantly greater for combination and ETA than for MTX: 18.3%-years (17.1-19.6) vs. 14.7%-years (13.5-16.0) vs. 12.2%-years (11.0-13.4)
	• ACR-N AUC at 24 weeks, mean differences:
	  • Combination vs. MTX: 6.1 (4.5-7.8) ($P < 0.0001$)
	  • ETA vs. MTX: 2.5 (0.8-4.2) ($P = 0.0034$)
	  • Combination vs. ETA: reported as "greater" ($P < 0.0001$)
	• ACR20/50/70 response rates at 52 weeks were significantly greater for combination than for ETA and MTX; No statistically significant difference between ETA and MTX
	  • ACR20: 85% (80-89) vs. 76% (70-81) vs. 75% (69-80); combination vs. ETA: $P = 0.0151$; combination vs. MTX: $P = 0.0091$
	  • ACR50: 69% (63-75) vs. 48% (42-55) vs. 43% (36-49); combination vs. ETA: $P < 0.0001$; combination vs. MTX: $P < 0.0001$
	  • ACR70: 43% (36-50) vs. 24% (19-30) vs. 19% (14-25); combination vs. ETA: $P < 0.0001$; combination vs. MTX: $P < 0.0001$
	• Proportion in remission at 52 weeks (DAS < 1.6): 35% (29-41) vs. 16% (11-21) vs. 13% (9-18) (combination vs. ETA: $P < 0.0001$; combination vs. MTX: $P < 0.0001$; ETA vs. MTX: $P = 0.5031$)
	• HAQ, mean decline at 52 weeks: 1.0 vs. 0.7 vs. 0.6 (CIs NR) (combination vs. ETA: $P < 0.0001$; combination vs. MTX: $P < 0.0001$; ETA vs. MTX: $P = 0.3751$)
	• EQ-5D VAS mean (SD) 72.7 (3.1) 63.7 (3.2), 66.8 (3.2), 63.7 (3.2) (CIs NR)
	Health Outcome Measures at 100 weeks: (combination vs. ETA or MTX)
	▪ ACR20 86% vs. 75% or 71% $P < 0.01$ for combination vs. ETA or MTX
	▪ ACR50 71% vs. 54% or 42% $P < 0.01$ for combination vs. ETA or MTX
	▪ ACR70 49% vs. 27% or 21% $P < 0.01$ for combination vs. ETA or MTX
	▪ DAS 2.2 vs. 2.9 or 3.0 $P < 0.01$ for combination vs. ETA or MTX
	▪ Remission (DAS < 1.6) 40.7% vs. 23.3% vs. 18.9% $P < 0.01$ for combination vs. ETA or MTX and ETA vs. MTX $P < 0.05$
	Health Outcome Measures at 3 years: (combination vs. ETA or MTX)
	▪ ACR20 85.3% vs. 70.9% or 70.2% $P < 0.01$ for combination vs. ETA or MTX
	▪ ACR50 67.1% vs. 45.7% or 43.9% $P < 0.01$ for combination vs. ETA or MTX

Authors: Klareskog et al. and van der Heijde et al. **Year: 2004 and 2006**	
RESULTS (continued):	▪ ACR70 47.2% vs. 26.0% or 21.1% $P < 0.01$ for combination vs. ETA or MTX ▪ Remission (DAS < 1.6) 40.7% vs. 21.5% vs. 17.5% $P < 0.01$ for combination vs. ETA or MTX and ETA vs. MTX $P < 0.05$ **Intermediate Outcome Measures (combination v. ETA v. MTX) (95% CI)** • DAS, mean, at 52 weeks: 2.3 (2.1-2.5) vs. 3.0 (2.8-3.1) vs. 3.0 (2.8-3.2) o (combination vs. ETA: $P < 0.0001$; combination vs. MTX: $P < 0.0001$) • Total Sharp score, mean difference at 52 weeks: Combination vs. MTX: -3.34 (-4.86 - -1.81), $P < 0.0001$ ETA vs. MTX: -2.27 (-3.81 - -0.74), $P < 0.0001$ • Proportion of patients without progression (total Sharp score $\leq$ 0.5): 80% (74-85) vs. 68% (61-74) vs. 57% (50-64) o (combination v. ETA: $P = 0.0043$; combination vs. MTX: $P < 0.0001$; ETA vs. MTX: $P = 0.0213$) **Intermediate Outcome Measures at 100 weeks (combination v. ETA or MTX (95% CI)** ▪ Total Sharp score -0.56 (-1.05, -0.06) vs. 1.10 (0.13, 2.07) or 3.34 (1.18, 5.50) $P < 0.05$ for combination vs. ETA or MTX and ETA vs. MTX $P < 0.05$ ▪ Erosion score -0.76 (-1.113, -0.38) vs. 0.36 (-0.25, 0.97) or 2.12 (0.66, 3.57) $P < 0.05$ for combination vs. ETA or MTX and ETA vs. MTX $P < 0.05$ ▪ JSN score 0.20 (-0.03, 0.44) vs. 0.74 (0.25, 1.23) or 1.23 (0.39, 2.60) $P < 0.05$ for combination vs. MTX **Intermediate Outcome Measures at 3 years (combination v. ETA or MTX (95% CI)** ▪ Total Sharp score –0.14 (–1.07, 0.78) vs. 1.61 (0.41, 2.81) or 5.95 (2.96, 8.94) $P < 0.01$ for combination vs. ETA or MTX ▪ Erosion score –0.67 (–1.05, –0.28) vs. 0.39; (–0.44, 1.22) or 3.25 (1.50, 5.01)) $P < 0.01$ ▪ JSN score –0.67 (–1.05, –0.28) vs. 1.22 (0.59, 1.84) or 2.70 (1.26, 4.13) $P < 0.01$ for combination vs. MTX or ETA

Authors: Klareskog et al. and van der Heijde et al. **Year: 2004 and 2006**			
ADVERSE EVENTS (2 yrs):	**MTX**	**ETA**	**MTX + ETA**
Overall adverse effects reported:	185 (199)	192 (206)	187 (199)
• **Abdominal Pain, %**	18 (22)	12 (17)	18 (22)
• **Diarrhea, %**	9 (11)	10 (11)	8 (11)
• **Nausea**	32 (39)	10 (13)	24 (29)
• **Vomiting, %**	11 (14)	3 (4)	5 (9)
• **Headache, %**	14 (16)	15 (17)	15 (17)
• **ISR, %**	2 (2)	21 (22)	10 (11)
• **Rash, %**	9 (12)	7 (8)	10 (12)
Infections, number (%) (2 yrs %)	147 (64) (75)	131 (59) (71)	154 (67) (76)
• **Serious**	10 (4) (7)(8.3 3 yrs)	10 (4) (6)(6.7 3 yrs)	10 (4) (6)(7.4 3 yrs)
Significant differences in adverse events:	• ISR: ETA (21%) v. MTX (2%), $P < 0.0001$ • Nausea: ETA (10%) v. MTX (32%), $P < 0.0001$; • Vomiting: ETA (3%) v. MTX (11%), $P = 0.0009$ • At 2 yrs Nausea and ISR Combination vs. MTX or ETA $P < 0.01$ and ETA vs. MTX $P < 0.01$		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 23% (160/682) (2 yrs 38%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**MTX**	**ETA**	**MTX + ETA**
Loss to follow-up:	NR (2 yrs 48%)	NR (2 yrs 39%)	NR (2 yrs 29%)
Withdrawals due to adverse events:	14.0% (2 yrs 21%)	11.2% (2 yrs 16%)	10.4% (2 yrs 17%)
Lack of Efficacy	9.2% (2 yrs 14%)	7.2% (2 yrs 13%)	2.6% (2 yrs 4%)
QUALITY RATING:	**Good**		

Evidence Table 1. Targeted Immune Modulators—Rheumatoid Arthritis

STUDY:	**Authors: Kristensen et al.**[33] **Year: 2006** **Country:** Sweden	
FUNDING:	Supported by the Osterlund and Kock Foundations, Inc; the 80-year Fund of King Gustav V, and Reumatikerforbundet	
RESEARCH OBJECTIVE:	To describe the use of the LUNDEX index to compare long-term efficacy and tolerability of biologic therapies in RA patients treated in clinical practice.	
DESIGN:	**Study design:** Observational **Setting:** Multicenter **Sample size:** 949	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg SQ, twice weekly 3 years 309	**INF** 3 mg/kg at 0,2,6,& 12 weeks and then every 8 weeks 3 years 640
INCLUSION CRITERIA:	Patients diagnosed with RA according to clinical judgment of the treating physician; treated at 8 centers in Southern Sweden during the period March 1999 through January 2004; unsuccessful treatment with ≥ 2 DMARDs, including MTX;	
EXCLUSION CRITERIA:	Previous treatment with biologic therapy	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

<table>
<tr><td colspan="4">Authors: Kristensen et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No
Disease severity: NR (mean disease duration 13.4 years)</td></tr>
<tr><td></td><td><u>ETA</u></td><td><u>INF</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>55.1</td><td>56.2</td><td></td></tr>
<tr><td>Sex (% female):</td><td>82</td><td>75</td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Mean disease duration (years)</td><td>14.7</td><td>12.7</td><td></td></tr>
<tr><td>• DMARD use (No.)</td><td>4.2</td><td>3.6</td><td></td></tr>
<tr><td>• MTX use (%)</td><td>31</td><td>73</td><td></td></tr>
<tr><td>• DAS28 score</td><td>5.9</td><td>5.6</td><td></td></tr>
<tr><td>• HAQ score</td><td>1.6</td><td>1.4</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: LUNDEX = (fraction of starters still in the study at time T) x (fraction responding at time T)
Secondary Outcome Measures: HAQ; VAS for pain and general health; physician’s global assessment of disease activity (Evalglobal); 28-joint TJC & SJCs; ESR; CRP; ACR20; ACR50; ACR70; EULAR.
Timing of assessments: 0,3,6, & 12 months, then every 3-6 months</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• ETA had the highest overall LUNDEX values; ~55% of these patients fulfilled ACR20 response criteria at 12 months (~40% after 3 years).
• ~45% of patients started on INF fulfilled ACR20 response criteria at 12 months (~30% at 3 years)
• ACR 20: % response at 36 months = 63 (ETA) vs. 61 (INF) (P = NS)
  • % response at 24 months = 65 (ETA) vs. 56 (INF) (P = NS)
  • % response at 12 months = 69 (ETA) vs. 53 (INF) (P = 0.001)
  • % response at 6 months = 61 (ETA) vs. 47 (INF) (P = NS)
  • % response at 36 months = 63 (ETA) vs. 45 (INF) (P < 0.001)
• 36 months- ACR50: 39 (ETA) vs. 39 (INF) (P = NS),ACR 70: 16 (ETA) vs. 18 (INF) (P = NS)
• EULAR (moderate): % response at 36 months = 46 (ETA) vs. 29 (INF) (P = NS)
• EULAR (good): % response at 36 months = 36 (ETA) vs. 45 (INF) (P = NS)
Intermediate Outcome Measures:
• INF had significantly lower adherence compared to ETA (P < 0.001); study cites this as possible reason for lower response rates for INF</td></tr>
</table>

Authors: Kristensen et al. **Year: 2006**			
ADVERSE EVENTS: **Overall adverse effects reported:** •	**ETA** NR	**INF** NR	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	No		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	NR		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ETA** NR	**INF** NR	
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Launois et al.**[34] **Year: 2011** **Country: France** **Quality rating: Fair**
FUNDING:	
DESIGN & SIZE:	**Study design:** SR **Number of patients:** 7,158 **Trials:** 19
OBJECTIVE OF REVIEW:	To determine whether CZP is not inferior to the other anticytokines (anti-TNF-α, anti-interleukin 1 and 6) used for the treatment of RA in combination with conventional DMARD, in patients that showed inappropriate or no response to conventional DMARD, including MTX.
ELIGIBILITY CRITERIA:	Controlled, randomized double-blind trials published in English that included adult patients with RA who had an inadequate or no response to DMARD including MTX; studies that evaluated anticytokine biotherapies indicated for the treatment of RA versus placebo in combination with continuation of inadequate conventional DMARD; biologics used according to their Summary of Product characteristics; clinical efficacy assessed by ACR20, ACR50, and ACR70 response rates. Efficacy evaluation had to be available at 24 ± 8 weeks of treatment.
STUDIES INCLUDED IN REVIEW:	Efficacy (19 trials, 76 articles): **Infliximab (4 studies):** Maini, 1999; Schiff, 2008; Westhovens, 2006; Zhang, 2006 **Etanercept (2 studies):** Combe, 2006; Weinblatt, 1999 **Adalimumab (4 studies):** Furst, 2003; Keystone, 2004; Kim, 2007; Weinblatt, 2003 **Golimumab (2 studies):** Kay, 2008; Keystone, 2009 **Certolizumab pegol (2 studies):** Keystone, 2008; Smolen, 2009 **Anakinra (1 study):** Cohen, 2004 **Tocilizumab (4 studies):** Genovese, 2008; Kremer, 2009; Maini, 2006; Smolen, 2008
LITERATURE SEARCH DATES:	January 1, 1980 to June 30, 2009
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	All trials were randomized and were comparative versus placebo. 14 evaluated the efficacy of an anti-TNF-α therapy and 5 an anti-interleukin treatment. In most studies, the DMARD combined with active treatment or placebo was MTX (17 studies). The populations of patients included in the different studies were homogeneous regarding age and functional score as measured by the HAQ. The proportion of patients who were positive for RF was generally high (>70%), except for 2 studies of adalimumab. RA duration differed between studies (median 8 years; range 5–13 years.

Authors: Launois, et al. **Year: 2011**	
DATA SYNTHESIS METHODS:	Mixed-treatment comparison model using Bayesian techniques
MAIN RESULTS: (RESULTS IN SUBGROUPS)	Results of fixed-effects mixed-treatment analysis:* **Infliximab** ACR20: OR (95% CI)=3.31 (2.05, 5.03) ACR50: OR (95% CI)=3.59 (1.97, 6.13) ACR70: OR (95% CI)=3.55 (1.77, 7.15) **Etanercept** ACR20: OR (95% CI)=8.07 (3.34, 16.75) ACR50: OR (95% CI)=11.45 (3.45, 31.02) **Adalimumab** ACR20: OR (95% CI)=3.72 (2.35, 5.93) ACR50: OR (95% CI)=5.66 (3.15, 10.01) ACR70: OR (95% CI)=6.63 (3.12, 12.69) **Golimumab** ACR20: OR (95% CI)=3.62 (1.62, 6.97) ACR50: OR (95% CI)=5.72 (2.07, 13.69) **Certolizumab pegol** ACR20: OR (95% CI)=11.82 (5.98, 21.71) ACR50: OR (95% CI)=10.81 (4.41, 24.02) ACR70: OR (95% CI)=15.84 (4.64, 43.89) **Anakinra** ACR20: OR (95% CI)=2.40 (0.96, 5.03) ACR50: OR (95% CI)=2.84 (0.81, 7.26) **Tocilizumab** ACR20: OR (95% CI)=4.13 (2.64, 6.19) ACR50: OR (95% CI)=5.68 (2.78, 9.93) ACR70: OR (95% CI)=8.63 (3.70, 16.99) * fixed-effects model and noninferiority analysis data are also reported
ADVERSE EVENTS:	NR
LIMITATIONS OF PRIMARY STUDIES	Wide variation in disease duration at entry to the study (ranged from 6 to 13 years in the different groups of patients for the studies published before 2006, and from 5 to 11 years for those published after 2006). Exclusion of non-English-language studies may lead to selection bias. Only 1 study used anakinra, and there were only 2 studies each for several other treatments.

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Lee et al.**[35] **Year: 2008** **Country:** Multinational
FUNDING:	NR
DESIGN:	**Study design:** Systematic Review and meta-analysis **Number of patients:** 1040
AIMS OF REVIEW:	Indirect comparisons of INF. ETA and ADA plus MTX vs. MTX and each other
STUDIES INCLUDED IN META-ANALYSIS	Lipsky 2000 Klareskog 2001 and Keystone 2004
TIME PERIOD COVERED:	until 2006
CHARACTERISTICS OF INCLUDED STUDIES:	it was published before February 2006; it was original data (independence among the studies); it was a double blind, randomized and controlled trial that completed 50–55 weeks
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adults with RA

Authors: Lee et al. **Year: 2008**				
CHARACTERISTICS OF INTERVENTIONS:	TNF inhibitors plus MTX vs. MTX			
MAIN RESULTS:	RR (95% CI) *P* value	ETA vs. INF	ETA vs. ADA	INF vs. ADA
	ACR20	0.45 (0.27-0.73) 0.001	0.46 (0.34-0.61) < 0.0001	1.03 (0.59-1.78) 0.92
	ACR50	0.59 (0.27-1.29) 0.19	0.37 (0.22- 0.60) < 0.0001	0.62 (0.25-1.49) 0.28
	ACR70	0.44 (0.10-2.03) 0.29	0.44 (0.21-0.93) 0.03	0.99 (0.19-5.13) 0.99
ADVERSE EVENTS:	RR (95% CI) *P* value	ETA vs. INF	ETA vs. ADA	INF vs. ADA
	WD due to lack of efficacy	0.52 (0.19-1.42) 0.20	1.12 (0.32-3.94) 0.86	2.16 (0.77-6.07) 0.14
	WD due to side effect	1.01 (0.30 – 3.42) 0.98	0.38 (0.17-0.86) 0.02	0.37 (0.11-1.36) 0.14
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes			
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes			
QUALITY RATING:	Fair			

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Malottki et al.**[36] **Year: 2011** **Country: U.K.** **Quality rating: Good**
FUNDING:	Health Technology Assessment program of the National Institute for Health Research.
DESIGN & SIZE:	**Study design:** Systematic Review **Number of patients:** 7661 **Trials:** 5RCTs, 1 comparative study, 1 controlled study, 28 uncontrolled studies
OBJECTIVE OF REVIEW:	(Objectives of interest to our review) 1) Whether significant differences in clinical effectiveness exist between ADA, ETN, IFX, RTX and ABT when used within their licensed indications in adults with active RA who have had an inadequate response to a first TNF inhibitor prescribed according to current NICE guidance. 2) Whether the interventions are clinically effective compared with other biologic agents [including TOC, golimumab (Simponi□, Schering-Plough Ltd) and certolizumab pegol (Cimzia□, UCB)].
ELIGIBILITY CRITERIA:	Population: majority of adults with active RA who have had an inadequate response to a TNF inhibitor Intervention: ADA, ETN, INF, RTX or ABT Outcomes: clinical outcomes related to efficacy, safety or tolerability Study design: primary study or a systematic review Study duration: at least 12 weeks Participant numbers: for non randomized studies- at least 20 patients in one arm.
STUDIES INCLUDED IN REVIEW:	Adalimumab: Bennett 2005, Wick 2005,Nikas 2006, Bombardieri 2007, van der Bijl 2008 Etanercept: Haroui 2004, Buch 2005, Cohen 2005, Buch 2007, Iannone 2007, Laas 2008, Bingham 2009 Infliximab: Ang 2003, Hansen 2004, Yazici 2004, TNF inhibitors as a class: Hyrich 2009, Gomez-Reino 2006, Solau-Gervais 2006, Hjardem 2007, Duftner 2008, Karlsson 2008, Blom 2009, Finckh 2009 Rituximab: REFLEX, Bokarewa 2007, Jois 2007, Keystone 2007, Assous 2007, Thurlings 2008, Finckh 2009, REFLEX extension and pooled analysis Roche data submitted to NICE 2009 Abatacept: ATTAIN,ATTAIN LTE, ARRIVE, Weinlatt 2007, ASSURE
LITERATURE SEARCH DATES:	Up until July 2009 Bibliographic databases: Cochrane Library (CENTRAL) 2009 Issue3, MEDLINE (Ovid) 1,950 to July week 1 2009, MEDLINE In-Process & Other Non-Indexed Citations (Ovid) 13 July 2009, EMBASE (Ovid) 1980–2009 week 28.
INCLUDED STUDIES: (Study design,	(Baseline characteristics presented from studies that reported them) Adalimumab: 5 uncontrolled prospective and retrospective studies-Bennett 2005, Wick 2005,Nikas 2006,

characteristics of included population, characteristics of included interventions)	Bombardieri 2007, van der Bijl 2008. 81 to 92% female, mean age 50-57 yrs, RA duration 11.6-16.6 years Etanercept: 7 uncontrolled observational studies- Haroui 2004, Buch 2005, Cohen 2005, Buch 2007, Iannone 2007, Laas 2008, Bingham 2009. 60-88%female, mean age 49-57 years, disease duration 8.3 to 12.2 years Infliximab: 1 uncontrolled prospective study Yazici 2004, 2 uncontrolled retrospective studies- Ang 2003, Hansen 2004. 60-90% female, mean age 48-61 years, disease duration 9.3 years to 13.4 years. TNF inhibitors as a class:1 controlled study Hyrich 2009, 6 uncontrolled studies -Gomez-Reino 2006, Solau-Gervais 2006, Hjardem 2007, Duftner 2008, Karlsson 2008, Blom 2009, Finckh 2009. 67 to 89% female, mean age 51-58 years, disease duration 8.0 to 14.7 years Rituximab: 1 RCT- REFLEX, 6 uncontrolled studies-Bokarewa 2007, Jois 2007, Keystone 2007, Assous 2007, Thurlings 2008, Finckh 2009. Additional data described from REFLEX extension and pooled analysis Roche data submitted to NICE 2009. 77 to 86% female, mean age 52-58 years in 4 studies , disease duration 10-15 years Abatacept: 1 RCT ATTAIN,1 extension of RCT-ATTAIN LTE, and one uncontrolled prospective study-ARRIVE Population: majority of adults with active RA who have had an inadequate response to a TNF inhibitor Intervention: ADA, ETN, INF, RTX or ABT

Authors: Malottki et.al. **Year: 2011**	
DATA SYNTHESIS METHODS:	Dichotomous measures-data presented as relative risks and percentages. For continuous outcomes, mean differences (for RCTs) and means (for other study designs) were used. Pooling not attempted for assessment of effectiveness of individual technologies, because majority of the studies had no control group and due to substantial methodological and clinical heterogeneity between included studies.
MAIN RESULTS: (RESULTS IN SUBGROUPS)	(Outcomes from TNF inhibitors combined group not discussed) **ACR 20 response** Adalimumab: at 3 months 46% to 60%, at 6 months: 70%, at 12 months: 75% Etanercept: after 3 months 37.5% to 72.0% Infliximab: NR Rituximab: RCT-at wk 24 response from treatment 3 times more than from placebo RR 2.85(95% CI 2.08 to 3.91), at wk 48 RR 1.53 (95% CI 0.84 to 2.76), data from non randomized studies: 65.2% at 24 weeks after first course of treatment compared to 51%in the RTX arm from Reflex trial. Abatacept: RCT(vs placebo) response at 3 months RR 2.53 (95% CI 1.72 to 3.73), at 6 months: RR 2.56 (95% CI 1.77 to 3.69). Non-RCT: response at 6 months 57.3% in the group originally randomized to abatacept and 63.6% in the group initially randomized to placebo, at 12 months. In the arm initially randomized to abatacept, there was further increase in response at 12 months followed by a decrease up to 5 years. Among those initially randomized to placebo , decrease in % of responders from 12 months onwards, at 54 months, response: 30.3% **ACR 50 response** Adalimumab: response at 3 months 26.8% to 33% Etanercept: response after 3 months 18.4% to 64.0% Infliximab: NR Rituximab: RCT(vs placebo): response at 24 months RR 5.40, 95% CI 2.87 to 10.16) Abatacept: RCT (vs placebo): response at 6 months RR 5.36, 95%CI 2.19 to 13.10) : non-RCTs: response at 6 months in ATTAIN LTE: 22.9% patients in the arm initially randomized to abatacept and 37.4% in the arm initially randomized to placebo. Response increased up to 18 months (33.9%) and then decreased to 20.6% at 5 years. In the arm initially randomized to placebo, there was a decrease after 6 months to 21.2% achieving response at 48 months. **ACR 70 response** Adalimumab: response at 3 months 12% to 13%, at 12 months 33% Etanercept: response after 3 months 4.2% to 20.0% Infliximab: NR Rituximab: RCT(vs placebo): response at wk 24 RR 12.14 (95% CI 2.96 to 49.86)

	: Non RCT: response at 24 weeks after first course of treatment 12.3% compared to 12.1% achieving response in the RTX arm of the REFLEX trial. Abatacept: RCT(vs placebo): response at 6 months RR 6.70 (95% CI 1.62 to 27.8) : Non-RCT response at 6 months in ATTAIN LTE: 11.5% among patients initially treated with abatacept vs 13.1% among those initially treated with placebo. Further increase to 17.0% in 12 months followed by decrease to 9.6% at 5 years. In the arm initially randomized to placebo, increase in response up to 15.2% at 30 months followed by a decrease to 7.1 at 54 months. **DAS 28** Adalimumab: Mean change from baseline between 3-6 months (range -1.30 to -1.90) Etanercept: Mean change from baseline between 3 and 12 months -0.47 to -1.80. Infliximab: improved significantly, data NR Rituximab: RCT (vs placebo): Change from baseline at wk 24: -1.40, 95% CI -1.67 to -1.13) vs -1.50(95% CI -1.74 to -1.26) :Non-RCT: 3 months median score 5.60, median score at 6 months: range 3.97 to 5.50 Abatacept: RCT (vs placebo) mean change from baseline -1.98 vs -0.71, difference -1.27 (95% CI -1.62 to -0.93),p<0.001 RR 2.15 (95% CI 1.54 to 2.99). DAS 28≤3.2 at 6 months RR 5.67,(95% CI 2.08 to 15.44) DAS28<2.6 at 6 months RR 13.40, (95% CI 1.84 to 97.69) : Non-RCT ATTAIN LTE and ARRIVE: <u>Mean change in score</u> 6 months: -1.99 in the arm initially randomized to ABT and -2.14 in the arm initially randomized to placebo, mean change in ARRIVE -2.00. 5 years: -2.90 at in the arm initially randomized to Abatacept and -2.96 in the arm initially randomized to placebo (at 54 months or 4.5 years). <u>Data below are from ATTAIN LTE unless specified otherwise</u> <u>% of patients with DAS score ≤3.2 at</u> 6 months abatacept =10.6% (abatacept =22.4% in ARRIVE; placebo = 22.2%) 18 months abatacept =28% 5 years abatacept =15.1% Placebo: % decreased over 54 months: 7.1% <u>% of patients with DAS score<2.6</u> 6 months: abatacept = 10.6% (abatacept =13% in ARRIVE; placebo = 17.2%) 18 months: abatacept =17% 5 years: abatacept = 9.6% 54 months: Placebo = 6.1%.

	EULAR Adalimumab: at 3 months: good response17% to 23%, good /moderate response 76% to 78% Etanercept: at 3 months: good response 12.5% to 45.8%, good /moderate response 58.2 to 61.1% Infliximab: NR Rituximab: RCT (vs placebo) at 12 weeks: Good response: RR 2.23 (95% CI 1.64 to 2.49) Good or moderate response RR 2.02, (95% CI 1.64 to 2.49). at 24 weeks: Good response: RR 7.59 (95% CI 2.77 to 20.77), Good or moderate response 2.96(95% CI 2.25 to 3.89) : Non RCT :at 6 months good response rate 15.1% to 36%good or moderate 64.2% to 82%, Abatacept: NR **Health Assessment Questionnaire (HAQ)** Adalimumab: Mean change in HAQ measured between 3 and 8.5 months : range -0.21 to -0.48(significant decrease) Etanercept: Results varied among 3 studies, in one study change was not significant, in the 2nd study results remained unchanged compared to baseline, in the third study, the change the statistically significant. Infliximab: NR Rituximab: RCT(vs placebo)Change from baseline at wk 24: mean difference -0.30 (95% CI -0.40 to -0.20. % of patients with decrease of >0.25 in score from baseline to wk 12 RR 1.63 (1.29 to 2.07), at wk 24 2.55 (95% CI 1.89 to 3.43) Non-RCT: results from 2 uncontrolled studies: i) median HAQ score at 3 months 2.13 (0.63 to 2.88), 1.86 at 6 months, change compared to baseline not statistically significant. ii) % of patients with a decrease in mean HAQ ≥0.22 at wk 24 after 1 course of rituximab treatment was 71.8% similar to the observed rate in the RTX arm of the REFLEX trial. Abatacept: RCT (vs placebo) change at 6 months -0.45 vs -0.11, p<0.001, HAQ score decrease of at least 0.3 RR 2.01, 95% CI 1.44 to 2.81). Non-RCT: ATTAIN: mean change from baseline at 6 months -0.51 in the arm initially randomized to ABT, -0.40 in the arm initially randomized to placebo, -0.38 in the monotherapy subgroup of ARRIVE. **Quality of life** Adalimumab: NR Etanercept: NR Infliximab: NR Rituximab: RCT(vs placebo): SF 36 physical health score mean difference RR 4.80 (95% CI 3.29 to 6.31), SF 36 mental health score mean difference RR 3.60 (95% CI 1.45 to 5.75) : non-RCT: NR Abatacept: RCT(vs placebo): SF 36 physical health score mean difference RR 5.50 (95% CI 3.74 to 7.26),

	SF36 mental health score mean difference 3.70 (95% CI 1.45 to 5.95) :non-RCT: Reported in ARRIVE in a subgroup of 43 patients receiving monotherapy ARRIVE monotherapy subgroup vs abatacept arm of ATTAIN trial Mean improvement from baseline in SF 36 physical component: 4.80 vs 6.50 Mean improvement from baseline in SF 36 mental component: 7.34 vs 5.40
ADVERSE EVENTS:	**Withdrawals due to AE** Adalimumab: at 3-12 months: 0 to 14.6%, etanercept at 3-12 months: 0-16.3%, infliximab: NR, rituximab (RCT vs placebo) RR=2.71, (95% CI 0.58 to 12.65), non RCT :2.6% abatacept: RCT data at wk 24 abatacept vs placebo: RR=0.93, (95% CI 0.32 to 2.71) non-RCT: between 6 and 24 months ATTAIN 3.5% to 7.6% **Serious AE** Adalimumab: 18%, withdrew because of SAE 13% Etanercept: 0 to 5% Infliximab: None Rituximab: RCT(vs placebo) RR 0.74,(95% CI 0.42 to 1.31), non-RCTs: 2% -16.7% Abatacept: RCT(vs placebo): RR 0.93 (95% CI 0.51 to 1.68), non-RCT: ARRIVE:10.4% at 6 months, 32.5% at 2 years ATTAIN LTE **Serious infection** Adalimumab: 10.0/1000 patients –years Etanercept: 1% Infliximab: NR Rituximab: RCT (vs placebo): RR 1.58, (95% CI 0.41 to 6.05), non-RCT: 1 study reported 1 SAE requiring hospitalization, another study reported 1 SAE requiring hospitalization among 30 patients over 2 years of follow-up. Abatacept: RCT(vs placebo): RR 1.03 (95% CI 0.26 to 4.06), non RCT: abatacept arm of ATTAIN vs ARRIVE: at 6 months 2.3% vs 2.4% ATTAIN LTE at 2 years: 7.9%
LIMITATIONS OF PRIMARY STUDIES	Paucity of evidence from RCTs for assessing the clinical effectiveness of the three TNF inhibitors and a complete absence of genuine head-to head trials comparing the five technologies against each other, against other biologics or against newly initiated, previously untried DMARDs. Data from observational studies can be confounded by many factors such as patients' baseline disease activity, past history of therapy and methods of selecting and following up patients and analysis of data.

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Maxwell et al.[37]** **Year: 2009** **Country: Canada/US** **Quality rating: Good**
FUNDING:	Reported that "this systematic review did not receive specific funding."
DESIGN & SIZE:	**Study design: SR of RCTs** **Number of patients: 2908** **Trials: 7**
OBJECTIVE OF REVIEW:	To assess the efficacy and safety of abatacept in reducing disease activity, pain, and improving function in people with rheumatoid arthritis.
ELIGIBILITY CRITERIA:	RCTs comparing abatacept alone, or in combination with disease-modifying anti-rheumatic drugs (DMARDs) or biologics, to placebo or other DMARDs or biologics in patient with moderate to severe rheumatoid arthritis. Patients had to be at least 16 years of age meeting the ACR 1987 revised criteria for RA (Arnett, 1988).
STUDIES INCLUDED IN REVIEW:	Genovese, 2005 Kremer, 2003 Kremer, 2006 Moreland, 2002 Schiff, 2008 Weinblatt, 2006 Weinblatt, 2007
LITERATURE SEARCH DATES:	Search: Cochrane Central Register of Controlled Trials: The Cochrane Library 2007, Issue 1 Search: MEDLINE 1966-2008 Search: EMBASE 1980-2008 Search: ACP Journal Club 2000-2008 Biosis Previews 1990-2008 Updated search in January 2009 to capture publications between 1 January 2007 and 31 December 2008.
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	Study design: RCTs only with the generation of the allocation sequence truly random that were at least 3 months in duration. Trials of less than 6 months duration were used to investigate short-term efficacy and safety while studies longer than 6 months addressed longer-term efficacy and safety. **Types of participants** Patients at least 16 years of age meeting the ACR 1987 revised criteria for rheumatoid arthritis (Arnett 1988). **Types of interventions**

	RCTs comparing abatacept alone or in combination with DMARDs or biologics to placebo or otherDMARDs or biologics. There were no restrictions with regard to dosage or duration of intervention. **Genovese, 2005**: multicenter (89 sites) double-blind RCT, phase III trial; 2:1 abatacept to placebo; duration 6 months; stratification by former vs current users of anti-TNF; Participants: TX: Mean age 53.4, 77.1% female, duration of RA 12.2 years. Control: Mean age 52.7, 79.7 % female, duration of RA 11.4 years. Interventions: abatacept (10mg/kg) + DMARD or placebo, administered in a 30-minute IV on days 1, 15, and 29 and every 28 days thereafter, up to and including day 141. **Kremer, 2003**: 6-month, double-blind, randomized, placebo-controlled trial; phase II. Multicenter, multinational, 2:1 abatacept to placebo ration of random assignment; Participants: TX: Mean age 54.7, 66% female, duration of RA 8.9 years. Control: Mean age 55.8, 75% female, duration of RA 9.7 years. Intervention: Abatacept 2mg/kg + MTX (N=105)); Abatacept 10mg/kg + MTX (N=115); Placebo + MTX (N=119); Abatacept or placebo was infused IV over a 30-minute period on days 1, 15, and 30 and monthly thereafter for a total of 6 months. Only 10 mg/kg arm reported for this review. **Kremer, 2006**: 1-year, multicenter, multinational, randomized, double-blind, placebo-controlled study; phase III, 2:1 abatacept to placebo ratio of random assignment; Participants: TX: Mean age 51.5, 77.8% female, duration of RA 8.5 years; Control: Mean age 50.4, 81.7% female; duration of RA 8.9 years. Intervention: Abatacept (10mg/kg)(N=258) + MTX or placebo + MTX (N=133). Study medication given by 30-minute IV on days 1, 15, and 29 and then every 28 days up to and including day 337. No premedication was required. All patients received MTX, 15 mg or more per week, although MTX at 10mg per week was acceptable if the patient had a history of toxicity. **Moreland, 2002**: Multicenter, multi-national, double-blind, placebo-controlled trial. Phase II; trial duration 85 days. Participants: TX: Mean age 51.5, 69% female, duration of RA 3.4 years; Control: Mean age 48.3, 48.3% female, duration of RA 3.2 years. Intervention: Patients were randomized to 1 of 7 treatment groups: abatacept at 0.5 mg/kg, 2 mg/kg, or 10 mg/kg; LEA29Y at 0.5mg/kg, 2mg/kg, or 10mg/kg; or placebo. Study medication was administered on days 1, 15, 29, and 57. No concurrent DMARDs were allowed. Days 1 to 85 were considered to be the treatment period; follow up continued through day 169; For this review, abatacept 10mg/kg (N=32) and placebo (N=32) were considered. **Schiff, 2008**: ATTEST was a randomized, double-blind, double-dummy, placebo- and active (infliximab)-controlled, 12-month global trial. Participants: TX: Mean age 49 years, 83.3% female, duration of RA 7.9 years; Control: Mean age 49.4 years, 97.3% female, duration of RA 8.4 years. Intervention: adult patients with active RA and an inadequate response to MTX were randomized by centre in a 3:3:2 ratio to 6 months of abatacept (approximating 10mg/kg, N=156), infliximab (3mg/kg, N=165), or placebo (N+110) treatment by IV infusion on a background of MTX. **Weinblatt, 2006**: 1-year, multicenter, randomized, double-blind, placebo-controlled trial; 2:1 abatacept to

	placebo ratio of random assignment. Participants: overall age 52.3 years, overall duration of RA 9.7 years. Intervention: Abatacept) 10mg/kg, N+959) or placebo (N+482) by IV infusion. Medication was administered via a 30-minute IV on days 1, 15, and 29, and every 4 weeks thereafter, for a total of 14 doses. All patients were required to continue to receive their background RA therapies (biologic DMARDs, non biologic DMARDs, or a combination of both) at study entry. Stable, low-dose oral corticosteroids (10mg/day or less) and/or stables doses of NSAIDs were allowed. **Weinblatt, 2007**: Multicenter, randomized, double-blind, placebo-controlled trial with an open-label long-term extension phase, conducted at 40 centers with the US between 26 February 2001 and 13 October 2004; Participants: TX: Mean age 49.8 years, 78 % female, duration of RA 13 years; Control: Mean age 54.3years, 72% female, duration of RA 12.8 years. Intervention: Abatacept (2mg/kg) and etanercept (25mg twice weekly) (N+85) or placebo and etanercept (25mg twice weekly)(N=36) 2:1 ratio for randomization. Etanercept (25mg twice weekly) was continued in all patients for the duration of the study. Abatacept was administered IV on days 1, 15, and 30, and every 4 weeks thereafter. MTX and other DMARDs were stopped at least 28 days before randomization, with the exception of leflunomide, which was stopped >60 days before randomization. Low-dose corticosteroids (10mg/day) or NSAIDS were allowed, provided the dose remained stable during the study. Analgesics were also permitted at all times except 12 hours before a joint evaluation. Addition of hydroxychloroquine, sulfasalazine, leflunomide or MTX was allowed after 6 months of double-blind treatments. Patients completing double-blind treatment were eligible to enter the long-term extension (LTE). All patients entering the LTX were switched to receive abatacept at a fixed dose approximating 10mg/kg. During the LTE, patients were permitted to increase, decrease, or discontinue corticosteroids (to a maximum maintenance dose of 10 mg prednisone equivalent daily), etanercept (to a maximum of 25 mg twice weekly) and NSAIDs according to their condition.

Authors: Maxwell et al.
Year: 2009

DATA SYNTHESIS METHODS: meta-analysis, fixed and random effects

MAIN RESULTS: (RESULTS IN SUBGROUPS)

Compared with placebo, patients in the abatacept group were 2.2 times more likely to achieve an ACR 50 response at one year (RR 2.21, 95% CI 1.73-2.82) with a 21% (95% CI 16% to 27%) absolute risk difference between groups. Then number needed to treat to achieve an ACR 50 response was 5 ((5% CI 4 to 7). Significant improvements in physical function and a reduction in disease activity and pain were found in abatacept-treated patients compared to placebo. One RCT found abatacept significantly slowed the radiographic progression of joint damage at 12 months compared to placebo, although it is not clear what the clinical relevance of this difference may be. There may be a risk of attrition bias.

Abatacept (2 mg/kg and 10 mg/kg) + DMARDs/biologic versus placebo + DMARDs/biologic

	Outcome	*# studies*	*# participants*	*Statistical Method*	*Effect Size*
1	ACR 20% improvement	6		RR (M-H, Fixed, 95% CI)	Subtotals only
	3 months	1	64	RR (M-H, Fixed, 95% CI)	1.7 [0.93, 3.12]
	6 months	5	1648	RR (M-H, Fixed, 95% CI)	1.79 [1.59, 2.02]
	12 months	3	993	RR (M-H, Fixed, 95% CI)	1.79 [1.55, 2.07]
2	ACR 50% improvement	6		RR (M-H, Fixed, 95% CI)	Subtotals only
	3 months	1	64	RR (M-H, Fixed, 95% CI)	2.5 [0.52, 11.96]
	6 months	5	1648	RR (M-H, Fixed, 95% CI)	2.47 [2.00, 3.07]
	12 months	3	993	RR (M-H, Fixed, 95% CI)	2.21 [1.73, 2.82]
3	ACR 70% improvement	6		RR (M-H, Fixed, 95% CI)	Subtotals only
	3 months	1	64	RR (M-H, Fixed, 95% CI)	5.0 [0.25, 100.20]
	6 months	5	1648	RR (M-H, Fixed, 95% CI)	3.53 [2.41, 5.16]
	12 months	3	993	RR (M-H, Fixed, 95% CI)	4.02 [2.62, 6.18]

Abatacept (2 mg/kg) + etanercept versus placebo + etanercept

	Outcome	*# studies*	*# participants*	*Statistical Method*	*Effect Size*
1	ACR 20% improvement	1		RR (M-H, Fixed, 95% CI)	Subtotals only
	6 months	1	121	RR (M-H, Fixed, 95% CI)	1.58 [0.92, 2.71]
	12 months	1	121	RR (M-H, Fixed, 95% CI)	1.58 [0.92, 2.71]
2	ACR 50% improvement	1		RR (M-H, Fixed, 95% CI)	Subtotals only
	6 months	1	121	RR (M-H, Fixed, 95% CI)	1.33 [0.63, 2.83]
	12 months	1	121	RR (M-H, Fixed, 95% CI)	1.69 [0.76, 3.79]
3	ACR 70% improvement	1		RR (M-H, Fixed, 95% CI)	Subtotals only

	6 months	1	121	RR (M-H, Fixed, 95% CI)	8.17 [0.49, 136.81]
	12 months	1	121	RR (M-H, Fixed, 95% CI)	1.69 [0.38, 7.59]
	Abatacept versus placebo (by dosage)				
	Outcome	*# studies*	*# participants*	*Statistical Method*	*Effect Size*
	1 ACR 20% improvement	5		RR (M-H, Fixed, 95% CI)	Subtotals only
	6 months - 2 mg/kg	1	121	RR (M-H, Fixed, 95% CI)	1.58 [0.92, 2.71]
	6 months - 10 mg/kg	4	1527	RR (M-H, Fixed, 95% CI)	1.81 [1.60, 2.04]
	6 months - combined dosage	5	1648	RR (M-H, Fixed, 95% CI)	1.79 [1.59, 2.02]
	2 ACR 50% improvement	5		RR (M-H, Fixed, 95% CI)	Subtotals only
	6 months - 2 mg/kg	1	121	RR (M-H, Fixed, 95% CI)	1.33 [0.63, 2.83]
	6 months - 10 mg/kg	4	1527	RR (M-H, Fixed, 95% CI)	2.59 [2.07, 3.25]
	6 months - combined dosage	5	1648	RR (M-H, Fixed, 95% CI)	2.47 [2.00, 3.07]
	3 ACR 70% improvement	5		RR (M-H, Fixed, 95% CI)	Subtotals only
	6 months - 2 mg/kg	1	121	RR (M-H, Fixed, 95% CI)	8.17 [0.49, 136.81]
	6 months - 10 mg/kg	4	1527	RR (M-H, Fixed, 95% CI)	3.43 [2.34, 5.04]
	6 months - combined dosage	5	1648	RR (M-H, Fixed, 95% CI)	3.53 [2.41, 5.16]
	Abatacept versus placebo (by study eligibility criteria)				
	Outcome	*# studies*	*# participants*	*Statistical Method*	*Effect Size*
	1 ACR 20% improvement	5		RR (M-H, Fixed, 95% CI)	Subtotals only
	MTX failures	3	1138	RR (M-H, Fixed, 95% CI)	1.68 [1.48, 1.91]
	Biologic failures	2	510	RR (M-H, Fixed, 95% CI)	2.27 [1.67, 3.07]
	2 ACR 50% improvement	5		RR (M-H, Fixed, 95% CI)	Subtotals only
	MTX failures	3	1138	RR (M-H, Fixed, 95% CI)	2.38 [1.89, 3.00]
	Biologic failures	2	510	RR (M-H, Fixed, 95% CI)	2.96 [1.67, 5.25]
	3 ACR 70% improvement	5		RR (M-H, Fixed, 95% CI)	Subtotals only
	MTX failures	3	1138	RR (M-H, Fixed, 95% CI)	3.16 [2.12, 4.71]
	Biologic failures	2	510	RR (M-H, Fixed, 95% CI)	7.05 [1.98, 25.14]
ADVERSE EVENTS:	Total adverse events were greater in the abatacept group (RR 1.05, 95% CI 1.01-1.08). Other harm outcomes were not significant with the exception of a greater number of serious infections at 12 months in the abatacept group (Peto OR 1.91 ((5% CI 1.07-3.42). Serious adverse events were increased when abatacept was given in combination with other				

biologics (RR 2.30, 95% CI 1.15-4.62).

Abatacept (2 mg/kg and 10 mg/kg) + DMARDs/biologic versus placebo + DMARDs/biologic

	Outcome	*# studies*	*# participants*	*Statistical Method*	*Effect Size*
1	Withdrawals due to AEs	6	3105	Peto OR (Peto, Fixed, 95% CI)	1.30 [0.91, 1.85]
	6 months	2	657	Peto OR (Peto, Fixed, 95% CI)	1.11 [0.42, 2.96]
	12 months	4	2448	Peto OR (Peto, Fixed, 95% CI)	1.33 [0.90, 1.95]
3	All withdrawals	7	3169	RR (M-H, Fixed, 95% CI)	0.60 [0.52, 0.70]
	3 months	1	64	RR (M-H, Fixed, 95% CI)	0.33 [0.12, 0.92]
	6 months	2	657	RR (M-H, Fixed, 95% CI)	0.65 [0.44, 0.96]
	12 months	4	2448	RR (M-H, Fixed, 95% CI)	0.61 [0.51, 0.72]
3	Serious infections	5	2871	Peto OR (Peto, Fixed, 95% CI)	1.56 [0.93, 2.61]
	6 months	2	657	Peto OR (Peto, Fixed, 95% CI)	0.76 [0.25, 2.28]
	12 months	3	2214	Peto OR (Peto, Fixed, 95% CI)	1.91 [1.07, 3.42]
4	Total adverse events	5	2871	RR (M-H, Fixed, 95% CI)	1.05 [1.01, 1.08]
	6 months	2	657	RR (M-H, Fixed, 95% CI)	1.06 [0.97, 1.15]
	12 months	3	2214	RR (M-H, Fixed, 95% CI)	1.04 [1.01, 1.08]
5	Total serious AEs	6	3151	RR (M-H, Fixed, 95% CI)	1.05 [0.86, 1.29]
	6 months	2	703	RR (M-H, Fixed, 95% CI)	0.80 [0.49, 1.31]
	12 months	4	2448	RR (M-H, Fixed, 95% CI)	1.12 [0.89, 1.39]
6	Death	6	3105	Peto OR (Peto, Fixed, 95% CI)	0.82 [0.26, 2.60]
	6 months	2	657	Peto OR (Peto, Fixed, 95% CI)	5.02 [0.29, 88.42]
	12 months	4	2448	Peto OR (Peto, Fixed, 95% CI)	0.58 [0.17, 2.04]
7	Malignancies	5	2710	Peto OR (Peto, Fixed, 95% CI)	1.00 [0.59, 1.71]
	6 months	1	266	Peto OR (Peto, Fixed, 95% CI)	0.70 [0.04, 11.72]
	12 months	4	2444	Peto OR (Peto, Fixed, 95% CI)	1.02 [0.59, 1.75]

Abatacept (2 mg/kg) + etanercept versus placebo + etanercept

	Outcome	*# studies*	*# participants*	*Statistical Method*	*Effect Size*
1	Withdrawals due to AEs				
	12 months	1	121	Peto OR (Peto, Fixed, 95% CI)	2.94 [0.76, 11.34]
2	All withdrawals				
	12 months	1	121	RR (M-H, Fixed, 95% CI)	0.82 [0.49, 1.37]
3	Serious infections				
	12 months	1	121	Peto OR (Peto, Fixed, 95% CI)	4.25 [0.35, 51.61]
4	Total adverse events				

	12 months	1	121	RR (M-H, Fixed, 95% CI)	1.05 [0.92, 1.19]
	5 Total serious AEs				
	12 months	1	121	Peto OR (Peto, Fixed, 95% CI)	3.49 [1.08, 11.34]
	Abatacept (2 mg/kg and 10 mg/kg) + biologic versus placebo + biologic				
	Outcome	*# studies*	*# participants*	*Statistical Method*	*Effect Size*
	1 Withdrawals due to AEs				
	12 months	2	288	Peto OR (Peto, Fixed, 95% CI)	2.68 [1.07, 6.72]
	2 All withdrawals				
	12 months	2	706	RR (M-H, Random, 95% CI)	Not estimable
	3 Serious infections				
	12 months	2	288	Peto OR (Peto, Fixed, 95% CI)	3.20 [0.86, 11.97]
	4 Total adverse events				
	12 months	2	288	RR (M-H, Fixed, 95% CI)	1.06 [0.98, 1.14]
	5 Total serious AEs				
	12 months	2	288	RR (M-H, Fixed, 95% CI)	2.30 [1.15, 4.62]
LIMITATIONS OF PRIMARY STUDIES	The only RCT that reported results of structural joint change was the Kremer, 2006 trial. Moreland, 2002 only provided 3-month data. Although there was symmetry in the funnel plot, there were only 5 studies used. Four trials did not perform an intention-to-treat analysis. Two studies excluded patients from efficacy analysis due to protocol violations. All trials were sponsored by Bristol-Meyers Squibb, the manufacturer of abatacept.				

Evidence Table 1. Targeted Immune Modulators—Rheumatoid Arthritis

STUDY:	**Authors: Mertens and Singh**[38] **Year: 2009** **Country:** Multinational
FUNDING:	Cochrane
DESIGN:	**Study design:** Systematic review and meta-analysis **Number of patients:** 2876
AIMS OF REVIEW:	To evaluate the clinical effectiveness and safety of AKA in adult patients with rheumatoid arthritis
STUDIES INCLUDED IN META-ANALYSIS:	Bresnihan 1998, Cohen 2002, Cohen 2004, Fleischman 2003, Genovese 2004
TIME PERIOD COVERED:	1950 to 4th week January 2008
CHARACTERISTICS OF INCLUDED STUDIES:	All randomized controlled trials (RCTs) comparing AKA alone or in combination with DMARDs or biologics to placebo or other DMARDs or biologics in patients with rheumatoid arthritis
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adults aged 18 years and above meeting the ACR 1987 revised criteria for rheumatoid arthritis

Authors: Mertens and Singh **Year: 2009**	
CHARACTERISTICS OF INTERVENTIONS:	AKA alone or in combination with other drugs.
MAIN RESULTS:	ACR 20 at 24 weeks AKA 50-150 mg/day 38% vs. placebo 23%, (RR 1.61; 95% CI 1.32 to 1.98). The absolute treatment benefit for AKA 50 to 150mg/day 15%with NNTB 8 ACR20 at 24 weeks AKA < 50 mg/day 33% vs. placebo 26% RR of 1.38 (95% CI 1.01 to 1.89), ACR50 at 24 weeks AKA 50-150 18% vs. placebo 7% (RR 2.51; 95%CI 1.56 to 4.03). The absolute treatment benefit for AKA 50-150 11% and NNTB- 9 ACR70 at 24 weeks AKA 50-150 7% vs. placebo 2% (RR3.71; 95% CI 1.44 to 9.57) The absolute treatment benefit for AKA50-150 was 5% and NNTB was 22 HAQ scores AKA vs. placebo MD of -0.19 (95% CI -0.30 to -0.09)
ADVERSE EVENTS:	Withdrawals AKA50-150 22% vs. placebo 22% (RR 1.04; 95% CI 0.86 to 1.27) Adverse events AKA 92% vs. placebo 87% (RR 1.05; 95%CI 0.94 to 1.17) AKA(w/o MTX) vs. Placebo(w/o MTX) RR1.00; 95% CI 0.96 to 1.04 AKA + MTX vs. placebo +MTX subgroup, (RR 1.11; 95% CI 1.03 to 1.20) ISRs AKA50-150 71% vs. placebo 28% RR 2.45; 95% CI 2.17 to 2.77 SAEs AKA50-150 7%vs. placebo 6%, RR 1.04; 95% CI 0.70 to 1.56 Infections AKA50-150 40% vs. placebo 35% RR 1.08; 95%CI 0.80 to 1.45
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	Good

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Moreland et al.**[39] **Year: 2002** **Country:** Multinational			
FUNDING:	Bristol-Myers Squibb			
RESEARCH OBJECTIVE:	To investigate determine safety and preliminary efficacy of costimulatory blockade using CTLA-4Ig (abatacept) and LEA29Y in RA patients who have been treated unsuccessfully with at least 1 DMARD.			
DESIGN:	**Study design:** RCT, double blind, placebo-controlled **Setting:** multicenter **Sample size:** 214 (only 122 of which were of interest to this study)			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 85 days 32	**ABA 0.5** 0.5 mg/kg 85 days 26	**ABA 2** 2 mg/kg 85 days 32	**ABA 10** 10 mg/kg 85 days 32
INCLUSION CRITERIA:	Age 18-65 years; meeting ACR criteria for RA and in functional class I, II, or III; disease duration < 7 years; ≥ 10 swollen and 12 tender joints at study entry; Westergren ESR ≥ 28 mm/hour or morning stiffness of ≥ 45 minutes; unsuccessful treatment with at least 1 classic DMARD; negative result of purified protein derivative (PPD) tuberculin skin test, or if there was history of positive PPD, either bacillus Calmette-Guerin immunization or completion of adequate course of chemoprophylaxis for TB; hemoglobin level ≥ 8.5 gm/dl; platelet count ≥ 125,000/mm3; white blood cell count ≥ 3,000/mm3; serum creatinine not more than twice the upper limit of normal.			
EXCLUSION CRITERIA:	NR			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable dose of low-dose corticosteroids (≤ 10 mg / day) or NSAIDS			

Authors: Moreland et al.
Year: 2002

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: NR (mean disease duration 3.4 years)

	Placebo	ABA 0.5	ABA 2	ABA 10
Mean age (years):	48.3	46.9	46.2	51.5
Sex (% female):	81	85	72	69
Ethnicity: % White	94	88	94	94
Other germane population qualities:				
• MTX use (%)	72	85	81	75
• Corticosteroids	97	100	91	84
• NSAIDS	84	73	94	84
• Other DMARDS	88	88	78	81
• TJC	32.10	32.87	32.13	29.53
• SJC	24.21	18.78	26.94	23.27
• Pain score	3.55	3.48	3.50	3.47
• Physician global assessment	3.62	3.52	3.50	3.70

OUTCOME ASSESSMENT:

Primary Outcome Measures: ACR20 and ACR70 responses at day 85; individual components of the ACR core data set
Secondary Outcome Measures: NR
Timing of assessments: day 15, 29, 43, 57, 71, and 85

RESULTS:

Health Outcome Measures:

- A dose response was noted for the primary outcome.
- ABA was associated with numeric improvements in ACR20 compared to placebo.
- On day 85, 100% improvement in both swollen and tender joints had occurred in 0%, 16%, and 9%, respectively of the patients who had received ABA at 0.5, 2, and 10mg/kg.
- Mean % improvement in TJC at day 85 = 29.3% (placebo) vs. 26.1%, 49.0%, and 54.6% (ABA at 0.5, 2, and 10mg/kg, respectively).
- Mean % improvement in SJC at day 85 = 32.1%(placebo) vs. 15.4%, 41.6%, and 40.7% (ABA at 0.5, 2, and 10mg/kg, respectively).
- Mean % improvement in pain score at day 85 = 4.6% (placebo) vs. 5.1%, 25.6%, and 28.1% (ABA at 0.5, 2, and 10mg/kg, respectively).
- Mean % improvement in function score at day 85 = 5.1% (placebo) vs. 0.7%, 11.8%, and 20.3% (ABA at 0.5, 2, and 10mg/kg, respectively).

Authors: Moreland et al. **Year: 2002**				
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Serious adverse events • Headache • Nausea and vomiting • Fatigue • Arthritis • Hypotension	**Placebo** 75 12.5 3.1 6.3 3.1 9.4 6.3	**ABA (all doses)** 81.1 4.4 8.9 5.6 4.4 4.4 3.3		
Significant differences in adverse events:	No			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 2			
ADEQUATE RANDOMIZATION:	No			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	NR; Data safety monitoring board was unblinded			
ATTRITION (*overall*):	**Overall loss to follow-up:** 25% (day 169; 19% at day 85) **Loss to follow-up differential high:** Cannot tell; (combined attrition =22.2% for ABA all doses)			
ATTRITION (*treatment specific*):	**Placebo**	**ABA 0.5**	**ABA 2**	**ABA 10**
Loss to follow-up:	37.5	NR	NR	NR
Withdrawals due to adverse events:	NR	2	2	1
QUALITY RATING:	**Fair**			

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Nixon, Bansback, and Brennan[40]** **Year: 2007** **Country:** UK
FUNDING:	Funding has been previously received from Wyeth, Interleukin Genetics Inc., Abbott Laboratories, British Society of Rheumatology, the US Agency for Healthcare Research and Quality and AstraZeneca.
DESIGN:	**Study design:** Systematic review and meta-analysis **Number of patients:** 4694
AIMS OF REVIEW:	**Relative treatment effects and adjusted indirect comparisons of TNF-α (ETA, INF, ADA) and IL-1 (AKA) inhibitors for RA**
STUDIES INCLUDED IN META-ANALYSIS:	13 - Bresnihan 1998; Cohen 2002; Cohen 2004; Bathon 2000; Klareskog 2004; Moreland 1999; Weinblatt 1999; St Clair 2004; Maini 1999; Keystone 2004; van de Putte 2004; Weinblatt 2003; Breedveld 2006;
TIME PERIOD COVERED:	January 1990 to January 2005
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs comparing cytokine antagonists with placebo or MTX; > 6 months; sufficient data provided to determine the odds ratios for the ACR20 and ACR50.
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients with a clinical diagnosis of RA. Mean disease duration at baseline 1 to 13 yrs, the mean number of previously used DMARDs ranges from 0 to 4, and mean HAQ disability score from 1.3 to 1.9. Various MTX naiveties. Odds ratios based on 8 year disease duration and baseline HAQ of 1.6.

Authors: Nixon, Bansback, and Brennan **Year: 2007**	
CHARACTERISTICS OF INTERVENTIONS:	AKA 0.04mg/kg/day – 150mg/day, ETA 10-25mg/twice weekly, INF 3-10mg/kg every 4-8 weeks, and ADA 20-40mg/week
MAIN RESULTS:	**AKA vs. placebo** OR for ACR20 1.70 (95% CI 0.90–3.19) OR for ACR50 2.13 (95% CI 1.27–4.22) **ETA vs. placebo** OR for ACR20 3.58 (95% CI 2.09–6.91) OR for ACR50 4.21 (95%CI 2.74–7.43) **INF vs. placebo** OR for ACR20 3.47 (95% CI 1.66–7.14) OR for ACR50 4.14 (95% CI 2.42–7.46) **ADA vs. placebo** OR for ACR20 3.19 (95% CI 1.97–5.48) OR for ACR50 3.97 (96% CI 2.73–6.07) **TNF-α antagonists vs. AKA** OR for ACR20 1.96 (95% CI 1.03-4.01) OR for ACR50 1.93 (95% CI 1.05-3.50) **ETA vs. AKA** OR for ACR20 2.11 (95% CI 0.90-5.68) OR for ACR50 1.94 (95% CI 0.87-4.36) **INF vs. AKA** OR for ACR20 2.05 (95% CI 0.74-5.5) OR for ACR50 1.93 (95% CI 0.79-4.29) **ADA vs. AKA** OR for ACR20 1.88 (95% CI 0.83-4.49) OR for ACR50 1.84 (95% CI 0.84-3.7) **ADA vs. ETA** OR for ACR20 0.89 (95% CI 0.42-1.79) OR for ACR50 0.94 (95% CI 0.54-1.62) **ADA vs. INF** OR for ACR20 0.92 (95% CI 0.39-2.37) OR for ACR50 0.96 (95% CI 0.48-1.9)
ADVERSE EVENTS:	NR
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	No appraisal
QUALITY RATING:	**Fair**

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Ruiz Garcia et al.**[41] **Year: 2011** **Country: Spain** **Quality rating: Good**
FUNDING:	
DESIGN & SIZE:	**Study design:** Systematic Review **Number of patients: 2394 for effectiveness, 2094 for safety** **Trials: 5**
OBJECTIVE OF REVIEW:	**To assess the effectiveness and safety of certolizumab pegol in patients with RA who have not responded well to conventional disease modifying anti-rheumatic drugs (DMARDs).**
ELIGIBILITY CRITERIA:	Randomised controlled trials that compared certolizumab pegol with any other agent including placebo or methotrexate (MTX) in adult RA patients with active rheumatoid arthritis despite current or prior treatment with conventional DMARDs, such as methotrexate (MTX).
STUDIES INCLUDED IN REVIEW:	Anonymous (CDP870-004 2001) - published and unpublished data, 2001 UCB (CDP870-014 2009) - unpublished data only, 2008 Choy et al., 2002 Fleischmann, 2007 (FAST4WARD 2005 – published data only) RAPID 1, 2005 (published data only) RAPID 2, 2007 (published data only)
LITERATURE SEARCH DATES:	1966 – November 2009
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	1. RCTs that compared certolizumab pegol with any other agent including placebo in adult RA patients with active RA despite current or psior treatment with DMARDs 2. Trials that were fully published as a paper or available as a complete trial report. Where published only abstracts the trial reports were requested from the manufacturers 3. Studies having at least three months of follow-up to assess effectiveness 4. To assess safety: studies having a suboptimal length of follow-up, from eight weeks. Types of participants: adults (18 years and older) with RA who have persistent disease activity despite current or previous use of conventional DMARDs. Types of intervention: Certolizumab (CDP870) at any dose. The comperators were placebo or any disease modifying anti-rheumatic drug including other biologic agents used to treat RA.

Authors: Ruiz Garcia et al. **Year: 2011**	
DATA SYNTHESIS METHODS:	Authors used fixed-effect models throughout, except where heterogeneity exists in which case a random-effects model was used as it introduces less bias than excluding trials altogether. When studies were homogeneous they pooled them. Forest plots (mean differences and risk ratios) were done. They chose the fixed-effect model to pool the data because statistical heterogeneity was not high and it was reasonable from a clinical point of view. They used the GRADE software to provide an overall grading of the quality of the evidence by outcome.
MAIN RESULTS: (RESULTS IN SUBGROUPS)	ACR 50 (Follow-up: mean 24 weeks): Assumed Risk: 58 per 1000, corresponding risk: 349 per 1000 (223 to 545), RR 6.01 (3.84 to 9.4) [2 studies, N=965] HAQ change from baseline (Follow-Up: mean 24 weeks): control group: mean change: 1.6, intervention group: 0.39 lower (0.45 to 0.32 lower) [2 studies, N=965] Proportion of patients achieving DAS <2.6 (Remission): Assumed Risk: 12 per 1000, corresponding Risk: 45 per 1000 (28 to 73), OR 3.88 (2.33 to 6.45) [2 studies, N=957] All Withdrawals: Assumed Risk: 715 per 1000, corresponding risk: 279 per 1000 (257 to 307), RR 0.39 (0.36 to 0.43) [5 studies, N=2107] ---------- Assumed risk: Control Corresponding risk: Summary of findings Certolizumab pegol 200mg sc (with or without MTX) versus Placebo (with or without MTX)
ADVERSE EVENTS:	Serious adverse events (Follow-Up: mean 24 weeks): assumed risk: 46 per 1000, corresponding risk: 89 per 1000 (56 to 137), OR 2.02 (1.24 to 3.3) [2 studies, N=964] Withdrawals due to adverse events (Follow-up: 24-52 weeks): Assumed Risk: 23 per 1000, corresponding risk: 43 per 1000 (26 to 71), OR 1.93 (1.15 to 3.23) [4 studies, N=2071]
LIMITATIONS OF PRIMARY STUDIES	Absence of publication of some of the trials carried out with certolizumab pegol in RA

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Salliot et al.[42]** **Year: 2011** **Country: Conducted in Canada – component studies multinational** **Quality rating: Fair**
FUNDING:	None reported – Cochrane Review
DESIGN & SIZE:	**Study design:** Meta-analysis- indirect comparisons **Number of patients: 10,419** **Trials: 18 - 17published and 1 abstract**
OBJECTIVE OF REVIEW:	To compare the relative efficacy of biologicals (anti-tumour necrosis factor (TNF) agents, rituximab, abatacept, tocilizumab) in patients with RA with active disease and (i) an inadequate response (IR) to methotrexate (IR-MTX), (ii) an IR to anti-TNF agents (IR-anti-TNFs) using indirect comparisons.
ELIGIBILITY CRITERIA:	Double-blinded RCTs of adult patients with established RA after an IR to MTX or to anti-TNF treatments, and who received a biological agent or a placebo in combination with MTX or another DMARD for at least 24 weeks.
STUDIES INCLUDED IN REVIEW:	Schiff et al., 2008 Maini et al., 1999 Weinblatt et al., 1999 Weinblatt et al., 2003 Keystone et al., 2004 Kim et al., 2007 Keystone et al., 2008 Smolen et al., 2009 Keystone et al., 2009 Edwards et al., 2004 Emery et al., 2006 Emery et al., 2008 Kremer et al., 2003 Kremer et al., 2006 Smolen et al., 2008 Cohen et al., 2006 Genovese et al., 2005 Emery et al., 2008 Smolen et al., 2009

LITERATURE SEARCH DATES:	Up to October 2009 in the three following electronic databases: Medline, Cochrane Central and Embase and ACR and EULAR abstracts of the past 2 years (2007–2009)), and when needed they contacted the pharmaceutical firms involved in biotherapies for RA.
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	Double-blinded RCTs of adult patients with established RA after an IR to MTX or to anti-TNF treatments, and who received a biological agent or a placebo in combination with MTX or another DMARD for at least 24 weeks.

Authors: Salliot et.al. **Year: 2011**	
DATA SYNTHESIS METHODS:	Indirect comparisons - random effect model (Mantel–Haenszel method). Heterogeneity for ACR50 response rate was measured by I^2 statistic.
MAIN RESULTS: (RESULTS IN SUBGROUPS)	In IR-MTX, anti-TNFs had the same probability of reaching an ACR50 compared to 'non-anti-TNF biologicals' taken together (OR 1.30, 95 % CI 0.91 to 1.86). However, when compared to specifi c biological agents, anti-TNFs demonstrated a higher probability of reaching an ACR50 than abatacept (OR 1.52, 95 % CI 1.0 to 2.28), but not in comparison to rituximab and tocilizumab. In IR-anti-TNF, rituximab demonstrated a higher probability of achieving an ACR50 than tocilizumab (OR 2.61, 95% CI 1.10 to 6.37), but no significant differences existed between rituximab, tocilizumab, abatacept and golimumab. ACR 50 at 24 weeks Odds Ratio (95% CI) Abatacept vs. placebo 3.28 (2.44-4.41) Rituximab vs. placebo 3.12 (2.07-4.71) Anti-TNF vs. placebo 6.01 (4.74-7.62) Indirect comparisons between biologicals in active rheumatoid arthritis (RA) despite methotrexate (MTX) expressed in ORs for American College of Rheumatology 50% improvement (ACR50) response rate at 6 months (weeks 24 to 30), Abatacept vs. rituximab 1.12 (0.66 to 1.89), $P = 0.67$ Rituximab vs. tocilizumab 0.57 (0.29 to 1.12), $P = 0.10$ Tocilizumab vs. abatacept 1.97 (1.08 to 3.59), $P = 0.02$ Indirect comparisons between biologicals in active rheumatoid arthritis (RA) with inadequate response to anti-tumournecrosis factor (TNF), in ORs for American College of Rheumatology 50% improvement (ACR50) response rate at 6 months (week 24) Tocilizumab vs. Rituximab 1.26 (0.42-3.78) $P = 0.67$ Tocilizumab vs. Abatacept 1.43 (0.39-5.21) $P = 0.58$ Abatacept vs. rituximab 0.88 (0.28 to 2.77) $P = 0.83$ Golimumab vs. rituximab 0.74 (0.24 to 2.30) $P = 0.60$ Golimumab vs. abatacept 0.84 (0.22 to 3.16) $P = 0.79$ Golimumab vs. tocilizumab 0.58 (0.16-2.11) $P = 0.41$
ADVERSE EVENTS:	NR
LIMITATIONS OF PRIMARY STUDIES	

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Schiff et al.**[43] **Year: 2008** **Country:** International		
FUNDING:	Bristol-Myers Squibb, Princeton, New Jersey, USA		
RESEARCH OBJECTIVE:	To evaluate the mean change from baseline in Disease Activity Score (based on erythrocyte sedimentation rates; DAS28 (ESR)) for the ABA vs. placebo groups at day 197		
DESIGN:	**Study design:** RCT **Setting:** International, Multi-center **Sample size:** 431		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ABA** 500-1000mg, days 1, 15, 29, and every 28 days thereafter 365 days (12 months) 156	**Placebo** N/A 197 days (6 months) 110	**INF** 3mg/kg, days 1, 15, 43, 85, and every 56 days thereafter 365 days (12 months) 165
INCLUSION CRITERIA:	(ACR) criteria for RA, age ≥ 18, RA ≥ 1 year, inadequate response to MTX, as demonstrated by ongoing active disease (at randomization SJC >10, TJC >12, and CRP >1 mg/dl. All patients had received MTX >15 mg/week for >3 months prior to randomization (stable for at least 28 days) and washed out all DMARDs (>28 days prior) except for MTX. Anti-TNF-therapy naïve.		
EXCLUSION CRITERIA:	All patients were screened for TB by purified protein derivative (PPD) testing and chest x ray.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids ((10 mg of prednisone or equivalent daily (stable for >25 out of 28 days prior to randomization)), and/or stable NSAIDs (including acetyl salicylic acid, and analgesics not containing aspirin or NSAIDs). No MTX dose adjustments were permitted except in the occurrence of adverse events (AEs). Between days 198–365, dose modification was permitted for MTX ((25 mg weekly) and oral corticosteroids ((10 mg prednisone or equivalent daily); hydroxychloroquine, sulfasalazine, gold, or azathioprine were also permitted. Premedication prior to infusions of study drug was left at the discretion of the investigator (not required by protocol).		

<table>
<tr><td colspan="4">Authors: Schiff et al.
Year: 2008</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>ABA</u></td><td><u>Placebo</u></td><td><u>INF</u></td></tr>
<tr><td>Mean age (years):</td><td>49.0 (12.5)</td><td>49.4 (11.5)</td><td>49.1 (12.0)</td></tr>
<tr><td>Sex (% female):</td><td>83.3%</td><td>87.3%</td><td>82.4%</td></tr>
<tr><td>Ethnicity:</td><td>80.8% caucasian</td><td>76.4% caucasian</td><td>80.6% caucasian</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Tender joint count (SD)</td><td>31.3 (13.9)</td><td>30.3 (11.7)</td><td>31.7 (14.5)</td></tr>
<tr><td>• Swollen joint count (SD)</td><td>21.3 (8.6)</td><td>20.1 (7.0)</td><td>20.3 (8.0)</td></tr>
<tr><td>• Mean disease duration (SD)</td><td>7.9 (8.5)</td><td>8.4 (8.6)</td><td>7.3 (6.2)</td></tr>
<tr><td>• DMARD use (%)</td><td>100%</td><td>100%</td><td>100%</td></tr>
<tr><td>• MTX use (%)</td><td>100%</td><td>100%</td><td>100%</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>75.6%</td><td>70.0%</td><td>71.5%</td></tr>
<tr><td>• DAS28 (ESR) score</td><td>6.9</td><td>6.8</td><td>6.8</td></tr>
<tr><td>• HAQ-DI score</td><td>1.8 (0.6)</td><td>1.8 (0.7)</td><td>1.7 (0.7)</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures:
reduction in disease activity, measured by DAS28 (ESR), with ABA vs. placebo at 6 months
Secondary Outcome Measures:
Mean reduction in DAS28 (ESR) with INF vs. placebo at 6 months.
6 months & 1 year: ABA vs. INF mean reduction in DAS28 (ESR); DAS28 (ESR) EULAR responses; low disease activity score (LDAS; DAS28 (ESR) ≤ 3.2); DAS28 (ESR)-defined remission (DAS28 (ESR), < 2.6); ACR 20, 50, 70 responses; HAQ-DI response rates (>0.3 improvement from baseline); SF-36: mean changes in PCS, MCS, & 8 subscales.
Tertiary endpoints: comparative safety at 1 year ABA vs. INF.
Timing of assessments: Baseline, 6 months, 1 year</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Primary Health Outcome Measures (6 months):
• reduction in DAS28 (ESR), ABA vs. placebo (–2.53 vs. –1.48, P < 0.001)
• ABA vs. placebo ACR20: 66.7 vs. 41.8%, P < 0.001, ACR50: 40.4 vs. 20.0%, P < 0.001; and ACR70: 20.5 vs. 9.1%, P = 0.019.
• INF vs. placebo ACR20: 59.4 vs. 41.8%, P = 0.006; ACR 50: 37.0 vs. 20.0%, P = 0.004; and ACR70: 24.2 vs. 9.1%, P = 0.002.</td></tr>
</table>

	Health Outcome Measures (head-to-head, day 365): • a greater reduction in DAS28 (ESR) was observed with ABA than with INF –2.88 vs. –2.25; estimate of difference (95% CI) = –0.62 (–0.96, –0.29). **Intermediate (Secondary) Outcome Measures (head-to-head, day 365):** • proportion of patients achieving a good EULAR response (ABA 32.0 vs. INF 18.5%, estimate of difference (95% CI) = 13.5% (3.6, 23.3)), • LDAS (ABA 35.3 vs. INF 22.4%, estimate of difference (95% CI) = 12.9 (2.1, 23.7)), • DAS28 (ESR)-defined remission (ABA 18.7 vs. INF 12.2%, estimate of difference (95% CI) = 18.7 (–2.2, 15.2)) • ACR20 responses were higher with ABA than with INF (ACR20: 72.4 vs. 55.8%, difference of 16.7, 95% CI = 5.5, 27.8). • percentages of ACR50 and 70 responders were numerically higher with ABA vs. INF treatment (with overlapping 95% CIs for the estimate of difference for ACR50: 45.5 vs. 36.4%, estimate of difference (95% CI) = 9.1 (–2.2, 20.5); ACR70: 26.3 vs. 20.6%, estimate of difference (95% CI) = 5.7 (–4.2, 15.6), respectively) • HAQDI responses were maintained in the ABA and INF groups (57.7 and 52.7%, respectively, estimate of difference (95% CI) = 5.0 (–6.5, 16.5)) • greater improvements from baseline in the PCS were observed with ABA vs. INF (difference of 1.93, 95% CI = 0.02, 3.84). Improvements in the MCS (difference of 1.92, 95% CI = –0.30, 4.15) and in all eight subscales were also numerically higher with ABA vs. INF

Authors: Schiff et al. **Year: 2008**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Serious infections • Serious AEs • Acute infusional AEs • Infections and infestations	**ABA (365 days)** 89.1% 1.9% 9.6% 7.1% 1.9%	**Placebo (6 months)** 83.6% 4.2% 11.5% 10.0% 2.7%	**INF (365 days)** 93.3% 8.5% 18.2% 24.8% 8.5%
Significant differences in adverse events:	A higher proportion of patients in the INF group compared with the placebo group reported related SAEs (4.8 vs. 2.7%), discontinued due to AEs (4.8 vs. 0.9%), and discontinued due to SAEs (2.4 vs. 0%). The higher frequency of SAEs in the INF vs. placebo groups was largely due to an increase in serious infections (4.2 vs. 2.7%, respectively)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** None		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 11% **Attrition differential high:** No		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**ABA** 10.9% 2.6%	**Placebo** 5.4% 0.9%	**INF** 14.5% 7.3%
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators—Rheumatoid Arthritis

STUDY:	**Authors: Schmitz et al.**[44] **Year: 2011** **Country: multinational** **Quality rating: Fair**
FUNDING:	Pharmaceutical
DESIGN & SIZE:	**Study design:** Systematic review and meta-analysis **Number of patients:** 6566 **Trials:** 16
OBJECTIVE OF REVIEW:	To estimate the relative efficacy among anti-TNFs in patients who have had an inadequate response to MTX
ELIGIBILITY CRITERIA:	Patients with established RA, an inadequate response to TMX, and who have been treated for at least 24 weeks (when 24-wk data not available, data within 6 wks either before or after 24 wks were used), and the study must be an RCT
STUDIES INCLUDED IN REVIEW: **(Author, Year, refID)**	Weinblatt et al., 2003 Keystone et al., 2004 Van de Putte et al., 2004 Miyasaka et al., 2008 Kim et al., 2007 Maini et al., 1999 Westhovens et al., 2006 Zhang et al., 2006 Schiff et al., 2008 Moreland et al., 1999 Weinblatt et al., 1999 Keystone et al., 2009 Kay et al., 2008 Keystone et al., 2008 Smolen et al., 2009 Fleischmann et al., 2009
LITERATURE SEARCH DATES:	Up to and including October 2010
INCLUDED STUDIES: **(Study design, characteristics of included population, characteristics of included interventions)**	Included studies were RCTs. Patients had RA and an inadequate response to MTX. Trial interventions included ADA (5 trials), CZP (3 trials), ETA (2 trials), GOL (2 trials), INF (4 trials). Both monotherapy and combination therapy were allowed. No MTX was given in 4 studies. Baseline HAQ ranged from 1.3 to 1.9. Mean MTX dose ranged from 13 mg in CZP trials and 18.5 mg in ETA trials.

Authors: Schmitz et al. Year: 2011	
DATA SYNTHESIS METHODS:	Bayesian mixed-treatment comparisons
MAIN RESULTS: (RESULTS IN SUBGROUPS)	**ACR20, RR (80% credible interval)** INF vs. ADA: 0.8 (0.6, 1.1) ETA vs. ADA: 1.5 (1.0, 2.3) ETA vs. INF: 1.9 (1.3, 2.9) GOL vs. ADA: 0.8 (0.6, 1.1) GOL vs. INF: 1.0 (0.7, 1.4) GOL vs. ETA: 0.5 (0.3, 0.8) CZP vs. ADA: 2.1 (1.5, 2.9) CZP vs. INF: 2.6 (1.9, 3.7) CZP vs. ETA: 1.4 (0.9, 2.3) CZP vs. GOL: 2.6 (1.8, 4.0) **ACR50, RR (80% credible interval)** INF vs. ADA: 0.7 (0.5, 1.0) ETA vs. ADA: 1.7 (0.9, 2.9) ETA vs. INF: 2.4 (1.2, 4.2) GOL vs. ADA: 0.8 (0.5, 1.3) GOL vs. INF: 1.2 (0.8, 1.7) GOL vs. ETA: 0.5 (0.3, 1.0) CZP vs. ADA: 1.7 (1.2, 2.5) CZP vs. INF: 2.4 (1.7, 3.5) CZP vs. ETA: 1.0 (0.6, 2.1) CZP vs. GOL: 2.1 (1.2, 3.4) **HAQ, RR (80% credible interval)** INF vs. ADA: -0.1 (-0.15, -0.05) ETA vs. ADA: 0.11 (0.04, 0.17) ETA vs. INF: 0.21 (0.13, 0.28) GOL vs. ADA: 0.02 (-0.05, 0.20) GOL vs. INF: 0.12 (0.05, 0.20) GOL vs. ETA: -0.09 (-0.07, 0.00) CZP vs. ADA: 0.05 (0.00, 0.09)

	CZP vs. INF: 0.15 (0.10, 0.21) CZP vs. ETA: -0.06 (-0.13. 0.01) CZP vs. GOL: 0.03 (-0.04, 0.09)
ADVERSE EVENTS:	NA
LIMITATIONS OF PRIMARY STUDIES	Heterogeneity amongst studies: some included RCTS allowed background of MTX, others did not; differences in disease severity and mean MTX dose; anti-TNF doses ranged across studies (information not provided)

Evidence Table 1. Targeted Immune Modulators—Rheumatoid Arthritis

STUDY:	**Authors: Singh et al.[45]** **Year: 2010** **Country: USA** **Quality rating: Good**							
FUNDING:	none declared							
DESIGN & SIZE:	**Study design:** Systematic Review **Number of patients:** 3334 (Intervention: 2233, Controls: 1101) **Trials:** 8							
OBJECTIVE OF REVIEW:	To assess the benefit and safety of tocilizumab in adults with rheumatoid arthritis based on randomized controlled trial (RCT) data.							
ELIGIBILITY CRITERIA:	Published randomized or quasirandomized (methods of allocating participants to a treatment that are not strictly random, e.g., date of birth, hospital record number, or alternation) clinical trials comparing tocilizumab alone or in combination with DMARD or biologics to placebo and/or DMARD and/or biologics for treatment of adults (age 18 years or older) with RA who met the 1987 American College of Rheumatology (ACR) classification criteria for RA. No restrictions with regard to dosage or duration of intervention.							
STUDIES INCLUDED IN REVIEW:	Choy 2002, Emery 2008 (RADIATE), Genovese 2008 (TOWARD), Maini 2006 (CHARISMA), Nishimoto 2004, Nishimoto 2007 (SAMURAI), Nishimoto 2009 (SATORI), and Smolen 2008 (OPTION)							
LITERATURE SEARCH DATES:	(1) The Cochrane Central Register of Controlled Trials, via The Cochrane Library, Wiley InterScience (www.thecochranelibrary. com), issue 3, 2009; (2) OVID Medline, 1966-October 1, 2009; (3) CINAHL (via EBSCOHost), 1982-2009, week 39; (4) EMBASE 1980-2009; (5) Science Citation Index (Web of Science) 1945-2009; and (6) Current Controlled Trials.							
INCLUDED STUDIES:	**Study**	**% Women**	**Age (yrs), M (SD); Median[rng]**	**MTX, mg/wk, M(SD)**	**BS HAQ**	**BS DAS28**	**RA Dur yrs (SD)**	**No. DMARD Failed, M (D) [rng]**
	Nishimoto 2009 (SATORI) TCZ + PL vs. MTX + PL	90	52.6 (10.6)	NR	NR	6.1 (0.9)	8.5 (8.4)	3.3 [1–8]
	Nishimoto 2007 (SAMURAI) TCZ vs.	80	52.9 (11.6)	6.9 (2.0)	NR	6.5 (0.8)	2.2 (1.4)	2.7 ([1–7]

	Conventional DMARD							
	Nishimoto 2004 TCZ Vs. PL	84	Md. 56[21-74]	NR	NR	NR	Md. 8.3[1.3-46]	Md. 5[1-1]8.3[1.3-46]
	Maini 2006 (CHARISMA) TCZ or TCZ +MTX vs. MTX+ PL	73	50.1 (NR)	NR	NR	6.4 (NR)	9.2 (NR)	NR
	Choy 2002 TCZ vs. PL	**71**	61.5 (7.8)	NR	NR	NR	13 (11)	3 (2)
	Emery 2008 (RADIATE) TCZ + MTX vs. PL + MTX	80	53.9 (12.7)	15.7 (4.4)	1.7 (0.6)	6.79 (0.93)	12.6 (9.3)	NR
	Genovese 2008 (TOWARD) TCZ + DMARD vs. PL + DMARD	81	53 (11)	14.7 (NR)	1.5 (0.6)	6.7 (1.0)	9.8 (8.8)	NR
	Smolen 2008 (OPTION) TCZ + MTX vs. PL + MTX	85	50.8 (11.8)	14.5 (4.4)	1.6 (0.6)	6.8 (0.9)	7.5 (7.3)	NR

<table>
<tr><td colspan="6">Authors: Singh et al.
Year: 2010</td></tr>
<tr><td>DATA SYNTHESIS METHODS:</td><td colspan="5">Benefit and safety - Calculated relative risk for dichotomous outcomes and mean differences for continuous outcomes which was used to calculate the absolute change (benefit). Rare events (such as death, etc.), risk difference was calculated using the Mantel-Haenszel test, and 95% CI were calculated.
Determined heterogeneity by calculating the I-squared (I2), if substantial heterogeneity was detected, used random effects models instead of fixed effects and tried to analyze it using subgroup analyses.</td></tr>
<tr><td rowspan="11">MAIN RESULTS: (RESULTS IN SUBGROUPS)</td><td colspan="5">Summary of findings for 7 key outcomes comparing tocilizumab to placebo: Genovese, 2008; Smolen, 2008; Emery, 2008; and Maini, 2006)</td></tr>
<tr><td></td><td>Assumed Risk Control</td><td>Corresponding Risk TCZ 8 mg/kg + MTX/DMARD vs placebo + MTX/DMARD</td><td>Relative Effect (95% CI)</td><td>No Participants (studies)</td></tr>
<tr><td>ACR 50% Followup: mean 16-24 wks</td><td>95 per 1000</td><td>301 per 1000 (258 to 349)</td><td>RR 3.17 (2.72,3.67)</td><td>2063(4)</td></tr>
<tr><td>DAS 28<2.6 Followup: mean 16-24 wks</td><td>28 per 1000</td><td>245 per 1000 (175 to 330)</td><td>RR 8.74 (6.26,11.8)</td><td>1946(4)</td></tr>
<tr><td>HAQ improvement of > 0.3 or MHAQ decrease of > 0.22 (changes exceeding MCID) Followup: mean 24 wks</td><td>340 per 1000</td><td>609 per 1000 (551 to 660)</td><td>RR 1.79 (1.62,1.94)</td><td>1220(1)</td></tr>
<tr><td colspan="5">Studies included: Genovese, 2008; Smolen, 2008; Emery, 2008; and Maini, 2006</td></tr>
<tr><td>Secondary efficacy</td><td>No. Studies</td><td>No. Participants</td><td colspan="2">RR or Mean Difference (95% CI)</td></tr>
<tr><td>ACR20 (16-24)</td><td>4</td><td>2063</td><td colspan="2">2.53 (1.88, 3.39)</td></tr>
<tr><td>ACR70 (16-24)</td><td>4</td><td>2063</td><td colspan="2">5.94 (2.83, 12.48)</td></tr>
<tr><td>DAS28 (16-14 wks)</td><td>3</td><td>1728</td><td colspan="2">–2.00 (–2.10, –1.91)</td></tr>
<tr><td>HAQ (24 wks)</td><td>3</td><td>1964</td><td colspan="2">–0.29 (–0.34, –0.23)</td></tr>
<tr><td colspan="5">Tocilizumab 8 mg/kg plus placebo versus placebo plus methotrexate: Maini, 2006; Nishimoto, 2007; and Nishimoto, 2009</td></tr>
</table>

		No. Studies	No. Participants	RR or Mean Difference (95% CI)
	ACR20 (16-52 wks)	3	528	2.25 (1.58, 3.20)
	ACR50 (16-52 wks)	3	528	3.14 (1.35, 7.28)
	ACR70 (16-52 wks)	3	528	2.31 (0.32, 16.66)
	DAS remission (16-52 wks)	3	528	11.84 (5.88, 23.85)
	DAS28 (16-52 wks)	3	528	–2.29 (–3.33, –1.25)
	MHAQ (16-52 wks)	2	427	1.77 (1.46, 2.15)

ADVERSE EVENTS:	**Studies included:** Genovese, 2008; Smolen, 2008; Emery, 2008; Maini, 2006				
		Assumed Risk Control	**Corresponding Risk** TCZ 8 mg/kg + MTX/DMARD vs placebo + MTX/DMARD	**Relative Effect (95% CI)**	**No Participants (studies)**
	Serious Adverse Events Follow-up: mean 24 wks	67 per 1000	78 per 1000 (56 to 110)	RR 1.17 (.83, 1.64)	1961 (3)
	Total Withdrawals mean 16-24 wks	123 per 1000	75 per 1000 (60 to 95)	RR 0.61 (.49 , .77)	2064(4)
	Withdrawals due to adverse events mean 16-24 wks	36 per 1000	51 per 1000 (34 to 76)	RR 1.43 (.95, 2.12)	2064(4)
	Studies included: Genovese, 2008; Smolen, 2008; Emery, 2008; Maini, 2006				
			No. Studies	**No. Participants**	**RR or Mean Difference (95% CI)**
	Any Adverse Event (AE)		4	2060	1.14 (1.07, 1.21)
	Patients with at Least 1 serious AE		3	1725	1.50 (0.99, 2.25)
	Infections (24 wks)		3	1961	1.18 (1.04, 1.34)
	Serious infections and infestations (16–24 wks)		4	2060	1.80 (0.98, 3.32)
	Any gastrointestinal disorder (24 wks)		3	1961	1.42 (1.18, 1.71)
	Rash (24 wks)		1	410	3.63 (1.03, 12.82)
	Withdrawals due to inefficacy (16–24 wks		4	2064	0.28 (0.19, 0.43)
	Death (24 wks)		2	1551	0.52 (0.07, 3.65)
	Studies Included: Maini, 2006; Nishimoto, 2007; Nishimoto, 2009				
			No. Studies	**No. Participants**	**RR or Mean Difference (95% CI)**
	Serious adverse events (16–52 wks)		3	528	1.37 (0.84, 2.22)
	Rash (52 wks)		2	427	2.49 (1.13, 5.51)

	Paronychia (52 wks)	1	302	8.31 (1.07, 64.80)
	Infusion reactions/anaphylactic reactions (16–52 wks)	2	403	0.05 (0.02, 0.09)
	Cancer (52 wks)	1	302	6.93 (0.71, 67.29)
	All withdrawals (16–52 wks)	2	427	0.61 (0.10, 3.76)
	Withdrawals due to AE (16–52 wks)	2	427	2.26 (1.00, 5.09)
	Withdrawals due to inefficacy (16–52 wks)	1	302	0.62 (0.22, 1.69)
LIMITATIONS OF PRIMARY STUDIES	Sample size, short followup, and lack of safety outcomes as primary outcomes in RCT			

Evidence Table 1. Targeted Immune Modulators—Rheumatoid Arthritis

STUDY:	**Authors:** Singh et al.[46] **Year:** 2009 **Country:** NR **Quality rating:** Fair
FUNDING:	Sources of support: Cochrane Collaboration; The Oak Foundation, Switzerland; NIH CTSA Award
DESIGN & SIZE:	**Study design:** Systematic Review **Number of patients:** NR **Trials:** 6 systematic reviews (6 Cochrane reviews; data from 7 studies on abatacept, 8 on adalimumab, 5 on anakinra, 4 on etanercept, 4 on infliximab, 3 on ritixumab)
OBJECTIVE OF REVIEW:	To compare the efficacy and safety of abatacept, adalimumab, anakinra, etanercept, infliximab, and ritixumab in RA pts
ELIGIBILITY CRITERIA:	Completed/updated/available Cochrane systematic reviews of biologic DMARDs for RA.
STUDIES INCLUDED IN REVIEW:	Six Cochrane Reviews: Maxwell, 2008 Navarro-Sarabia, 2005 Blumenauer, 2003 Lopez-Olivo, 2008 Mertens, 2008 Lethaby, 2003
LITERATURE SEARCH DATES:	NR
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	**Characteristics of Included Studies:** Cochrane systematic reviews of randomized controlled trials (RCTs) of biologic DMARDs including but not limited to abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab in patients with RA. A review was included if it contained at least one RCT, had clinically relevant outcomes, and included clear inclusion and exclusion criteria for studies. **Characteristics of Included Populations:** 18 years or older; RA according to 1987 ACR criteria (populations characteristics similar among reviews) **Characteristics of Interventions:** Biologic DMARDs alone or combined with other biologics/traditional DMARDs compared to placebo along or placebo + biologics/traditional DMARDs. Biologics were of the following dosing regimens: • Abatacept: 500 mg IV q 4 weeks for 2 weeks if <60 kg (750 mg if 60-100kg; 1000 mg if >100 kg) • Adalimumab: 40 mg SQ q 2 wks

	• Anakinra: 100 mg SQ QD • Etanercept: 25 mg SQ twice a wk • Infliximab: 3 mg/kg IV q 8 wks • Rituximab: 2x 1000 mg IV doses 2 wks apart

Authors: Singh et al. Year: 2009	
DATA SYNTHESIS METHODS:	Network meta-analysis
MAIN RESULTS: (RESULTS IN SUBGROUPS)	Results are for 3-, 6-, and 12-month data combined ACR50 (OR, 95% CI, reference group is placebo) abatacept: 2.98 (1.79 to 4.97) [6 studies] adalimumab: 3.70 (2.40 to 5.70) [8 studies] anakinra: 1.68 (0.83 to 3.41) [3 studies] etanercept: 4.97 (2.70 to 9.13) [4 studies] infliximab: 2.92 (1.37 to 6.14) [3 studies] rituximab: 4.10 (2.02 to 8.33) [3 studies] overall: 3.35 (2.62 to 4.29) [27 studies] Indirect comparisons (only significant OR reported): Anakinra less efficacy than etanercept: 0.34 (0.14 to 0.81, P = 0.05) Adalimumab greater efficacy than anakinra: 2.20 (1.01 to 4.75, P = 0.046)
ADVERSE EVENTS:	Superseded by Singh, 2011[47]
LIMITATIONS OF PRIMARY STUDIES	The use of biologic DMARD therapy was associated with a significantly higher likelihood of achieving an ACR50 response, compared to placebo with an OR of 3.35 (2.62 to 4.29) (Figure 2) although based on results with a substantial degree of heterogeneity, with I^2 of 69%. Abatacept for RA Seven studies were included in this review (Maxwell 2008). Intention to treat analysis was not performed in two studies. There was risk of attrition bias with < 80 %completion rate in the treatment groups at 12 months in two studies. Radiographic data were not obtained for 90% of the study population. Physical function was measured as a categorical outcome of HAQ by a decrease in the minimal clinically important change. The quality of the evidence was moderate because of these limitations in the study design. Adalimumab for RA Eight studies were included from this review (Navarro-Sarabia 2005). There were limitations in the study design of six studies - the method of randomization was not described, allocation concealment was not reported, and blinding was not described. There was unexplained substantial heterogeneity or inconsistency of results. Reported data were sparse. The quality of the evidence was moderate for efficacy outcomes. The quality for safety outcomes was downgraded to low because the data reported included both

	standard and non-standard doses. Anakinra for RA Five studies were included from this review (Mertens 2008) with limitations in study design including methods of randomization not described in all five, allocation concealment was not reported in one study, and blinding was not described in one study. Intention to treat analysis was not performed in four studies. There was >20%attrition in two studies. Data on all withdrawals from therapy were not reported. This resulted in a downgrading of the GRADE quality of evidence to moderate. Etanercept for RA Four studies were included from this review (Lethaby 2003) and four had limitations in study design including one or more of the following: method of randomization was not described, allocation concealment was not reported, and blinding was not described There was unexplained substantial heterogeneity in the results. There was imprecision of results due to wide confidence interval and sparse data. The quality of the evidence was moderate. Infliximab for RA Only four studies were included from this review (Blumenauer 2003) and intention-to-treat analysis was not performed in one. Data were missing for important outcomes such as total adverse events and infections as well as physical function (HAQ). The quality of the evidence was high as a result of high quality studies. Rituximab for RA Only three studies were included (Lopez-Olivo 2008). The method of randomization and allocation concealment was not described in all three studies. Blinding was not described in two and there was risk of attrition bias in one study. There was unexplained substantial heterogeneity in some results. Radiographic scores were not reported. The evidence for rituximab was moderate.

Evidence Table 1. Targeted Immune Modulators—Rheumatoid Arthritis

STUDY:	**Authors:** Singh et al.[48] **Year:** 2010 **Country:** Multinational **Quality rating:** Good
FUNDING:	
DESIGN & SIZE:	**Study design:** Systematic Review **Number of patients:** 1714 **Trials:** 4
OBJECTIVE OF REVIEW:	To compare the efficacy and safety of golimumab in adults with rheumatoid arthritis
ELIGIBILITY CRITERIA:	(RCTs) or Controlled Clinical Trials (CCTs) (methods of allocating participants to a treatment which are not strictly random, e.g., date of birth, hospital record number or alternation)
STUDIES INCLUDED IN REVIEW:	Smolen, 1999 Keystone, 2009 Kay, 2008 Emery, 2009
LITERATURE SEARCH DATES:	June 30, 2009 (original search), August 16, 2009 (update search)
INCLUDED STUDIES: **(Study design, characteristics of included population, characteristics of included interventions)**	**Characteristics of Included Studies:** RCTs or Controlled Clinical Trials (CCTs) (methods of allocating participants to a treatment which are not strictly random, e.g., date of birth, hospital record number or alternation) **Characteristics of Included Populations:** Adults 18 years or older, with RA meeting the 1987 American College of Rheumatology Classification criteria for RA. 1 study was prior methotrexate failure and biologic failure (Smolen 99), 3 studies were naïve populations **Characteristics of Interventions:** Interventions compared are golimumab alone or in combination with DMARDs or biologics vs. placebo plus methotrexate or golimumab alone or in combination with DMARDs or biologics compared to other DMARDs or biologics. There were no restrictions with regard to dosage or duration of intervention.

Authors: Singh et al. **Year: 2010**	
DATA SYNTHESIS METHODS:	Meta-analysis
MAIN RESULTS: (RESULTS IN SUBGROUPS)	Results reported as Risk Ratio and 95% CI [RR (95% CI)] for golimumab 50 mg every 4 weeks + methotrexate vs. placebo + methotrexate ACR20 (14-24 wk): 1.53 (1.3-4.9) [4 studies] ACR 50 (14-24 wk): 2.57 (1.3-4.9) [4 studies] ACR70 (14-24 wk): 2.8 (1.3-5.98) [4 studies] Good EULAR response (14-24 wk): 1.47 (1.15-1.89) [4 studies] DAS Low Disease Activity (14-16 wk): 1.64 (1.15-2.34) [2 studies] DAS remission (risk difference): 0.10 (0.06 -0.14) [4 studies] HAQ change≥.22 (14 wk): 1.79 (1.38-2.31) [1 study] Change in HAQ score (14 wk): -0.25 (-0.29 to - 0.21) [1 study] HAQ scores (14 wk): -0.20 (-0.25 to -0.15) [1 study] Change in DAS scores (16 wk): -1.1 (-1.69 to -0.51) [1 study]
ADVERSE EVENTS:	Results reported as Risk Ratio and 95% CI [RR (95% CI)] for golimumab 50 mg every 4 weeks + methotrexate vs. placebo + methotrexate Adverse Events (16-24 wk) 1.05 (0.93, 1.18) [4 studies] Serious Adverse Events (16-24 wk) 1.05 (0.62, 1.78) [4 studies] Infections (16-24 wk) 1.03 (0.84, 1.25) [4 studies] Serious Infections (16-24 wk) 1.06 (0.40, 2.86) [4 studies] Tuberculosis (16-24 wk) 3.04 (0.12, 74.01) [4 studies] Lung Infections (16-24 wk) 0.97 (0.55, 1.70) [2 studies] Cancer (16-24 wk) 0.81 (0.16, 4.18) [4 studies] All Withdrawals (14-24 wk) 0.50 (0.31, 0.81) [4 studies] Withdrawals due to Adverse Events (14-16 wk) 0.56 (0.24, 1.29) [3 studies] Withdrawals due to Inefficacy (14-16 wk) 0.43 (0.15, 1.21) [3 studies] Death (24-52 wk) 1.02 (0.11, 9.71) [4 studies]
LIMITATIONS OF PRIMARY STUDIES	For the primary outcome of ACR50, there was statistically significant heterogeneity in the golimumab 50 mg and 100 mg every four weeks plus methotrexate versus placebo plus methotrexate groups with I2 values of 76%and 77% (P values of 0.005 for each). None of the studies were designed with safety as primary outcome.

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: St. Clair et al.[49] and Smolen et al.[50,51]** **Year: 2004 and 2006** **Country:** Multinational		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To compare the benefits of initiating treatment with methotrexate and infliximab with those of methotrexate treatment alone in patients with RA of ≤ 3 years duration and to identify disease characteristics which lead to progression of joint damage and the impact of treatment on patient employment status.		
DESIGN:	**Study design:** RCT **Setting:** University hospitals **Sample size:** 1049		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**MTX** N/A 54 weeks 298	**MTX-INF 3** 3 mg/kg 54 weeks 373	**MTX-INF 6** 6 mg/kg 54 weeks 378
INCLUSION CRITERIA:	At least 18years old but not older than 75 years, met the 1987 revised criteria of the ACR for the classification of RA, and had persistent synovitis for ≥ 3 months and ≤ 3 years; ≥ 10 swollen joints, and ≥ 12 tender joints; one or more of the following: a positive test result for serum RF, radiographic erosions of the hands or feet, or a serum CRP level of ≥ 2.0 mg/dl		
EXCLUSION CRITERIA:	Prior treatment with MTX; received other DMARDs within 4 weeks of entry; used ETA, INF, ADA or other anti-TNF-α agent; infection with HIV, hepatitis B or C virus; history of active or past TB, CHF, or lymphoma or other malignancy within the past 5 years (excluding excised skin cancers)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids; NSAIDS; 20 mg MTX		

Authors: St Clair et al. and Smolen et al. **Year: 2004 and 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Early RA with moderate to severe disease activity (mean disease duration 0.9 years)		
	MTX	**MTX-INF 3**	**MTX-INF 6**
Mean age (years):	50	51	50
Sex (% female):	75	71	68
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• Tender joint count	34	32	33
• SJC	22	21	22
• DMARD naïve (%)	65	71	68
• MTX use (%)	100	100	100
• Glucocortiod use (%)	38	37	39
• HAQ score	1.5	1.5	1.5
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR-N; HAQ, SF-36, vdH-Sharp score; employment rates **Secondary Outcome Measures:** ACR20; ACR50; ACR 70, DAS28, **Timing of assessments:** weeks 0, 2, 4, 6, and every 8 weeks thereafter through week 46		

Authors: St Clair et al. and Smolen et al. Year: 2004 and 2006	
RESULTS:	**Health Outcome Measures:** • HAQ scores improved significantly more from weeks 30-54 in the MTX-3mg/kg and MTX-6mg/kg INF groups than in the MTX group: 0.80 and 0.88 vs. 0.68; *P* = 0.03; *P* < 0.001 • From baseline to weeks 54 significantly more patients in the MTX-3mg/kg and MTX-6mg/kg INF groups than in the MTX group improved HAQ by more than 0.22 (minimum level for clinical significance): 76.0% and 75.5% vs. 65.2%; *P* = 0.003; *P* = 0.004 • ACR20/50/70 were significantly higher in the MTX-INF 3mg and 6mg groups than in the MTX group: o ACR20: 62.4% and 66.2% vs. 53.6%; *P* = 0.028; P = 0.001 o ACR50: 45.6% and 50.4% vs. 32.1%; *P* < 0.001; *P* < 0.001 o ACR70: 32.5% and 37.2% vs. 21.2%; *P* = 0.002; *P* < 0.001 • Change (loss) in actual employment between patients receiving MTX plus INF and those receiving MTX plus placebo 0.5% versus 1.3%; *P* > 0.5 (NS). • Proportion of patients whose status changed from employable at baseline to unemployable at week 54 MTX 8% versus MTX + INF 14%; *P* = 0.05. **Intermediate Outcome Measures:** • ACR-N was significantly higher for MTX-INF 3mg/kg and 6 mg/kg vs. MTX: 38.9% and 46.7% vs 26.4%; *P* < 0.001 • ACR20/50/70 were significantly higher in the MTX-INF 3mg and 6mg groups than in the MTX-placebo group: o ACR20: 62.4% and 66.2% vs. 53.6%; *P* = 0.028; *P* = 0.001 o ACR50: 45.6% and 50.4% vs. 32.1%; *P* < 0.001; *P* < 0.001 o ACR70: 32.5% and 37.2% vs. 21.2%; *P* = 0.002; *P* < 0.001 • MTX-INF 3 and 6 mg/kg groups showed significantly less radiographic progression than MTX (mean +/-SD changes in van der Heijde modification of the total Sharp score at week 54: 0.4+/-5.8 and 0.5+/-5.6 versus 3.7+/-9.6 ; *P* < 0.001 • Change in modified Sharp/van der Heijde score from baseline to week 52 MTX-3mg vs. MTX-6mg INF vs MTX group mean ± SD 0.4 ± 5.8, 0.5 ± 5.6 and 3.7 ± 9.6, respectively; *P* < 0.001 for each comparison. • High CRP level, high ESR, or persistent disease activity was associated with greater radiographic progression in the group taking MTX alone, while little radiographic progression was seen in patients receiving both MTX and INF, regardless of the abnormal levels of these traditional predictors.

Authors: St. Clair et al. and Smolen et al. **Year:2004 and 2006**			
ADVERSE EVENTS: **Overall adverse effects reported** • URTIs (%) • Nausea (%) • Sinusitis (%) • Pneumonia (%) • TB (%) • Sepsis (%) • Infusion reaction	**MTX** NR 21 18 8 0.7 0 0 0	**MTX-INF 3** NR 25 20 12 2 0.8 0.5 0.5	**MTX-INF 6** NR 28 17 10 3 0.3 0.3 0.5
Significant differences in adverse events:	• Serious infections were significantly more common in the MTX-3mg and MTX-6mg INF groups than in the MTX group: 5.6% and 5.0% vs. 2.1%; *P* = 0.02; *P* = 0.04		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 14.9% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**MTX** 17.8% 3.2%	**MTX-INF 3 mg** 13.4% 9.5%	**MTX-INF 6 mg** 14% 9.6%
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Turkstra et al.**[52] **Year: 2011** **Country: Australia** **Quality rating: Fair**
FUNDING:	
DESIGN & SIZE:	**Study design:** SR **Number of patients: 6,503** **Trials: 27**
OBJECTIVE OF REVIEW:	To compare the short-term efficacy of abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab in patients with established RA.
ELIGIBILITY CRITERIA:	Double-blind RCTs which presented data on efficacy at approximately six months, included patients with active established RA, and included a comparison of bDMARD versus control treatment
STUDIES INCLUDED IN REVIEW:	Cohen et al, 2004 Cohen et al., 2006 Combe et al, 2006 Edwards et al, 2004 Emery et al., 2006 Emery et al., 2008 Fleischmann et al, 2009 Furst et al, 2003 Genovese et al, 2005 Genovese et al., 2008 Kay et al, 2008 Keystone et al, 2004 Keystone et al, 2008 Keystone et al, 2009 Klareskog et al, 2004 Kremer et al, 2006 Maini et al, 1999 Moreland et al, 1999 Schiff et al, 2008 Smolen et al, 2009 Smolen et al, 2009 Smolen et al., 2008

	van de Putte et al, 2004 Weinblatt et al, 1999 Weinblatt et al, 2003 Westhovens et al, 2006 Jones et al., 2010
LITERATURE SEARCH DATES:	1998 to October 2010
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	The 27 studies included two abatacept trials, four adalimumab trials, one anakinra trial, three certolizumab trials, four etanercept trials, three golimumab trials, two infliximab trials, three rituximab trials, four tocilizumab trials, and one trial comparing abatacept and infliximab with methotrexate. All trials were RCTs, with patients, providers and outcome assessors blinded. Randomization was stated and no important differences in baseline characteristics were reported in the trials.

Authors: Turkstra, et al. **Year: 2011**	
DATA SYNTHESIS METHODS:	Mixed-treatment comparison
MAIN RESULTS: (RESULTS IN SUBGROUPS)	Results of mixed treatment comparison* **Abatacept** ACR20: OR (95% CI)=4.05 (2.29, 6.58) ACR50: OR (95% CI)=4.55 (2.57, 7.50) ACR70: OR (95% CI)=4.46 (1.98, 8.88) **Adalimumab** ACR20: OR (95% CI)=2.79 (1.71, 1.71) ACR50: OR (95% CI)=3.34 (1.98, 5.39) ACR70: OR (95% CI)=4.86 (2.18, 9.46) **Anakinra** ACR20: OR (95% CI)=2.02 (0.81, 4.33) ACR50: OR (95% CI)=2.03 (0.78, 4.40) ACR70: OR (95% CI)=3.16 (0.66, 9.86) **Certolizumab pegol** ACR20: OR (95% CI)=19.18 (9.46, 34.17) ACR50: OR (95% CI)=22.23 (9.93, 43.91) ACR70: OR (95% CI)=41.17 (10.64, 126.00) **Etanercept** ACR20: OR (95% CI)=6.19 (3.53, 10.38) ACR50: OR (95% CI)=8.13 (4.39, 14.89) ACR70: OR (95% CI)=10.21 (3.88, 25.97) **Golimumab** ACR20: OR (95% CI)=2.93 (0.82, 7.63) ACR50: OR (95% CI)=6.48 (1.52, 19.60) ACR70: OR (95% CI)=19.18 (1.70, 86.81) **Infliximab** ACR20: OR (95% CI)=3.05 (1.75, 5.09) ACR50: OR (95% CI)=4.05 (2.23, 7.01) ACR70: OR (95% CI)=5.36 (2.16, 12.42) **Rituximab** ACR20: OR (95% CI)=4.02 (2.06, 7.19)

	ACR50: OR (95% CI)=4.29 (2.07, 8.03) ACR70: OR (95% CI)=5.98 (1.93, 14.76) **Tocilizumab** ACR20: OR (95% CI)=4.72 (2.98, 7.20) ACR50: OR (95% CI)=6.31 (3.99, 9.55) ACR70: OR (95% CI)=10.60 (5.44, 19.60) * Using swollen joint count and baseline disease duration as covariates
ADVERSE EVENTS:	NR
LIMITATIONS OF PRIMARY STUDIES	Variations in the trial design between trials. Variation in average disease duration in included trials. Only 1 study used anakinra, and there were at least 2 studies each for the other treatments.

Evidence Table 1. Targeted Immune Modulators—Rheumatoid Arthritis

STUDY:	**Authors: Weaver et al.**[53] **Year: 2006** **Country:** US				
FUNDING:	Immunex Corporation				
RESEARCH OBJECTIVE:	To evaluate the effectiveness of select biologics, methotrexate, and DMARDs in the management of adult RA in routine clinical practice.				
DESIGN:	**Study design:** Prospective observational **Setting:** 509 rheumatology practices **Sample size:** 5397 (includes 762 patients whose treatment strategies were not of interest to this review)				
INTERVENTION: **Dose (median wkly at baseline):** **Duration:** **Sample size:**	**MTX** 10 mg 12 months 941	**ETA** 50 mg 12 months 1251	**INF** 3.8 mg/kg every 8 wks 12 months 120	**ETA+MTX** 50 mg+15 mg 12 months 1783	**INF+MTX** 3.8mg/kg every 8 wks+15mg 12 months 540
INCLUSION CRITERIA:	Patients requiring a change in their existing RA treatment: ≥ 18 years; met ACR criteria for RA.				
EXCLUSION CRITERIA:	Active infection; pregnancy; concurrent enrollment in a clinical trial				
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes				

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Weinblatt et al.**[54] **Year: 2007** **Country:** Multicenter US		
FUNDING:	Bristol-Myers Squibb		
RESEARCH OBJECTIVE:	Efficacy and safety of ABA in combination with ETA in active RA		
DESIGN:	**Study design:** RCT with an open-label long-term extension (LTE) phase **Setting:** Multicenter (40 centers in the US) **Sample size:** 121(2:1 ratio), LTE 80		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ABA + ETN 25 mg twice wkly** 2 mg/kg intravenously on days 1, 15, 30, every 4 weeks 6 months 85	**Placebo + ETN 25 mg twice wkly** 6 months 36	LTE **ETN 25 mg twice wkly+abatacept 10 mg/kg** 80
INCLUSION CRITERIA:	>18 years of age and met the criteria of the American College of Rheumatology (ACR) for RA, functional class I, II or III. Patients must have received ETA 25 mg twice weekly for >3 months, >8 swollen joints (66-joint count) and >10 tender joints (68-joint count).		
EXCLUSION CRITERIA:	Active or latent infection, recent opportunist infection, TB requiring treatment within the previous 3 years, history of cancer within the previous 5 years or history of drug or alcohol misuse. Pregnant and nursing women		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Low-dose corticosteroids (≤10 mg/day) or NSAIDs stable during the study (6mo). hydroxychloroquine, sulfasalazine, leflunomide or MTX was allowed after 6 months (LTE)		

Authors: Weinblatt et al. **Year: 2007**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** active RA	
	ABA	**Placebo**
Mean age (years):	49.8 (23–73) 1	54.3 (28–71)
Sex (% female):	78	72
Ethnicity/Caucasian%:	94	100
Other germane population qualities:		
• Tender joint count	28.7 (14)	29.2 (13.2)
• Swollen joint count	19.6 (9.4)	20.1 (10.5)
Mean disease duration years	13 (10.1)	12.8 (8.6)
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** of the double-blind phase: modified ACR20 response rate at 6 months. of the of the LTE: safety and tolerability of abatacept in combination with ETA during long-term administration **Secondary Outcome Measures:** double-blind phase: modified ACR 50 response at 6 months **Timing of assessments: RCT** at 6 mo, LTE at 1 year	
RESULTS:	**Health Outcome Measures:** ABA 2 mg/ kg and ETA vs. placebo and ETA at 6 mo ACR 20 48.2% vs. 30.6%; *P* = 0.072 ACR 50 25.9% vs. 19.4% *P* = 0.448 ACR 70 10.6% vs. 0% *P* = 0.042 ABA 2 mg/ kg and ETA vs. placebo and ETA at 1 year ACR 20 48.2% vs. 30.6% ACR 50 28.2% vs. 16.7% ACR 70 9.4% vs. 5.6% *P* = 0.481 Modified HAQ response Change (from baseline to 1 year) abatacept 2 mg/ kg and ETA vs. placebo and ETA - 0.3 (0.5) vs - 0.2 (0.4)	

Authors: Weinblatt et al. **Year: 2007**			
ADVERSE EVENTS: **Overall adverse effects reported:** • URTI • Serious infections • Discontinuations due to AEs • Deaths	**ABA** 79 (92.9) 20 (23.5) 3 (3.5) 10 (11.8) 0	**Placebo** 32 (88.9) 5 (13.9) 0 1 (2.8) 0	**LTE** 78 (97.5) 23 (28.8) 1 (1.3) 8 (10) 1 (1.3)
Significant differences in adverse events:	Yes		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 1 pt.		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:**	**Overall loss to follow-up:** 34 **Loss to follow-up differential high:** Yes **ABA** 20 6	 **Placebo** 14 1	
QUALITY RATING:	**Fair**		

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors:** Wiens et al.[55-57] **Year:** 2009, 2010 **Country:** Brazil/Multinational **Quality rating:** Good
FUNDING:	
DESIGN & SIZE:	**Study design:** Systematic review and meta-analysis of 21 Randomized, double-blind, placebo controlled trials **Number of patients:** Adalimumab: 2691 Infliximab: 2100 Etanercept: 1612 **Trials:** 21
OBJECTIVE OF REVIEW:	To evaluate the efficacy and safety of using the anti–tumor necrosis factor-alpha (anti–TNF-alpha) drugs adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis.
ELIGIBILITY CRITERIA:	Studies were included that compared the anti–TNF-alpha drug with placebo, with or without concomitant methotrexate in both groups. From these RCTs, those that received a Jada score of 3 or more (0 to 5 scale) and used the usual dosages for each of the anti–TNF- alpha drugs—adalimumab 20 mg once/week or 40 mg every other week subcutaneously, etanercept 25mg twice/week or 50 mg once/week subcutaneously, and infliximab 3 mg/kg intravenously at weeks 0, 2, 6, and then every 8 weeks—were eligible for inclusion in the meta-analysis. Studies that evaluated different routes of administration of the drugs were excluded from the meta-analysis, as were trials without a placebo group, studies with laboratory measures but without clinical results, and articles that were only available as abstracts.
STUDIES INCLUDED IN REVIEW:	**Adalimumab (8 studies)**: Furst, 2003; van de Putte, 2003; Weinblatt, 2003; van de Putte, 2004; Keystone, 2004; Breedveld, 2006; Kim, 2007; Miyasaka, 2008 **Infliximab (7 studies, 8 articles)**: Lipsky, 2000; Maini, 1999; St Clair, 2004; Quinn, 2005; Westhovens, 2006; Zhang, 2006; Abe, 2006; Schiff, 2008 **Etanercept (6 studies, 9 articles)**: Moreland, 1999; Weinblatt, 1999; Keystone, 2004; Lan, 2004; Klareskog, 2004; van der Heijde, 2007; van der Heijde, 2006; Emery, 2008
LITERATURE SEARCH DATES:	January 1995–December 2008
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	Randomized, double-blind, placebo-controlled studies of adalimumab, infliximab, and etanercept (with or without methotrexate) in adults with rheumatoid arthritis. Studies that used the usual dosages for each of the anti–TNF- alpha drugs—adalimumab 20 mg once/week or 40 mg every other week subcutaneously, etanercept 25mg twice/week or 50 mg once/week subcutaneously, and infliximab 3 mg/kg intravenously at weeks 0, 2, 6, and then every 8 weeks—were eligible for inclusion in the meta-analysis.

Authors: Wiens et al. **Year: 2009, 2010**	
DATA SYNTHESIS METHODS:	Meta-analysis
MAIN RESULTS: (RESULTS IN SUBGROUPS)	Adalimumab ACR20 after 12 - 26 wks: RR (95% CI) = 2.26 (1.82, 2.81) [7 studies, 9 arms] ACR50 after 12 - 26 wks: RR (95% CI) = 3.50 (2.75, 4.44) [7 studies, 9 arms] ACR70 after 12 - 26 wks: RR (95%CI) = 5.36 (3.76, 7.64) [7 studies, 9 arms] ACR20 after 52 wks RR (95% CI) = 1.85 (1.07, 3.19) [2 studies, 3 arms] ACR50 after 52 wks RR (95% CI) = 2.80 (1.16, 6.77) [2 studies, 3 arms] ACR70 after 52 wks RR (95% CI) = 3.23 (1.37, 7.61) [2 studies, 3 arms] Infliximab ACR20 after 14 - 30 wks: RR (95% CI) = 1.87 (1.43, 2.45) [5 studies] ACR50 after 14 – 30 wks: RR (95% CI) = 2.68 (1.79, 3.99) [6 studies] ACR70 after 14 – 30 wks: RR (95%CI) = 2.68 (1.78, 4.03) [6 studies] ACR20 after 1 – 2 years RR (95% CI) = 1.67 (0.99, 2.80) [3 studies] ACR50 after 1 – 2 years RR (95% CI) = 1.55 (1.16, 2.08) [3 studies] ACR70 after 1 – 2 years RR (95% CI) = 1.60 (0.91, 2.82) [3 studies] Etanercept ACR20 after 6 months: RR (95% CI) = 2.94 (2.27, 3.81) [4 studies, 5 arms] ACR50 after 6 months: RR (95% CI) = 5.28 (3.12, 8.92) [4 studies, 5 arms] ACR70 after 6 months: RR (95%CI) = 4.83 (1.74, 13.47) [4 studies, 5 arms] ACR20 after 1 – 3 years RR (95% CI) = 1.22 (1.14, 1.31) [4 studies] ACR50 after 1 – 3 years RR (95% CI) = 1.51 (1.39, 1.64) [4 studies] ACR70 after 1 – 3 years RR (95% CI) = 1.62 (1.26, 2.08) [4 studies]
ADVERSE EVENTS:	Adalimumab Withdrawals due to Adverse Events: RR (95% CI) = 1.56 (1.04, 2.35) [5 studies] Withdrawals due to Lack of Efficacy: RR (95% CI) = 0.29 (0.20, 0.42) [5 studies] Infliximab Withdrawals due to Adverse Events: RR (95% CI) = 2.05 (1.33, 3.16) [7 studies] Withdrawals due to Lack of Efficacy: RR (95% CI) = 0.41 (0.18, 0.95) [3 studies] Etanercept Withdrawals due to Adverse Events: RR (95% CI) = 0.86 (0.63, 1.16) [6 studies] Withdrawals due to Lack of Efficacy: RR (95% CI) = 0.30 (0.21, 0.44) [5 studies]
LIMITATIONS OF PRIMARY STUDIES	Some studies are not published in full, some safety data are not available in the articles and thus were not used in the meta-analysis.

Evidence Table 1. Targeted Immune Modulators – Rheumatoid Arthritis

STUDY:	**Authors: Wiens et al.**[58] **Year: 2009** **Country: Brazil** **Quality rating: Fair**
FUNDING:	NR
DESIGN & SIZE:	**Study design:** Double blind RCTs **Number of patients:**2100 **Trials:** 7 (primary studies)
OBJECTIVE OF REVIEW:	To evaluate the efficacy and safety of infliximab for the treatment of rheumatoid arthritis
ELIGIBILITY CRITERIA:	RCTs that evaluated intravenous administered doses of infliximab(3mg/Kg body weight) at weeks 0, 2, 6 and then every 8 weeks were used. Included studies compared infliximab plus methotrexate vs placebo plus methotrexate. Studies evaluating different doses of infliximab or different routes of administration did not have control groups and had only laboratory measures without clinical results were excluded.
STUDIES INCLUDED IN REVIEW: **(Author, Year, refID)**	1) ATTRACT Maini and Colleagues, 1999 2) St Clair and Colleagues, 2004 3) Quinn and colleagues, 2004 4) Westhovens and colleagues, 2006 5) Zhang and colleagues, 2006 6) Abe and colleagues, 2006 7) ATTEST Schiff and colleagues, 2006
LITERATURE SEARCH DATES:	NR
INCLUDED STUDIES:	All were RCTs on rheumatoid arthritis patients. All studies included intravenous infliximab 3mg/kg + methotrexate vs placebo plus methotrexate. Trial duration-14 to 52 weeks.

Authors: Wiens et al. **Year: 2009**	
DATA SYNTHESIS METHOD:	The inverse variance model, with a 95% CI and random effect model chosen to measure effects of dichotomous variables. Statistical heterogeneity assessed using I^2. Sensitivity analysis was performed using a) data review with a reasonable range of values for missing data, b) data review using different statistical methods.
MAIN RESULTS: (RESULTS IN SUBGROUPS)	ACR responses after 14-30 weeks ACR 20 responder Infliximab vs control: Risk Ratio 1.87 (95% CI 1.43 to 2.45), % of patients achieving response: 59% vs 31%, total events 399 vs 188, heterogeneity Tau^2=0.05, Chi^2:12.46, df=4 (p=0.01; I^2:68%, Test for overall effect: Z=4.58(p<0.00001) ACR 50 responder Infliximab vs control: Risk Ratio 2.68 (1.79 to 3.99), % of patients achieving response: 33% vs 12%, total events 252 vs 85, heterogeneity Tau^2: 0.12; chi^2=11.80, df=5 (p=0.04), I^2=15%, Test for overall effect: Z=4.82, (p<0.00001) ACR 70 responder Infliximab vs control: Risk Ratio 2.68 (95%CI 1.78 to 4.03), % of patients achieving response: 17% vs 5%, total events: 126 vs 38, heterogeneity Tau^2=0.04, Chi^2=5.91, df=5(p=0.32); I^2=15%, test for overall effect Z=4.74, (p<0.00001) ACR responses after 1-2 years ACR20 responder Infliximab vs control: Risk Ratio 1.57(95% CI 0.92 to 2.69 total events: 273 vs 173, heterogeneity: Tau^2=0.17, Chi^2=9.42, df=2 (p=0.0009), I^2:79%, Test for overall effect: Z=1.64, p=0.10,),% of patients achieving response after at least 1 yr of treatment: 62% vs 26% ACR 50 responder Infliximab vs control: Risk Ratio 1.55 (95% CI 1.16 to 2.08), total events 192 vs 103, heterogeneity $Tau^2$0.02, Chi^2:2.50, df=2(p=0.29), I^2=20%, test for overall effect: Z=2.92 (p=0.003), % of patients achieving response after at least 1 yr of treatment: 43% vs 27% ACR 70 responder Infliximab vs control: Risk Ratio 1.60 (0.91 to 2.82), total events 132 vs 66, heterogeneity $Tau^2$0.12, Chi^2=3.43, df=2(p=0.18), I^2=42%, Test for overall effect: Z=1.62 (p=0.10), % of patients achieving response after at least 1 yr of treatment:29% vs 17%
ADVERSE EVENTS:	Any AE: Risk Ratio 0.83, (95% CI 0.64 to 1.08), p=0.17 SAE: Risk Ratio 1.12 (95% CI 0.90 to 1.41), p=0.32

	Serious infections: Risk Ratio 0.96 (0.39 to 2.38), p=0.93 Malignancy: Risk Ratio 1.64 (0.30 to 8.89), p=0.57 Deaths: Risk Ratio 0.71 (0.11 to 4.85), p=0.73 Withdrawals due to AE: Risk Ratio 2.05 (1.33 to 3.16), % of patients withdrew due to AE: 7% vs 3%, total events: 73 vs 30, heterogeneity: Tau^2=0.00, Chi^2=5.94, df=6 (p=0.43), I^2=0.%, test for overall effect: Z=3.27, p=0.001 Withdrawals due to lack of efficacy: Risk Ratio 0.41 (95% CI 0.18 to 0.95), total events 26 vs 60, % withdrew due to lack of efficacy: 4% vs 12%, heterogeneity Tau^2=0.29, Chi^2=4.75, df=2 (p=0.09), I^2=58%, Test for overall effect: Z=2.09(p=0.04)
LIMITATIONS OF PRIMARY STUDIES	Safety data obtained from studies of infliximab treatment for a short period of time. Only studies studying a fixed dose of infliximab were included.

Evidence Table 2. Targeted Immune Modulators – Juvenile Idiopathic Arthritis

STUDY:	**Authors: Horneff et al.**[59] **Year: 2004** **Country:** Germany
FUNDING:	Wyeth-Pharma
RESEARCH OBJECTIVE:	To assess efficacy and safety of etanercept treatment based on a registry for children with juvenile idiopathic arthritis in Germany and Austria
DESIGN:	**Study design:** Retrospective data analysis **Setting:** 36 pediatric rheumatology centers **Sample size:** 322
INTERVENTION: **Dose:** **Duration (mean follow-up):** **Sample size:**	**ETA** 0.4 mg/kg body weight/2x weekly 13.4 months 322
INCLUSION CRITERIA:	Failure to respond to MTX; have juvenile idiopathic arthritis
EXCLUSION CRITERIA:	None
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX and corticosteroids

Authors: Horneff et al. **Year: 2004**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease characteristic:** – Polyarticular, systemic & oligoarticular
	ETA
Mean age (years):	NR
Sex (% female):	NR
Ethnicity:	NR
Other germane population qualities:	
• TJC (%)	7
• SJC (%)	11
• DMARD use (%)	NR
• MTX use (%)	NR
• Corticosteroids use (%)	NR
• DAS score	NR
• HAQ score	NR
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Gianinni's criteria of improvement **Secondary Outcome Measures:** NR **Timing of assessments:** 1, 3, 6, 12, 18, 24, and 30 months (endpoint is not clearly specified)
RESULTS:	**Health Outcome Measures:** • The mean number of tender and swollen joints decreased from 9 and 8.4 to 3.0 and 4.5 after one month, and to 2.2 and 3.3 after three months; morning stiffness decreased from 45 minutes to 12 and 7 after one and three months ($P < 0.001$ for all) • Using Gianinni's criteria of 30, 50, and 70% improvement, a therapeutic response in JIA patients was achieved by 67%, 54%, and 30%, respectively, after one month, 79%, 61%, and 38% after 3 months, 82%, 70%, and 50% after 6 months, and 80%, 71%, and 54% after 12 months

Authors: Horneff et al. **Year: 2004**	
ADVERSE EVENTS: **Overall adverse effects reported:** • Infections overall • Infection prolonged or w/fever • Herpes simplex labilas • Local skin rxn • Raised liver enzymes • Itching • Leucocytopenia • Abdominal pain	**ETA** 17% 6.2% 0.6% 1.5% 0.6% 2.8% 2.8% 1.9% 1.2% 1.9%
Significant differences in adverse events:	20% of cases were discontinued because of AEs
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** N/A
ADEQUATE RANDOMIZATION:	N/A
ADEQUATE ALLOCATION CONCEALMENT:	N/A
BLINDING OF OUTCOME ASSESSORS:	N/A
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Treatment discontinuation:** **Discontinuation due to adverse events:**	**ETA** 17.7% 3.4%
QUALITY RATING:	**N/A**

Evidence Table 2. Targeted Immune Modulators – Juvenile Idiopathic Arthritis

STUDY:	**Authors: Lovell et al.**[60-62] **Year: 2000, 2003 and 2006** **Country:** US		
FUNDING:	Immunex Corporation, Children's Hospital Foundation of Cincinnati, NIH		
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of etanercept in children with PJRA		
DESIGN:	**Study design:** RCT and open label extension **Setting:** Academic medical centers (children's hospitals) **Sample size:** 51 and 58		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 4 months 26	**ETA** 0.4 mg/kg body weight/2x weekly 4 months 25	**Extension** 0.4 mg/kg body weight/2x weekly up to 2 years/4 years 58/34
INCLUSION CRITERIA:	Ages 4-17 with active PJRA; active disease despite treatments with NSAIDs and MTX at doses of at least 10 mg/sq meter of body surface area per week; normal or nearly normal platelet, white cell, and neutrophil counts, hepatic aminotransferase levels, and results of renal function tests		
EXCLUSION CRITERIA:	Pregnant and lactating patients were excluded along with patients with major concurrent medical conditions		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs, low doses of corticosteroids (≤.2 mg of prednisone /kg/day with a max of 10 mg/day) or bother were permitted		

Authors: Lovell et al. **Year: 2000, 2003, 2006**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease characteristic:** Polyarticular (mean disease duration 5.8 years)			
	Placebo	**ETA**	**Extension 2 years**	**Extension 4 years**
Mean age (years):	12.2	8.9	10	10.6
Sex (% female):	58	76	67	81
Ethnicity: white (%)	88	56	74	84
Other germane population qualities:				
• Disease duration mean (years)	6.4	5.3	5.9	5.9
• TJC	NR	NR	NR	NR
• SJC	NR	NR	NR	NR
• DMARD use (%)	73	64	74	100
• MTX use (%)	69	64	72	100
• Corticosteroids use (%)	50	24	38	41
• DAS score	NR	NR	NR	NR
• HAQ score	NR	NR	NR	NR
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Number of patients with disease flare (disease flare is based on worsening of 30% of more in 3 or 6 response variables and a minimum of 2 active joints) **Secondary Outcome Measures:** Articular severity score, duration of morning stiffness, degree of pain, and CRP **Timing of assessments:** day 1, day 15, and at the end of each month			
RESULTS:	**Health Outcome Measures:** • Significantly more in placebo group (81%) than patients in ETA group (28%) had disease flare ($P = 0.003$) • Rates of flare were constant and significantly lower in ETA group ($P < 0.001$) after adjustment for baseline effects • At study endpoint , 72% of ETA group and 23% of placebo group met definition of 50% improvement (P = NR) • Over 4 years the rate of serious adverse events 0.13 per patient year; the rate of serious infections 0.04 per patient-year.			

Authors: Lovell et al. **Year: 2000; 2003; 2006**				
ADVERSE EVENTS:	**Open label**	**Double-blind portion**	**Extension 2 years**	**Extension 4 years**
Overall adverse effects reported:	NR	NR	NR	NR
▪ **Serious adverse events requiring hospitalization**	3%	NR	16% NR	NR NR
• ISR	39%	4%	NR	NR
• URTI	35%	NR	NR	NR
• Headache	20%	NR	NR	NR
• Abdominal pain	16%	NR	NR	NR
• Vomiting	14%	NR	NR	NR
• Rash	10%	NR	NR	NR
• Varicella-Zoster virus	NR	NR	5% requiring hospitalization	NR

Significant differences in adverse events:	Unable to determine- NR				
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No				
ADEQUATE RANDOMIZATION:	Yes				
ADEQUATE ALLOCATION CONCEALMENT:	NR				
BLINDING OF OUTCOME ASSESSORS:	NR				
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** Yes				
ATTRITION (*treatment specific*):	**Open label**	**ETA**	**Placebo**	**Extension 2 years**	**Extension 4 years**
Loss to follow-up:	5	6 (24%)	19 (63%)	10 (17%)	24 (42%)
Withdrawals due to adverse events:	1	6- Disease flare	18-Disease flare	2-Adverse events 7-lack of efficacy	4-Adverse events 6-lack of efficacy
QUALITY RATING:	**Fair**				

Evidence Table 2. Targeted Immune Modulators – Juvenile Idiopathic Arthritis

STUDY:	**Authors: Lovell et al.**[63] **Year: 2008** **Country:** Multinational					
FUNDING:	Abbott Labs					
RESEARCH OBJECTIVE:	Efficacy and safety of ADA, in children with polyarticular-course juvenile rheumatoid arthritis					
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 171					
INTERVENTION:	**Open MTX**	**Open No**	**MTX Pla**	**MTX ADA**	**No Pla**	**No ADA**
Dose:	24 mg/m eow	24 mg/m eow	N/A	24 mg/m eow	N/A	24 mg/m eow
Duration:	16 wks	16 wks	32 wks	32 wks	32 wks	32 wks
Sample size:	85	86	37	38	28	30
INCLUSION CRITERIA:	4 to 17 years of age with polyarticular-course juvenile rheumatoid arthritis who had active disease (at least five swollen joints and at least three joints with limitation of motion) that had not responded adequately to treatment with NSAIDs					
EXCLUSION CRITERIA:	Clinically significant deviations in hematologic, hepatic, or renal indicators; ongoing infection or had recently had a major infection requiring hospitalization or intravenous antibiotics; recent live or attenuated vaccines; previously treated with other biologic agents at any time or recently treated with intravenous immune globulin, cytotoxic agents, investigational agents, DMARDs other than MTX, or corticosteroids administered by the intraarticular, intramuscular, or intravenous route.					
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable dosages of NSAIDs and low-dose corticosteroids, pain medications were also allowed except for the 12 hours preceding an assessment of the joints.					

Authors: Lovell et al.
Year: 2008

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: Moderate-severe

	Open MTX	Open No	MTX Pla	MTX ADA	No Pla	No ADA
Mean age (years):	11.4	11.1	10.8	11.7	11.3	11.1
Sex (% female):	80	78	81	79	71	77
Ethnicity (% Caucasian):	95	88	97	95	96	87
Other germane population qualities:						
• Mean disease duration	4.0	3.6	4.0	4.3	2.9	3.6
• DMARD use (%)	9	9	19	3	11	13
• MTX use (%)	100	21	100	100	14	27
• Corticosteroids use (%)	5	2	5	5	4	0

OUTCOME ASSESSMENT:

Primary Outcome Measures: percentage of patients not receiving MTX who had a disease flare during the double-blind phase of the study (weeks 16 to 48).

Secondary Outcome Measures: ACR Pedi 30, 50, 70, 90, 100

Timing of assessments: screening, at baseline (day 1), between days 2 and 10, at weeks 2 and 4, and every 4 weeks through week 48 or withdrawal from the study.

RESULTS:

Health Outcome Measures:

- Open label portion
- ACR Pedi at week 16 ADA ACR PEDI 30 74% ACR PEDI 50 64% ACR Pedi 70 46% ACR Pedi 90 26%
- ACR Pedi at week 16 ADA+MTX ACR PEDI 30 94% ACR PEDI 50 91%ACR Pedi 70 71% ACR Pedi 90 28%
- 48 weeks (Double blinded portion)
- No MTX disease flares ADA 13 of 30 [43%] vs. placebo 20 of 28 [71%], *P*=0.03
- MTX disease flares, ADA 14 of 38 (37%) vs. placebo 24 of 37 (65%) (*P*=0.02)

Authors: Lovell et al. **Year: 2008**						
ADVERSE EVENTS per pt yr of exposure:	**Open MTX**	**Open No**	**MTX Pla**	**MTX ADA**	**No Pla**	**No ADA**
Overall adverse effects reported:	15.5	15.3	10.3	12.8	14.4	11.9
• ISR	5.2	5.7	3.8	4.0	1.9	4.9
• Contusion	0.5	0.2	0.5	0.7	0.5	0.1
• Nasopharyngitis	0.2	0.1	0.4	0.3	0.5	0
• URTI	0.3	0.4	0.3	0.3	0.6	0.4
• Viral infection	0.3	0.3	0.2	0.4	0.4	0.6
• Vomiting	0.2	0.1	0.1	0.2	0.1	0
• Excoriation	0.2	0.2	0.1	0.6	0.2	0.4
Significant differences in adverse events:	NR					
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR					
ADEQUATE RANDOMIZATION:	NR					
ADEQUATE ALLOCATION CONCEALMENT:	NR					
BLINDING OF OUTCOME ASSESSORS:	Yes					
ATTRITION (*overall*):	**Overall attrition:** 25% overall 6% open label **Attrition differential high:**					
ATTRITION (*treatment specific*):	**Open MTX**	**Open No**	**MTX Pla**	**MTX ADA**	**No Pla**	**No ADA**
Attrition overall:	2%	10%	3%	8%	0	3%
Attrition due to adverse events:	1%	2%	0	0	0	0
QUALITY RATING:	**Fair**					

Evidence Table 2. Targeted Immune Modulators – Juvenile Idiopathic Arthritis

STUDY:	**Authors: Ruperto et al.**[64] **Year: 2007** **Country:**	
FUNDING:	Centocor	
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of INF in the treatment of juvenile rheumatoid arthritis (JRA).	
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 122	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF + MTX** 3 mg/kg 14 weeks 62	**Placebo + MTX** N/A 14 weeks 60
INCLUSION CRITERIA:	At least 4 years but no more than 18 years old, a diagnosis of JRA, suboptimal response to MTX after 3 months, at least 5 active joints, and no active systemic symptoms.	
EXCLUSION CRITERIA:	Active uveitis, serious infection including tuberculosis, malignancy, or prior treatment with any TNF inhibitor.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX and intraarticular corticosteroid injections, low-dose corticosteroids , 1 NSAID, 1 analgesic that was not an NSAID, folic acid prophylaxis (required for all patients taking MTX), and narcotic or opioid analgesics	

Authors: Ruperto et al. **Year: 2007**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe	
	INF + MTX	**Placebo + MTX**
Mean age (years):	11.3	11.1
Sex (% female):	88.3	79.0
Ethnicity:	86.2	88.3
Other germane population qualities:		
• Tender joint count	NR	NR
• Swollen joint count	NR	NR
• Mean disease duration	4.2	3.6
• DMARD use (other than MTX) (%)	40	31.1
• MTX use (%)	100	100
• Corticosteroids use (%)	43.3	34.4
• DAS score	NR	NR
• C-HAQ score	1.2	1.2
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR Pedi 30 **Secondary Outcome Measures:** ACR Pedi 50 and ACR Pedi 70 and # patients with 0 joints with active arthritis **Timing of assessments:** "… recorded throughout the study"	
RESULTS:	**Health Outcome Measures:** ACR Pedi 30 - INF 37 of 58 [63.8%] versus placebo 29 of 59 [49.2%] $P = 0.12$ ACR Pedi 50 - INF 29 of 58 [50%] versus placebo 20 of 59 [33.9%]; $P = 0.078$ ACR Pedi 70 - INF 13 of 58 [22.4%] versus placebo 7 of 59 [11.9%]; $P = 0.130$ Number of joints with active arthritis INF vs. placebo $P = 0.016$	

Authors: Ruperto et al. **Year: 2007**		
ADVERSE EVENTS: **Overall adverse effects reported:** • **Serious adverse events** • Infections • Serious infections • Infusion reactions	**INF + MTX (0-52 weeks)** 96.7% 31.7% 68.3% 8.3% 9.1%	**Placebo + MTX (0-14 weeks)** 81.7% 5.0% 46.7% 3.3% 3.4%
Significant differences in adverse events:	N/A- denominators are different	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 5	
ADEQUATE RANDOMIZATION:	Yes	
ADEQUATE ALLOCATION CONCEALMENT:	Method NR	
BLINDING OF OUTCOME ASSESSORS:	Method NR	
ATTRITION (*overall*):	**Overall attrition:** 4% at 14 weeks, 19% at 52 weeks **Attrition differential high:** No	
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**INF + MTX** 3% at 14 weeks 0 at 14 weeks	**Placebo + MTX** 5% at 14 weeks 0 at 14 weeks
QUALITY RATING:	**Fair**	

Evidence Table 2. Targeted Immune Modulators – Juvenile Idiopathic Arthritis

STUDY:	**Authors: Ruperto et al.**[65,66] **Year: 2008, 2010** **Country:** Europe, Latin America and USA		
FUNDING:	Bristol-Myers Squibb		
RESEARCH OBJECTIVE:	To assess the safety and efficacy of ABA, in children with juvenile idiopathic arthritis who had failed previous treatments.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 190 run- in phase; and 122 RCT		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Open label run-in** 10 mg/kg days 1,15,29,57,85 4 months 190	**ABA** 10 mg/kg every 28 days 6 months 60	**Placebo** NA 6 months 62
INCLUSION CRITERIA:	Age 6 – 17 years; $\geq$ 5 active joints (those with swelling or, in the absence of swelling, limited range of motion, accompanied by either pain or tenderness) and active disease (at least two active joints and two joints with a limited range of motion)patients with inadequate response or intolerance to at least one DMARD, including biological agents		
EXCLUSION CRITERIA:	Active uveitis, major concurrent medical conditions; pregnant or lactating.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable MTX and folinic acid or folic acid.		

Authors: Ruperto et al. **Year: 2008, 2010**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Mild-moderate-severe		
	Open label	**ABA**	**Placebo**
Mean age (years):	12.4	12.6	12.0
Sex (% female):	72	72	73
Ethnicity:	77% white, 8% black, 15% other	77% white, 8% black, 15% other	79% white, 7% black, 15% other
Other germane population qualities:			
• Active joint count	12.7	12.6	12.0
• Swollen joint count	NR	NR	NR
• Mean disease duration	4.4	3.8	3.9
• DMARD use (%)	NR	NR	NR
• MTX use (%)	74	80	74
• Corticosteroids use (%)	NR	NR	NR
• DAS score	NR	NR	NR
• HAQ score	CHAQ 1.3	1.3	1.2
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Time to flare of juvenile idiopathic arthritis **Secondary Outcome Measures:** Proportion of patients who had disease flare; the changes from baseline in each of the six ACR core variables; and assessment of safety and tolerability, HRQOL via CHQ, pain, sleep quality, and participation in daily activity assessments **Timing of assessments:** screening, baseline, and at each dosing visit in the 4-month open-label lead-in period (days 1, 15, 29, 57, 85, 113) and the 6-month double-blind period (days 29, 57, 85, 113, 141, 169).		
RESULTS:	**Health Outcome Measures: ABA versus placebo at end of 6 month double blind period** • **Time to flare** - insufficient events to analyze * • Proportion of patients having flare - 12 (20%) vs. 33 (53%) *P* = NR • 30% or greater improvement at end, 49 (82%) vs. 43 (69%) *P* = 0.1712 • 50% or greater improvement at end, 46 (77%) vs. 32 (52%) *P* = 0.0071		

	• 70% or greater improvement at end, 32 (52%) vs. 19 (31%) *P* = 0.0185 • 90% or greater improvement at end, 24 (40%) vs. 10 (16%) *P* = 0.0062 • Inactive disease status 18 (30%) vs. 7 (11%) *P* = 0.0195 • Children's missed less school days per month 0.55 vs. 1.61 *P* = 0.033 • Parents' missed usual activity days per month 0.50 vs. 1.93 *P* = 0.109 • C-HAQ 0.5 (0.7) vs. 0.7 (0.7) *P* = NR • CSHQ total 42.8 (5.8) vs. 45.0 (6.0) *P* = 0.076 • No differences in sleep quality (*P* = 0.076) • No differences in pain reduction (*P* = 0.105)

Authors: Ruperto et al. **Year: 2008, 2010**			
ADVERSE EVENTS:	**Open label**	**ABA**	**Placebo**
Overall adverse effects reported:	70%	62%	55%
• Infections	36%	45%	44%
• Nausea	10%	3%	7%
• Headache	13%	5%	2%
• Cough	9%	0	3%
• Diarrhea	9%	2%	2%
Significant differences in adverse events:	None		
ANALYSIS:	**ITT:** Yes (no ITT-analysis for quality of life data) **Post randomization exclusions:** none		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 11% in open label run-in phase, 34% in RCT **Attrition differential high:** Yes		
ATTRITION (*treatment specific*):	**Open label**	**ABA**	**Placebo**
Overall attrition:	11%	18.3%	50%
Attrition due to adverse events:	0.5%	0	0
QUALITY RATING:	**Fair**		

Evidence Table 2. Targeted Immune Modulators – Juvenile Idiopathic Arthritis

STUDY:	**Authors: Yokota et al.**[67] **Year: 2008** **Study name: NA** **Country:** Japan **Quality rating: Fair**	
FUNDING:	Chugai Pharmaceuticals	
RESEARCH OBJECTIVE:	To examine the efficacy and safety of tocilizumab in children with juvenile idiopathic arthritis	
DESIGN & SIZE:	**Study design:** Randomized, double-blind, placebo-controlled trial **Setting:** 8 university hospitals and children's hospitals in Japan **Number screened:** NR **Number eligible:** NR **Number enrolled:** 56 **Run-in/Wash-out period:** 6 wk open-label lead-in	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**TOC** 8 mg/kg 12 wks 20	**Placebo** NA 12 wks 23
INCLUSION CRITERIA:	• 2-19 yrs of age • Onset of JIA before 16th birthday • Met the ILAR classification for systemic-onset JIA • Doses of oral corticosteroids had to be stable for 2 wks before the trial	
EXCLUSION CRITERIA:	• Treatment with intra-articular corticosteroids, methylprednisolone pulse treatment, immunosuppressive drugs, and DMARDs for 2 wks before first administration of TOC • Treatment with TNF agents was not allowed for 12 wks before patients started TOC • Patients with important concurrent medical or surgical disorders, with leucopenia or thrombocytopenia, cardiac disease, or developed macrophage-activation syndrome during the pre-study hospital admission	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids	

Authors: Yokota et al. **Year: 2008**		
POPULATION CHARACTERISTICS:	**TOC**	**Placebo**
Mean age (years):	8.0	9.3
Sex (% female):	65	65
Ethnicity:	NR	NR
Class naïve:		
Other germane population qualities:		
• **Duration of disease (yrs)**	4.6	4.7
• **TJC**	NR	NR
• **SJC**	NR	NR
• **DMARD use (%)**	NR	NR
• **MTX use (%)**	NR	NR
• **Previously received oral corticosteroids (%)**	100	100
• **DAS score**	NR	NR
• **HAQ score**	NR	NR
RESULTS:	**Primary Outcome Measures:** Disease flare base on ACR Pedi 30 After 12 weeks, 80% of the patients in the tocilizumab group and 17% of the patients in the placebo (P<0.0001) group maintained an ACR Pediatric Scale 30 response and C-reactive protein concentrations of less than 15 mg/L	

<table>
<tr><td colspan="3">Authors: Yokota et al.
Year: 2008</td></tr>
<tr><td>METHOD OF ADVERSE EVENTS REPORTING:</td><td colspan="2">Routine physical examinations every day during stay at hospital</td></tr>
<tr><td>ADVERSE EVENTS:</td><td colspan="2">Overall</td></tr>
<tr><td>Overall adverse effects reported:</td><td colspan="2">Adverse events frequently reported were symptoms of upper-respiratory-tract infections and gastroenteritis, but not of tuberculosis. In the double-blind phase, the occurrence of gastroenteritis was similar in the tocilizumab group (one [5%] of 21 patients) and placebo (one [4%] of 23 patients) groups, whereas the frequency of upper-respiratory-tract infection was increased in the placebo group (four [17%] of 23 patients) versus the tocilizumab group (two [10%] of 21 patients). Ten patients had mild infusion reactions during the open-label lead-in phase. Development of antitocilizumab IgE antibodies was noted in four patients.

In the open-label extension phase of the study, 13 serious adverse events were noted, which included bronchitis, gastroenteritis, and an anaphylactoid reaction (leading to patient withdrawal). The cases of bronchitis (n=2) and gastroenteritis (n=2) resolved with antibiotic treatment. The most common adverse events were nasopharyngitis (33 [59%]), upper-respiratory-tract infection (19 [34%]), gastro enteritis (16 [29%]), and bronchitis (14 [25%] of 56 patients). Increases in alanine aminotransferase (16 [29%]), aspartate aminotransferase (12 [21%]), and LDH (10 [18%]) were noted; increases of at least grade 2 in alanine aminotransferase and aspartate aminotransferase were recorded in 12 and eight patients, respectively. Transaminases tended to increase early during tocilizumab administration and then to subside during continuation of treatment. Mild increases, mostly within the normal range, in total cholesterol were noted. Tuberculosis was not reported.</td></tr>
<tr><td>ATTRITION (overall):

ATTRITION (treatment specific):
Attrition overall:
Attrition due to adverse events:</td><td colspan="2">Overall attrition: Of 44 randomized, 24 (54.5%) did not complete the double-blind phase
Attrition differential high:</td></tr>
<tr><td></td><td><u>TOC</u>
1 withdrawn, 3 early escape
1 withdrawn due to infectious mononucleosis associated with striking increases in liver enzymes and neutropenia</td><td><u>Placebo</u>
1 withdrawn, 18 early escape
1 withdrawn due to herpes zoster</td></tr>
</table>

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 3. Targeted Immune Modulators – Ankylosing Spondylitis

STUDY:	**Authors: Barkham et al.**[68] **Year: 2010** **Study name: -** **Country:** UK **Quality rating: FAIR**	
FUNDING:	Wyeth Pharmaceutical (pharmaceutical industry)	
RESEARCH OBJECTIVE:	To determine whether etanercept improves work instability as measured by the Ankylosing Spondylitis Work Instability Scale (AS-WIS)	
DESIGN & SIZE:	**Study design:** double-blinded RCT **Setting:** Leeds Teaching Hospital Trust. Leeds, UK, outpatients **Number screened:** 52 **Number eligible:** 40 **Number enrolled:** 40 **Run-in/Wash-out period:** no	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg twice weekly 12 weeks 20	**PLA** NA 12 weeks 20
INCLUSION CRITERIA:	Definite diagnosis of AS by modified New York Criteria and active disease as defined by at least 2 of the following: a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥40 (0-100), a pain score of ≥40 on a 100-mm visual analog scale, and early morning stiffness lasting ≥45 minutes. All were in work but were work unstable (AS-WIS score > 10)	
EXCLUSION CRITERIA:	past or current tuberculosis, congestive heart disease, treatment with glucocorticoids in the previous month	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	DMARDs (sulfasalazine, methotrexate), Oral NSAIDs	

Authors: Barkham et al. **Year: 2010**		
POPULATION CHARACTERISTICS:	**ETA**	**PLA**
Mean age (years):	40.8	28.2
Sex (% female):	15%	25%
Ethnicity:	NR	NR
Class naïve:	NR	NR
Other germane population qualities:		
• **DMARD use (%)**	NR	NR
• **MTX use (%)**	NR	NR
• **Corticosteroids use (%)**	NR	NR
• **BASDAI score (mean)**	NR	NR
• **BASFI score (mean)**	NR	NR

RESULTS:

Primary Outcome Measures:

No significant difference in the AS-WIS improvement in the etanercept group (-2.75) compared with the placebo group (-0.68) (*P* = 0.125)

Risk of job loss decreased for 11 (55%) of the etanercept group compared with 7 (35%) in the placebo group; risk of job loss increased for 1 (5%) of the etanercept group compared with 3 (15%) of the placebo group; (*P* = 0.160)

Secondary Outcome Measures:

	Etanercpt	Placebo	
BASDAI	**-1.97 (-2.98 to -0.97)**	**-0.10 (-1.11 to 0.90)**	**(P = 0.012)**
BASFI	**-1.35 (-2.20 to -0.50)**	**0.21 (-0.64 to 1.06)**	**(P = 0.012)**
ASQoL	**-3.26 (-5.16 to -1.37)**	**-0.11 (-2.01 to 1.78)**	**(P = 0.024)**
HAQ-DI	**-0.232 (-0.395 to -0.070)**	**0.020 (-0.142 to 0.182)**	**(P = 0.033)**

Authors: Barkham et al. **Year: 2010**		
METHOD OF ADVERSE EVENTS REPORTING:	Only reported in the additional data file: No specific method reported	
ADVERSE EVENTS (%):	**ETA**	**PLA**
Overall adverse effects reported:	95%	80%
• infections	45%	60%
• URTI	NR	NR
• abnormal LFT	NR	NR
• herpes simplex	NR	NR
• pneumonia	NR	NR
• tb	NR	NR
• ISR	0%	5%
• allergy	5%	NR
ATTRITION (*overall*):	**Overall attrition:** **Attrition differential high:**	
ATTRITION (*treatment specific*):	**ETA**	**PLA**
Attrition overall:	0%	0%
Attrition due to adverse events:	0%	0%

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 3. Targeted Immune Modulators – Ankylosing Spondylitis

STUDY:	**Authors: Deodhar et al.[69] and Inman et al.[70]** **Year: 2010** **Study name: GO-RAISE** **Country:** US, Canada, Europe, Asia **Quality rating: GOOD**		
FUNDING:	Centocor Research and the Schering-Plough Research Institute (pharmaceutical industry)		
RESEARCH OBJECTIVE:	Inman et al.: to evaluate the efficacy and safety of golimumab in patients with ankylosing spondylitis Deodhar et al.: to evaluate the effect of golimumab on sleep disturbance in patients with active ankylosing spondylitis (AS)		
DESIGN & SIZE:	**Study design:** RCT **Setting:** multicenter study, outpatients **Number screened:** 457 **Number eligible:** NR **Number enrolled:** 356 **Run-in/Wash-out period:** NR		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**GOL** 50 mg every 4 weeks 16/24 weeks 138	**GOL** 100 mg every 4 weeks 16/24 weeks 140	**PLA** every 4 weeks 16/24 weeks 78
INCLUSION CRITERIA:	Adult patients who had AS (diagnosed according to the modified New York Criteria) for ≥3 months, a Bath AS Disease Activity Index (BASDAI) score of ≥4 (0–10-point scale), a spinal pain assessment score of ≥4 on a visual analog scale (VAS; 0–10-cm scale), and an inadequate response to current or previous NSAIDs or DMARDs. Patients were also required to have normal results of a chest radiograph within 3 months before randomization and to have undergone screening for latent tuberculosis (TB) using a purified protein derivative skin test and the QuantiFERON TB Gold test.		
EXCLUSION CRITERIA:	complete ankylosis of the spine, any other inflammatory rheumatic disease, a serious infection within 2 months before randomization, active or latent TB or positive results of a tuberculin skin test before screening or recent contact with a person with active TB, an opportunistic infection within 6 months of screening, hepatitis, human immunodeficiency virus, a transplanted organ, malignancy, multiple sclerosis, or congestive heart failure		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	methotrexate (MTX), sulfasalazine, hydroxychloroquine, corticosteroids, and NSAIDs at stable doses		

Authors: Deodhar et al. and Inman et al. **Year: 2010, 2008**			
POPULATION CHARACTERISTICS:	**GOL 50 mg**	**GOL 100 mg**	**PLA**
Mean age (years):	38	38	41
Sex (% female):	26%	30%	30%
Ethnicity (white):	75%	73%	73%
Class naïve:	NR	NR	NR
Other germane population qualities:			
• **DMARD use (%)**	NR	NR	NR
• **MTX use (%)**	21.0%	20.0%	19.2%
• **Corticosteroids use (%)**	26%	18%	13%
• **BASDAI score (mean)**	6.6	7.0	6.6
• **BASFI score (mean)**	5.0	5.4	4.9
RESULTS:	**Primary Outcome Measures:** 59.4% in the 50-mg golimumab group and 60.0% in the 100-mg golimumab group achieved an ASAS20 response at week 14 compared with 21.8% in the placebo group (P < 0.001). **Secondary Outcome Measures:** Patients in the golimumab 50- and 100-mg groups had a significantly greater reduction from baseline in JSEQ scores at week 14 compared with the placebo group (*P* < 0.001). The mean reduction was -3 in both golimumamb and 0 in the placebo group. The mean reduction in the BASFI score was -1.4 in the golimumab 50-mg group and -1.5 in the golimumab 100-mg group compared with 0.1 in the placebo group (*P* < 0.001). Significantly more golimumab-treated patients achieved ≥50% improvement in the BASDAI score at week 14 compared with patients who received placebo (45.9% for 50 mg- and 40.9% for 100 mg compared with 15.4% in the placebo group).		

Authors: Deodhar et al. and Inman et al. **Year: 2010, 2008**			
METHOD OF ADVERSE EVENTS REPORTING:	NR		
ADVERSE EVENTS (%):	**GOL (all)**	**PLA**	
Overall adverse effects reported: • infections • URTI • abnormal LFT • herpes simplex • pneumonia • tb • ISR • Any serious infection • •	79.9% 45.1% 12.2% NR NR NR NR 7.2% 0.6%	76.6% 36.4% 7.8% NR NR NR NR 2.6% 1.3%	
ATTRITION (*overall*):	**Overall attrition:** 5% **Attrition differential high:** no		
ATTRITION (*treatment specific*):	**GOL 50 mg**	**GOL 100 mg**	**PLA**
Attrition overall:	7%	4%	3%
Attrition due to adverse events:	3%	3%	1%

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 3. Targeted Immune Modulators – Ankylosing Spondylitis

STUDY:	**Authors: Dougados et al.**[71] **Year: 2011** **Study name: SPINE** **Country:** Hungary, Germany, France, The Netherlands **Quality rating: Fair**	
FUNDING:	Wyeth Pharmaceuticals	
RESEARCH OBJECTIVE:	To evaluate the effect of etanercept (ETA) in patients with advanced AS	
DESIGN & SIZE:	**Study design:** Randomized double-blind placebo-controlled study **Setting:** multicenter (21 centers) **Number screened: 95** **Number eligible: 82** **Number enrolled: 82** **Run-in/Wash-out period: NA**	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 12 wks 43	**ETA** 50 mg subcutaneous injection 1 x week 12 wks 39
INCLUSION CRITERIA:	• Men and women 18-70 yrs old • Patients had a current diagnosis of AS (as defined by modified New York criteria) • Patients met criteria defining advanced and severe AS (evaluated by investigator as screening) • Patients had to have a baseline pain with axial involvement of the overall level of AS neck, back or hip for a score ≥30 on a 0-100 mm VAS • Patients had to have an active refractory disease defined by a score ≥40 on the BASDAI despite optimal NSAID treatment	
EXCLUSION CRITERIA:	• Patients previously exposed to a TNF inhibitor • Patients whose NSAID dose changed within 2 wks of baseline evaluation • Patients whose dose of concomitant conventional DMARD (if taken) had changed with 4 wks of baseline evaluation • Patients were also excluded if they had significant concurrent medical disorders and/or abnormal laboratory test results	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	• NSAIDs • DMARD	

Authors: Dougados et al. **Year: 2011**		
POPULATION CHARACTERISTICS:	**Placebo**	**ETA**
Mean age (years):	48±10	46±10
Sex (% female):	.09%	.05%
Ethnicity:	NR	NR
Class naïve:		
Other germane population qualities:		
• **DMARD use (%)**	NR	NR
• **MTX use (%)**	NR	NR
• **Corticosteroids use (%)**	NR	NR
• **BASDAI score (mean)**	58±15	64±12
• **BASFI score (mean)**	57±19	63±20
RESULTS:	**Primary Outcome Measures:** ASAS20: ETA 14 responders (33%); Placebo 25 responders (67%); *P*=0.003 ASAS40: ETA 10 responders (23%); Placebo 17 responders (44%); *P*=0.053 ASAS5/6: ETA 2 responders (5%); Placebo 8 (21%); *P*=0.044 ASAS partial remission: ETA 2 (5%); Placebo 7 (18%); *P*=0.073 BASDAI 50: ETA 10 responders (23%); Placebo 18 (46%); *P*=0.031 **ASDAS-CRP changes (W12-baseline)** ASDAS ≥1.1 (minimally important improvement): ETA 7 responders (17.1); Placebo 25 responders (64.1); *P*= <0.0001 ASDAS ≥2.0 (major improvement): ETA 1 (2.4) responders; Placebo 15 (38.5) responders; *P*=<0.0001 **ASDAS-CRP status at W12** ASDAS <1.3: ETA 2 (4.7%) responders; Placebo 5 (12.8%) responders; *P*=0.249 ASDAS <2.1: ETA 5 (11.6%) responders; Placebo 16 (41.0%) responders; *P*=0.005	

Authors: Dougados et al. **Year: 2011**		
METHOD OF ADVERSE EVENTS REPORTING:	NR	
ADVERSE EVENTS (%):	**Placebo**	**ETA**
Overall adverse effects reported:		
• infections	NR	NR
• URTI	NR	NR
• abnormal LFT	NR	NR
• herpes simplex	NR	NR
• pneumonia	NR	NR
• tb	NR	NR
• ISR	NR	NR
ATTRITION (*overall*):	**Overall attrition:** 6% **Attrition differential high:**	
ATTRITION (*treatment specific*):	**Placebo**	**ETA**
Attrition overall:	9%	3%
Attrition due to adverse events:	0%	3%

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 3. Targeted Immune Modulators – Ankylosing Spondylitis

STUDY:	**Authors: Inman et al.**[72] **Year: 2010** **Study name: CANDLE** **Country:** Canada **Quality rating: Fair**	
FUNDING:	Schering-Plough Canada Inc	
RESEARCH OBJECTIVE:	Safety and efficacy of low-dose (3 mg/kg q8w) IFX therapy in AS at 12 weeks and one year.	
DESIGN & SIZE:	**Study design:** RCT **Setting:** Multicenter (8 – all in Canada) **Number screened: 99** **Number eligible: 76** **Number enrolled:76** **Run-in/Wash-out period: NR**	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 12 weeks 37	**Infliximab** 3 mg/kg (given at weeks 0, 2, 6 and then every 8 weeks) 12 weeks 39
INCLUSION CRITERIA:	≥ 18 years of age at the time of screening, previously diagnosed with AS according to the modified New York criteria12 and have active disease (BASDAI score ≥ 4) at baseline and at screening. In those patients taking nonsteroidal antiinflammatory drugs (NSAID), disease-modifying antirheumatic drugs (DMARD), analgesics, or corticosteroids, the dose must have been stable for at least 14 days (30 days for DMARD) prior to the first infusion of study drug.	
EXCLUSION CRITERIA:	History of chronic/recurrent infectious disease, including tuberculosis, hepatitis B, or HIV, and/or a diagnosis of malignancy or lymphoproliferative disease currently or within the past 5 years.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes, NSAIDs and DMARDs at stable doses	

Authors: Inman et al. **Year: 2010**		
POPULATION CHARACTERISTICS:	**Placebo**	**Infliximab**
Mean age (years): **Sex (% female):** **Ethnicity:** **Class naïve:** Other germane population qualities: • **DMARD use (%)** • **MTX use (%)** • **Corticosteroids use (%)**	39.3 22 89% caucasian NR NR NR	42.9 18 87% caucasian NR NR NR
RESULTS:	**Primary Outcome Measures:** ASAS20 12 weeks Infliximab 53.8% (N=21/39) vs. placebo 30.6% (N=11/37) group ($P = 0.042$) **Secondary Outcome Measures:** 12 weeks ASAS40 Infliximab 46.2% vs placebo 8.3% $P < 0.001$ ASAS50 Infliximab 41.0% vs 5.6%; $P < 0.001$ ASAS70 Infliximab 20.5% (N=8/39) vs placebo 0% (N=0/37); $P = 0.005$ ASAS 5/6 Infliximab 51.3% (N=20/39) vs. placebo 2.8% (N=1/37) $P < 0.001$ mean change in BASDAI Infliximab –2.1 vs. placebo –0.7; $P = 0.003$ 50% improvement BASDAI scores Infliximab 28.2% (N=11/39) placebo 11.1% (N=4/37) $P = 0.064$ Mean change (±SD) in BASMI: infliximab -0.45 (±1.03) vs. Placebo 0.24 (±0.60) SF-36 survey Infliximab vs. placebo $P < 0.05$ "…for a number of domains, including role physical, bodily pain, vitality, social functioning, and mental health." (Data = NR)	

Authors: Inman et al. **Year: 2010**		
METHOD OF ADVERSE EVENTS REPORTING:	AEs were only reported at 50 weeks thus all patients were treated with infliximab	
ADVERSE EVENTS (%):	**Placebo**	**Infliximab**
Overall adverse effects reported:	NR	NR
ATTRITION (*overall*):	**Overall attrition:** 10 (13%) **Attrition differential high:** No	
ATTRITION (*treatment specific*):	**Placebo**	**Infliximab**
Attrition overall:	3	7
Attrition due to adverse events:	2	0

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 3. Targeted Immune Modulators – Ankylosing Spondylitis

STUDY:	**Authors: McLeod et al.**[73] **Year:** 2007 **Country:** Multinational
FUNDING:	The HTA Programme on behalf of NICE
DESIGN:	**Study design:** Systematic review and meta-analysis **Number of patients:** 1611
AIMS OF REVIEW:	To assess the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis (AS)
STUDIES INCLUDED IN META-ANALYSIS	9 placebo-controlled RCTs (2 of adalimumab, 5 of etanercept and 2 of infliximab)
TIME PERIOD COVERED:	Up to November, 2005
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs comparing an anti-TNFα agent (adalimumab, etanercept or infliximab) with placebo
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adults diagnosed with active AS

Authors: McLeod et al. **Year:** 2007 **Country:** Multinational	
CHARACTERISTICS OF INTERVENTIONS:	ADA (40 mg every 2 wks), ETA (25 mg twice/wk), or INF (5 mg/kg) vs. placebo
MAIN RESULTS:	Adalimumab vs. placebo ASAS 20 at 12 weeks RR (95% CI): 2.43 (1.76, 3.35); *P* < 0.00001 ASAS 70 at 12 weeks RR (95% CI): 5.47 (2.43, 12.31); *P* <0.00001 Etanercept vs. placebo ASAS 20 at 12 weeks RR (95% CI): 2.13 (1.73, 2.63); *P* < 0.00001 ASAS 20 at 24 weeks RR (95% CI): 2.53 (1.80, 3.57); *P* < 0.00001 ASAS 70 at 12 weeks RR (95% CI): 3.38 (2.10, 5.45) BASDAI score reduction at 12 weeks WMD (95% CI): -1.67 (-2.10, -1.24) BASDAI score reduction at 24 weeks WMD (95% CI): -2.00 (-2.61, -1.39) BASDAI % reduction at 12 weeks WMD (95% CI): -1797 (-23.37, -12.58) Infliximab vs. placebo ASAS 20 at 12 weeks RR (95% CI): 4.11 (2.62, 6.44); *P* < 0.00001 ASAS 20 at 24 weeks RR (95% CI): 3.18 (1.99, 5.08); *P* < 0.00001 Anti-TNF as a class vs. placebo ASAS 20 at 12 weeks RR (95% CI): 2.52 (2.14, 2.98); *P* < 0.00001 ASAS 20 at 24 weeks RR (95% CI): 2.80 (2.11, 3.71); *P* < 0.00001 ASAS 70 at 12 weeks RR (95% CI): 3.94 (2.61, 5.95); *P* < 0.00001 BASDAI at 12 weeks WMD (95% CI): -1.89 (-2.23, -1.55)
ADVERSE EVENTS:	NA
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes—the following electronic databases were searched: Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effectiveness (DARE), EMBASE, Health Technology Assessment (HTA) database, ISI Web of Science, MEDLINE and NHS Economic Evaluation database; reference lists of included studies and company submissions were also searched.
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Antoni et al.[74] and Kavanaugh et al.[75]** **Year: 2005, 2006** **Country:** Multinational	
FUNDING:	Centocor Inc and Schering-Plough	
RESEARCH OBJECTIVE:	The evaluation of infliximab with regards to efficacy, health related quality of life and physical function in patients with PsA. Patients with inadequate response at week 16 entered early escape.	
DESIGN:	**Study design:** RCT **Setting:** Clinical- 36 sites **Sample size:** 200	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 24 weeks 100	**INF** 5 mg/kg at weeks 0,2,6,14,22 24 weeks 100
INCLUSION CRITERIA:	Adults with active PsA (five or more swollen joints and five or more tender joints and either C reactive protein (CRP) levels of at least 15 mg/l and/or morning stiffness lasting 45 minutes or longer); diagnosed at least 6 months before the first infusion of study drug; an inadequate response to current or previous DMARDs or NSAIDs; patients had to have active plaque psoriasis with at least one qualifying target lesion at least 2 cm in diameter; negative test for RF in their serum.	
EXCLUSION CRITERIA:	Latent or active TB (that is, they had to have clear chest *x* ray findings and a negative purified protein derivative skin test); had chronic or clinically significant infection, malignancy, or CHF; or if they had used TNFα inhibitors previously.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable doses of MTX, oral corticosteroids, NSAIDs	

<table>
<tr><td colspan="3">Authors: Antoni et al. and Kavanaugh et al.
Year: 2005, 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: Yes, except for sex
Disease severity: Active plaque psoriasis and PsA (mean disease duration 8 years)</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>INF</u></td></tr>
<tr><td>Mean age (years):</td><td>46.5</td><td>47.1</td></tr>
<tr><td>Sex (% female):</td><td>49</td><td>29</td></tr>
<tr><td>Ethnicity:</td><td>94</td><td>95</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td></tr>
<tr><td>• Polyarticular arthritis</td><td>47</td><td>53</td></tr>
<tr><td>• DIP joints of hand/feet</td><td>23</td><td>26</td></tr>
<tr><td>• Asymmetric peripheral arthritis</td><td>22</td><td>18</td></tr>
<tr><td>• NSAID use (%)</td><td>73</td><td>71</td></tr>
<tr><td>• MTX use (%)</td><td>45</td><td>47</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>10</td><td>15</td></tr>
<tr><td>• SF-36 score (Physical/Mental)</td><td>31/47</td><td>33/45.5</td></tr>
<tr><td>• HAQ score</td><td>1.1</td><td>1.1</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: ACR20; HAQ; SF-36
Secondary Outcome Measures: ACR50/70; PsARC; PASI; dactylitis and enthesopathy
Timing of assessments: Weeks 0,2,6,14,22,24</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures (Placebo vs. INF):
• ACR 50 (%) at week 14 3 vs. 36 (P < 0.001) and week 24 4 vs. 41 (P < 0.001)
• ACR70(%) at week 14 1 vs. 15 (P < 0.001) and week 24 2 vs. 27 (P < 0.001)
• Achieving PsARC (%) at week 14 27 vs. 77 (P < 0.001) and week 24 32 vs. 70 (P < 0.001)
• HAQ (%) improvement at week 14 -18.4 vs. 48.6 (P < 0.001) and week 24 -19.4 vs. 46 (P < 0.001)
• SF-36 (change from baseline)
Physical week 14 1.1 vs. 9.1 (P < 0.001) and week 24 1.3 vs. 7.7 (P < 0.001)
Mental week 14-1.2 vs. 3.8 (P = 0.001) and week 24 0.4 vs. 3.9 (P = 0.047)
Intermediate Outcome Measures (Placebo vs. INF):
• ACR20 at Week 14 11% vs. 58% (P < 0.001) and Week 24 16% vs. 54% (P < 0.001)</td></tr>
</table>

Authors: Antoni et al. and Kavanaugh et al. **Year: 2005, 2006**		
ADVERSE EVENTS (%): **Overall adverse effects reported:** • URTI • Headache • Increased ALT • Pharyngitis • Sinusitis • Dizziness • Serious AEs • Infusion reactions	**Placebo n=97** 67 14 5 1 4 4 5 1 6 6	**INF n=150 (includes escape)** 67 10 6 6 5 5 4 4 9 7
Significant differences in adverse events:	None except for increased ALT (P = NR)	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No	
ADEQUATE RANDOMIZATION:	Yes	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	NR	
ATTRITION (*overall*):	**Overall loss to follow-up:** 7% **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Placebo** 8% 1%	**INF** 7% 4%
QUALITY RATING:	**Fair**	

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Antoni et al.**[76] and **Kavanaugh et al**.[77] **Year: 2005 and 2006** **Study name: IMPACT** (Infliximab Multinational Psoriatic Controlled Trial) **Country:** Multinational			
FUNDING:	NIH; Centocor, Inc.; Schering-Plough Research Institute; Competence Network "Inflammatory Rheumatic Diseases" of the German Federal Ministry of Education and Science			
RESEARCH OBJECTIVE:	To evaluate the efficacy and tolerability of infliximab therapy for the articular and dermatologic manifestations of active psoriatic arthritis (PsA).			
DESIGN:	**Study design:** RCT **Setting:** 9 sites in clinics **Sample size:** 104			
	Weeks 0-16		**Weeks 16-50**	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 16 weeks 52	**INF** 5 mg/kg at weeks 0,2,6,14 16 weeks 52	**Placebo/INF** 5 mg/kg every 8 weeks 34 weeks 50	**INF/INF** 5 mg/kg every 8 weeks 34 weeks 49
INCLUSION CRITERIA:	Previous failure of treatment with ≥ 1 DMARDs; active peripheral polyarticular arthritis, defined as the presence of ≥ 5 swollen and tender joints (based on joint counts of 66 and 68, respectively) in conjunction with at least 1 of the following criteria: ESR ≥28 mm/hour, CRP level ≥ 15 mg/liter, and/or morning stiffness lasting 45 minutes or longer; negative results of serum tests for RF and negative results for active or latent TB by purified protein derivative skin test and chest radiography.			
EXCLUSION CRITERIA:	Any investigational drug within 3 months, positive tests for RF or latent TB; previous treatment with monoclonal antibody or fusion protein.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX; dosage of 15 mg/week or more, with folic acid supplementation; leflunomide, sulfasalazine, hydroxychloroquine, intramuscular gold, penicillamine, or azathioprine stable for 4 weeks; oral corticosteroids (dosage of 10 mg prednisone equivalent/day or less); NSAIDs stable for at least 2 weeks.			

<table>
<tr><td colspan="3">Authors: Antoni et al.
Year: 2005</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: Generally, with the exception of CRP
Disease severity: Severe (mean disease duration 11.4 years)</td></tr>
<tr><td><u>Placebo</u></td><td><u>INF</u></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• Disease duration- years
• ACR 20 components
swollen joints
tender joints
• CRP mg/liter- mean(median)
• DAS
• PASI</td><td>45.2
42.3
NR

11

14.7
20.4
31.1(14.0)
5.4
4.2</td><td>45.7
42.3
NR

11.7

14.6
23.7
21.7(9.9)
5.5
5.1</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: ACR20 and modified van der Heijde-Sharp score for radiographic progression
Secondary Outcome Measures: PASI score; ACR50; ACR70; DAS; HAQ; ratings of enthesitis and dactylitis; the Psoriatic Response Criteria score.
Timing of assessments: 2,6,10,14,16, one year</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
• The proportion of INF patients that achieved a clinically significant response was significantly greater than the proportion of placebo patients at week 16 (All P < 0.001)
ACR50 Placebo 0/52 (0.0%) vs. INF 24/52 (46.2%)
ACR70 Placebo 0/52 (0.0%) vs. INF 15/52 (28.8%) # of tender joints Placebo -23.6 vs. INF 55.2
# of swollen joints Placebo -1.8 vs. INF 59.9 DAS Placebo 2.8 vs. INF 45.5 P < 0.001
HAQ Placebo -1.6 vs. INF 49.8 P < 0.001 PsARC Placebo -12% vs. INF +86% P < 0.001
• Treatment benefits were sustained through week 50
Intermediate Outcome Measures:
• The proportion of INF patients that achieved an ACR20 response was significantly greater than the proportion of placebo patients at week 16
Placebo 5/52 (9.6%) vs. INF 34/52 (65.4%) P < 0.001
• Mean (median) changes from baseline to week 50 in the total modified vdH-S score were –1.95 (–0.50) for PBO/IFX and –1.52 (–0.50) for IFX/IFX patients (p = NS).</td></tr>
</table>

Authors: Antoni et al. and Kavanaugh et al. **Year: 2005 and 2006**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Treatment related events • Infusion-associated All events Treatment-related events • Severe All events Treatment-related events • Serious All events Treatment-related events	**Placebo (-week 16)** 65 47 10 8 4 2 2 0	**INF 5 mg (-week 16)** 73 56 8 4 6 4 2 2	**INF 5 mg (week 16-50)** 84 69 8 8 12 6 16 6
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 5% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Placebo** 2 1	**INF** 3 2	
QUALITY RATING:	**Fair**		

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Kavanaugh et al.**[78] **Year: 2009** **Study name: GO-REVEAL** **Country:** USA **Quality rating:**		
FUNDING:	Centocor Research and Development, Inc. and Schering-Plough Corporation		
RESEARCH OBJECTIVE:	Assess efficacy and safety of GOL in patients with active PsA		
DESIGN & SIZE:	**Study design:** Placebo-controlled RCT **Setting: multicenter** **Number screened: 555** **Number eligible: 405** **Number enrolled: 405** **Run-in/Wash-out period: NA**		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Drug 1** Placebo, NA Every 4 weeks 113	**Drug 2** 50 mg every 4 weeks 146	**Drug 3** 100 mg every 4 weeks 146
INCLUSION CRITERIA:	• Treatment resistant active PsA despite therapy with DMARDs or NSAIDs (active PsA: ≥ 3 swollen and 3 tender joints, negative rheumatoid factor, at least 1 subset of PsA, presence of plaque psoriasis with lesion ≥ 2 cm in diameter) • Latent TB allowed if treated prior or concurrent to study		
EXCLUSION CRITERIA:	• Previous use of anti-TNF agents, RIT, natalizumab, or cytotoxic agents		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX, NSAIDs, corticosteroids allowed in stable doses		

Authors: Kavanaugh et al. **Year: 2009**			
POPULATION CHARACTERISTICS (%):	**Drug 1**	**Drug 2**	**Drug 3**
Mean age (years):	47.0	45.7	48.2
Sex (% female):	31	21	14
Ethnicity:	White: 97 Black/Lationo: NR	White: 97 Black/Lationo: NR	White: 97 Black/Lationo: NR
Class naïve:		100%	100%
Other germane population qualities:			
• **Polyarticular arthritis**	NR	NR	NR
• **DIP joints of hand/feet**	NR	NR	NR
• **Asymmetric peripheral arthritis**	NR	NR	NR
• **NSAID use (%)**	78	75	75
• **MTX use (%)**	48	49	47
• **Corticosteroids use (%)**	17	13	18
• **DAS28-CRP score, 0 - 10**	4.3 ± 1.0	4.4 ± 11	4.3 ± 1.0
• **HAQ score**	NR	NR	NR
RESULTS:	**Primary Outcome Measures:** **ACR response (% achieving response):** At Week 14: ACR 20: D1: 9 D2: 51 D3: 45 *P* < 0.001 (D1 vs. D2 and D3) At Week 24: ACR 20: D1: 12 D2: 52 D3: 61 *P* < 0.001 (D1 vs. D2 and D3) ACR 50 and ACR70 at weeks 14 and 24: shown in figure only		

	Secondary Outcome Measures: **PsARC, no. (%) achieving response:** At Week 14 D1: 24 (21) D2: 107 (73) D3: 105 (72) *P* < 0.001 (D1 vs. D2 and D3) At Week 24: D1: 33 (29) D2: 102 (70) D3: 124 (85) *P* < 0.001 (D1 vs. D2 and D3) **HAQ, mean change from baseline (SD)** At Week 24: D1: -0.01 (0.49) D2: 0.33 (0.55) D3: 0.39 (0.50) *P* < 0.001 (D1 vs. D2 and D3) **DAS, mean change (SD):** At Week 14: D1: -0.18 (0.78) D2: -1.38 (1.16) D3: -1.29 (1.16) *P* < 0.001 (D1 vs. D2 and D3) At Week 24: D1: -0.12 (0.97) D2: -1.43 (1.34) D3: -1.56 (1.10) *P* < 0.001 (D1 vs. D2 and D3) **EULAR response, %:** At week 14: D1: 27 D2: 96 D3: 98 *P* < 0.001 (D1 vs. D2 and D3)

	At week 24: D1: 27 D2: 94 D3: 114 *P* < 0.001 (D1 vs. D2 and D3) **SF-36 – PCS component, mean (SD)** At week 14: D1: 0.63 (7.68) D2: 6.53 (8.88) D3: 7.85 (9.55) *P* < 0.001 (D1 vs. D2 and D3) **Morning stiffness, mean change (SD):** At Week 14: D1: 23.4 (299.9) D2: -72.4 (201.3) D3: -86.3 (238.3) *P* < 0.001 (D1 vs. D2 and D3) At Week 24: D1: -20.4 (257.7) D2: -67.2(231.1) D3: -90.1 (234.5) *P* < 0.001 (D1 vs. D2 and D3) **PASI90, n:** At Week 14: D1: 0 D2: 22 D3: 26 *P* < 0.001 (D1 vs. D2 and D3) At Week 24: D1: 0 D2: 33 D3: 34 *P* < 0.001 (D1 vs. D2 and D3)

Authors: Kavanaugh et al. **Year: 2009**			
METHOD OF ADVERSE EVENTS REPORTING:	Safety evaluations included adverse events, routine laboratory analyses and the presence of antibodies to GOL.		
ADVERSE EVENTS (%):	**Drug 1**	**Drug 2**	**Drug 3**
Overall adverse effects reported:			
• Serious infections	4	<1	<1
• URTI	6	12	9
• abnormal LFT	NR	NR	NR
• herpes simplex	NR	NR	NR
• pneumonia (no.)	2	0	0
• tb	0	0	0
• Injection site reaction	3	3	4
• Malignancy (no.)	0	0	3
• Nasopharyngitis	4	7	13
• Hypertension	4	7	1
ATTRITION (*overall*):	**Overall attrition:** 93.8% **Attrition differential high:** no		
ATTRITION (*treatment specific*):	**Drug 1**	**Drug 2**	**Drug 3**
Attrition overall:	12	9	4
Attrition due to adverse events:	5	2	4

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Kavanaugh et al.[79] Gottlieb et al.[80]** **Year: 2010** **Study name: -** **Country:** North America, Europe **Quality rating: FAIR**	
FUNDING:	Centocor Research & Development (pharmaceutical industry)	
RESEARCH OBJECTIVE:	To use data from a phase II clinical trial to evaluate the effect of ustekinumab on physical disability and health-related quality of life (HRQoL) in patients with psoriatic arthritis (PsA)	
DESIGN & SIZE:	**Study design:** crossover study, RCT **Setting:** 24 sites in North America and Europe **Number screened:** NR **Number eligible:** NR **Number enrolled:** 146 **Run-in/Wash-out period:** NR	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**UST** 90 mg at weeks 0,1,2,3 12 weeks 76	**PLA** NA 12 weeks 70
INCLUSION CRITERIA:	adults with active PsA diagnosed at least 6 months before receipt of study agent were eligible for study enrollment. Active PsA was defined as three or more swollen and three or more tender joints and either a C-reactive protein level of at least 1.5 mg/dL or morning stiffness lasting 45 minutes or longer. Patients also had active plaque psoriasis, with a qualifying target lesion of 2 cm or larger, as well as an inadequate response to disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs, and/or anti-tumor necrosis factor (TNF) therapies for PsA.	
EXCLUSION CRITERIA:	patients who received biological treatment for psoriasis within 3 months, systemic drugs for psoriasis or phototherapy within 4 weeks, or topical agents for psoriasis within 2 weeks of randomisation	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

Authors: Kavanaugh et al. and Gottlieb et al. **Year: 2010**	
POPULATION CHARACTERISTICS:	**Combined**
Mean age (years):	49.0
Sex (% female):	44%
Ethnicity:	NR
Class naïve:	72.6%
Other germane population qualities:	
• **Polyarticular arthritis**	NR
• **DIP joints of hand/feet**	NR
• **Swollen joint count**	9.0
• **Tender joint count**	18.0
• **Asymmetric peripheral arthritis**	NR
• **NSAID use (%)**	NR
• **MTX use (%)**	52.7%
• **Corticosteroids use (%)**	92.5%
• **DAS score**	NR
• **HAQ score**	0.8
RESULTS:	**Primary Outcome Measures:** The primary efficacy endpoint of ACR20 response at week 12 was achieved in a greater proportion of patients in ustekinumab group than in the placebo group (difference 28% [95% CI; 14.0–41.6]; *P* =0.0002). Compared with the placebo group, more patients in the ustekinumab group achieved ACR50 (25% [19/76] vs 7% [5/70]) and ACR70 (11% [8/76] vs 0) responses at week 12 **Secondary Outcome Measures: (no ITT analyses for these outcomes)** Among patients with psoriasis involving at least 3% BSA at baseline, patients in the ustekinumab group had significantly greater improvement in DLQI score versus placebo at week 12 (-8.6 vs. -0.8; $P < 0.001$). At week 12, 58.7% (37/63) of patients in the ustekinumab group versus 5.5% (3/55) of those receiving placebo had a DLQI score of 0 or 1 ($P < 0.001$), indicating that neither the disease nor its treatment were negatively impacting patient HRQoL at that point. Significantly greater improvement (i.e., mean decrease) in HAQ-DI scores from baseline through week 12 was observed in the ustekinumab group (-0.31) versus the placebo group (-0.04; P < 0.001). In the ustekinumab-group, 46.7% (35/75) were HAQ-DI responders, compared with 21.9% (14/64, P = 0.002) of placebo patients at week 12.

Authors: Kavanaugh et al. and Gottlieb et al. **Year: 2010**		
METHOD OF ADVERSE EVENTS REPORTING:	NR in this paper	
ADVERSE EVENTS (%):	UST	PLA
Overall adverse effects reported:	61%	63%
• infections	36%	30%
• URTI	13%	9%
• abnormal LFT	NR	NR
• herpes simplex	NR	NR
• pneumonia	NR	NR
• tb	NR	NR
• ISR	4%	0%
• Influenza	1%	6%
• Serious adverse events	0%	4%
• Serious infections	0%	0%
ATTRITION (*overall*):	**Overall attrition:** 18% **Attrition differential high:** 20%	
ATTRITION (*treatment specific*):	**UST**	**PLA**
Attrition overall:	9%	29%
Attrition due to adverse events:	1%	6%

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Mease et al.**[81] **Year:** 2011 **Study name:** N/A **Country:** Multinational **Quality rating:** Fair			
FUNDING:	Bristol-Myers Squibb (pharmaceutical)			
RESEARCH OBJECTIVE:	To assess the safety and efficacy of abatacept, a selective T cell costimulation modulator, in patients with psoriatic arthritis (PsA)			
DESIGN & SIZE:	**Study design:** RCT, double-blind, placebo-controlled **Setting:** Multicenter **Number screened:** NR **Number eligible:** NR **Number enrolled:** 170 **Run-in/Wash-out period:** Patients with intolerance of, or an inadequate response to, infliximab, adalimumab, or etanercept discontinued these anti-TNF therapies at screening, and following a washout period of ≥28 days, these patients were assessed for arthritis and psoriasis before randomization.			
INTERVENTION:	**Drug 1**	**Drug 2**	**Drug 3**	**Drug 4**
Dose:	Abatacept 30/10 mg/kg 30 mg/kg given on Days 1, 15, followed by 10 mg/kg on day 29, and every 28 days there after	Abatacept 10 mg/kg	Abatacept 3 mg/kg	Placebo
Duration:		Days 1, 15, 29, and every 28 days there after	Days 1, 15, 29, and every 28 days there after	Days 1, 15, 29, and every 28 days there after
Sample size:	45	40	43	42
INCLUSION CRITERIA:	Adult patients who met the criteria of the Classification of Psoriatic Arthritis (CASPAR) Study Group and had active arthritis (defined as the presence of ≥3 swollen joints and ≥3 tender joints), active plaque psoriasis (with at least 1 qualifying target lesion [TL] ≥2 cm in diameter), and a disease duration of ≥3 months were eligible for enrollment in the study. Patients were required to have had an inadequate response to DMARDs, including, but not limited to, MTX or anti-TNF agents. Response to MTX was considered inadequate if it had been taken at a dosage of ≥15 mg/week for ≥2 months prior to randomization. Patients with intolerance of, or an inadequate response to, infliximab, adalimumab, or etanercept discontinued these anti-TNF therapies at screening, and following a washout period of ≥28 days, these patients were assessed for arthritis and psoriasis before randomization.			
EXCLUSION CRITERIA:	Key exclusion criteria: use of any investigational drug within 28 days before randomization, any prior treatment with abatacept, evidence of latent or active tuberculosis, or evidence of chronic or clinically significant infection or malignancy. Women who were pregnant or lactating were excluded.			

OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Aside from MTX, no DMARD was continued during the 6-month double-blind treatment period. MTX was continued at a stable dosage only if it had been taken at a stable dosage for ≥3 months prior to screening. A decrease in the MTX dosage was allowed in cases of toxicity. The dosage of nonsteroidal antiinflammatory drug (NSAID) remained unchanged throughout the study unless a decrease in dosage was required because of toxicity. Concomitant corticosteroid treatment was allowed if the dosage (no more than 10 mg of prednisone or its equivalent) had been stable for ≥28 days.

Authors: Mease et al. **Year: 2011**				
POPULATION CHARACTERISTICS:	**Drug 1**	**Drug 2**	**Drug 3**	**Drug 4**
Mean age (years):	51.5	50.8	50.3	52.6
Sex (% female):	54	35	51	45
Ethnicity (% Caucasian):	100	95	98	98
Class naïve:	NR	NR	NR	NR
Other germane population qualities:				
• **Mean # of tender joints**	19.6	25.2	22.7	21.3
• **Mean # of swollen joints**	10.3	12.5	10.3	10.5
• **Mean # w/ psoriasis covering ≥3% of BSA**	20	21	21	21
• **Previous NSAID use (%)**	58	68	73	55
• **Concomitant MTX use (%)**	58	60	60	55
• **Concomitant Corticosteroids use (%)**	21	28	27	19
• **HAQ DI score (range 0-3)**	1.2	1.3	1.1	1.2
RESULTS:	**Primary Outcome Measures:** **ACR20 at day 169** Drug 1: 42% (P = 0.022); Drug 2: 48% (P = 0.006); Drug 3: 33% (P = 0.121); Drug 4: 19% **Secondary Outcome Measures:** **Investigator's Global Assessment of Psoriasis (% clear or almost clear)** Drug 1: 21%; Drug 2: 25%; Drug 3: 38%; Drug 4: 26% **Target lesion 50 response (TL50)** Drug 1:36%; Drug 2:33%; Drug 3:30%; Drug 4: 17% **HAQ DI (% patients achieving a minimum clinically meaningful improvement defined as ≥0.3 point decrease from baseline to day 169)** Drug 1: 35; Drug 2: 45; Drug 3: 36; Drug 4: 19 **SF-36 (change from baseline)** PCS score (mean) – Drug 1: 7.3; Drug 2: 9.3; Drug 3: 6.3; Drug 4: 0.2 MCS score (mean) – Drug 1: 4.5; Drug 2 (4.4; Drug 3: 3.2; Drug 4: 2.4 **ACR50 at day 169** Drug 2: 25% (results for other doses reported in graph) **ACR70 at day 169**			

	Drug 2: 13% (results for other doses reported in graph) **PASI50 at day 169 (% (95% CI))** Drug 1: 35 (14 to 56); Drug 2: 29 (9 to 48); Drug 3: 43 (22 to 64); Drug 4: 14 (-1 to 29) **PASI70 at day 169 (% (95% CI))** Drug 1: 10 (-3 to 23); Drug 2: 14 (-1 to 29); Drug 3: 38 (17 to 59); Drug 4: 5 (-4 to 14)

Authors: Mease et al. **Year: 2011**				
METHOD OF ADVERSE EVENTS REPORTING:	Laboratory tests, monitoring (not described)			
ADVERSE EVENTS (%):	**Drug 1**	**Drug 2**	**Drug 3**	**Drug 4**
Overall adverse effects reported:	29 (67%)	31 (78%)	31 (69%)	30 (70)
• Serious Adverse Events	4 (9%)	2 (5%)	0	1 (2%)
• Cholecystitis	1 (2%)	0	0	0
• Osteomyelitis	1 (2%)	0	0	0
• Gastroenteritis	0	1 (3%)	0	0
• Basal cell carcinoma	1 (2%)	0	0	0
• Dizziness	0	1 (3%)	0	0
• Personality disorder	0	0	0	1 (2%)
• Psychiatric decompensation	0	0	0	1 (2%)
• Overdose	1 (2%)	0	0	0
• Infusion reaction	2 (5%)	2 (5%)	0	0
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall attrition:** 147 (86%) completed the study **Attrition differential high:** No (highest differential was 17% between group 3 (96%) and group 4 (79%))			
	Drug 1	**Drug 2**	**Drug 3**	**Drug 4**
Attrition overall:	6 (14%)	6 (15%)	2 (4%)	9 (21%)
Attrition due to adverse events:	1 (2%)	2 (5%)	1 (2%)	3 (7%)

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Mease et al.**[82] **Year: 2006** **Country:** Multinational	
FUNDING:	NR	
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of alefacept in combination with methotrxate for the treatment of PsA.	
DESIGN:	**Study design:** RCT- phase 2 **Setting:** Multi-center (27 sites) **Sample size:** 185	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ALE + MTX** 15 mg/weekly 12 wks trmt/12 wks follow-up 123	**Placebo + MTX** N/A 12 wks trmt/12 wks follow-up 62
INCLUSION CRITERIA:	18-70 years; persistently active PsA (defined as 3 swollen joints and 3 tender joints) despite treatment with MTX for 3 months immediately prior to enrollment; MTX (10-25 mg/week) was required to be stable for 4 weeks prior to enrollment; patients were required to have CD4+ T cell counts at or above the lower limit of normal.	
EXCLUSION CRITERIA:	Treatment with INF, ADA, or systemic retinoids within 3 months; ERA or cyclosporine within 2 months; phototherapy or other DMARDs within 4 weeks; history of malignancy; unstable erythrodermic, pustular, or guttate psoriasis; serious local or systemic infection within the previous 3 months; HIV; active TB.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX; stable doses of corticosteroids (≤10 mg/day of prednisone or equivalent) and NSAIDs	

<table>
<tr><td colspan="3">Authors: Mease et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: No; more NSAID use in ALE group, and more prednisone in placebo group.</td></tr>
<tr><td></td><td><u>ALE + MTX</u></td><td><u>Placebo + MTX</u></td></tr>
<tr><td>Mean age (years):</td><td>45.6</td><td>45.5</td></tr>
<tr><td>Sex (% female):</td><td>50</td><td>63</td></tr>
<tr><td>Ethnicity:</td><td>98% white</td><td>98% white</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td></tr>
<tr><td>• NSAID use (%) diclofenac</td><td>41</td><td>24</td></tr>
<tr><td>• MTX use (mean dose/week)</td><td>13.7</td><td>14.6</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>8</td><td>15</td></tr>
<tr><td>• HAQ score</td><td>1.0</td><td>1.1</td></tr>
<tr><td>• PASI</td><td>10.2</td><td>9.6</td></tr>
<tr><td>• BSA $\geq$ 3 % (%)</td><td>47</td><td>47</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: ACR20 response at 24 wks

Secondary Outcome Measures: ACR50 and 70; PASI50 and 75; PGA of clear or almost clear at week 14 and at any time. The pharmacodynamic end point was the change from baseline in CD4+ T cell counts

Timing of assessments: Screening and at baseline weeks 7, 14, 18, and 24.</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures at 24 weeks:
• ACR20 response was achieved by a significantly greater proportion of patients receiving ALE + MTX (54%) vs. placebo + MTX (23%) ($P < 0.001$)
• ACR50 ALE + MTX (17%) vs. placebo + MTX (10%) and ACR70 ALE + MTX (7%) vs. placebo + MTX (2%) (P = NS for either)
• PASI50 response ALE + MTX (45%) vs. placebo + MTX (31%) (P = NS)
• PASSI75 ALE + MTX (28%) vs. placebo + MTX (24%) (P = NS)
• PGA clear or almost clear ALE + MTX (31%) vs. placebo + MTX (24%) (P = NS)</td></tr>
</table>

Authors: Mease et al. **Year: 2006**		
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Increased ALT level • Back pain • Nasopharyngitis • URTI • Nausea	**ALE + MTX** NR 6 6 5 4 3	**Placebo + MTX** NR 2 3 11 8 6
Significant differences in adverse events:	NR but infection rates appear to be higher in placebo + MTX group (i.e., URTI and nasopharyngitis)	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** None	
ADEQUATE RANDOMIZATION:	Yes, but method NR	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	NR	
ATTRITION (*overall*):	**Overall loss to follow-up:** 3% **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ALE + MTX** 4 (3%) 2 (2%)	**Placebo + MTX** 1 (2%) 0
QUALITY RATING:	**Fair**	

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Rodgers et al. (Health Technology Assessment)[83]** **Year: 2011** **Country: UK** **Quality rating:**
FUNDING:	Health Technology Assessment programme of the National Institute for Health Research.
DESIGN & SIZE:	**Study design:** Systematic review **Number of patients:** 982 (effectiveness; safety NR) **Trials:** Effectiveness =6 (in 43 publications), Safety=32
OBJECTIVE OF REVIEW:	To determine the clinical effectiveness, safety and cost-effectiveness of etanercept, infliximab and adalimumab for the treatment of active and progressive psoriatic arthritis in patients who have an inadequate response to standard treatment (including DMARD therapy).
ELIGIBILITY CRITERIA:	Randomized controlled trials (including any open-label extensions of these RCTs) were included in the evaluation of efficacy. Information on the rate of serious adverse events was sought from regulatory sources [the US Food and Drug Administration (FDA), European Medicines Agency (EMEA)]. If these failed to report the necessary data to calculate event rates then nonrandomized studies that provided these data for etanercept, infliximab and adalimumab were included in the review. If multiple nonrandomized studies were identified, inclusion was limited to those studies reporting outcomes for a minimum of 500 patients receiving biologic therapy. For the evaluation of the effectiveness of etanercept, infliximab and adalimumab, included studies were of adults with active and progressive psoriatic arthritis with an inadequate response to previous standard therapy (including at least one DMARD). Trials of effectiveness had to specify that the patients had psoriatic arthritis, with the definition and/or the inclusion criteria for Psoriatic arthritis stated. For the assessment of adverse effects, studies of patients with other conditions were eligible for inclusion in the review.
STUDIES INCLUDED IN REVIEW:	**Effectiveness** (not including companions): ADEPT 2005, Genovese 2007, IMPACT 2005, IMPACT 2 2005, Mease 2000, Mease 2004. **Adverse events**: Antoni 2008, Brassard 2006, Breedveld 2006, Burmester 2007, Carmona 2005, Caspersen 2008, Colombel 2004, Colombel 2007, Curtis 2007, Dixon 2006, Dixon 2007, Dreyer 2009, Favalli 2009, Feltelius 2005, Fidder 2009, Fleischmann 2006, Gomez-Reino 2003, Gomez-Reino 2007, Horneff 2009, Klareskog 2006, Listing 2005, Mease 2006, Moreland 2006, Oka 2006, Rudwaleit 2009, Schiff 2006, Schnitzler 2009, St. Clair 2004, Takeuchi 2008, Westhovens 2006, Wolfe 2004.
LITERATURE SEARCH DATES:	June 9-17, 2009

INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	For effectiveness, six RCTs (total of 43 publications), consisting of two placebo-controlled RCTs for each of the three agents: etanercept (Mease 2000 and Mease 2004), infliximab (IMPACT 2005 and IMPACT 2 2005), and adalimumab (ADEPT 2005 and Genovese 2007). For adverse events, 32 publications were included, which reported treatment with etanercept, infliximab or adalimumab in 500 or more patients, and reported either adverse event rates directly or provided sufficient information to calculate these rates.

Authors: Rodgers et al. Year: 2011	
DATA SYNTHESIS METHODS:	Where sufficient clinically and statistically homogeneous data were available, data were pooled using standard meta-analytic method. Given the small number of trials available, a fixed-effects model was used to pool outcomes where pooling was appropriate. Sensitivity analyses were undertaken when permitted by sufficient data (e.g. exclusion of concomitant MTX treatment). The rates of serious adverse effects of these biologic agents were synthesized narratively. As trials conducting head-to-head comparisons of etanercept, infliximab and adalimumab were not available the possibility of conducting some form of indirect comparison was investigated. Meta-analysis using indirect comparisons enables data from several sources to be combined, while taking into account differences between the different sources, in a similar way to, but distinct from, how a random-effects model takes into account between-trial heterogeneity. As with a mixed-treatment comparison (MTC), Bayesian indirect comparisons need a 'network of evidence' to be established between all of the interventions of interest.
MAIN RESULTS: (RESULTS IN SUBGROUPS)	**Psoriatic Arthritis Response Criteria (PsARC):** Etanercept (at 12 weeks): RR 2.60; 95% CI, 1.96 to 3.45; P<0.00001; I^2=34% Infliximab (at 14 weeks): RR 3.44; 95% CI, 2.53 to 4.69; P<0.0001; I^2=68% Adalimumab (at 12 weeks): RR 2.24; 95% CI, 1.74 to 2.88; P<0.0001; I^2=0% Mean probability of a PsARC response: 71% for etanercept, 79% for infliximab, and 59% for adalimumab, compared with 25% for placebo. **American College of Rheumatology (ACR) 20:** Etanercept (at 12 weeks): RR 4.19; 95% CI, 2.74 to 6.42; P<0.00001; I^2=0% Infliximab (at 14 weeks): RR 5.47; 95% CI, 3.43 to 8.71; I^2=0% Adalimumab (at 12 weeks): RR 3.65; 95% CI, 2.57 to 5.17; P<0.0001; I^2=38% Mean probability of an ACR 20 response: 61% for etanercept, 68% for infliximab and 56% for adalimumab, compared with 14% for placebo. **ACR 50:** Etanercept (at 12 weeks): RR 10.84; 95% CI, 4.47 to 26.28; P<0.00001; I^2=0% Infliximab (at 14 weeks): RR 13.75; 95% CI, 5.11 to 37.00; P<0.0001; I^2=0% Adalimumab (at 12 weeks): RR 10.08; 95% CI, 4.74 to 21.44; P<0.0001; I^2=0% Mean probability of an ACR 20 response: 36% for etanercept, 43% for infliximab and 32% for adalimumab, compared with 5% for placebo. **ACR 70:**

	Etanercept (at 12 weeks): RR 16.28; 95% CI, 2.20 to 120.54; P=0.006; I^2=0% Infliximab (at 14 weeks): RR 17.67; 95% CI, 3.46 to 90.14; P=0.001; I^2=0% Adalimumab (at 12 weeks): RR 26.05; 95% CI, 5.18 to 130.88; P<0.0001; I^2=0% Mean probability of an ACR 20 response: 16% for etanercept, 20% for infliximab and 13% for adalimumab, compared with 2% for placebo. **Health Assessment Questionnaire (HAQ):** Etanercept (at 12 weeks), percent change from baseline: RR -48.99; 95% CI, 38.53 to 59.44; P<0.0001; I^2=0% Infliximab (at 14 weeks), percent change from baseline: WMD -60.37; 95% CI, -75.28 to -45.46); I^2=3% Adalimumab (at 12 weeks), change from baseline: WMD -0.27; 95% CI, -0.36 to -0.18; P<0.0001; I^2=0.6% Mean change in HAQ in patients achieving a PsARC response: -0.630 for etanercept, -0.657 for infliximab, and -0.477 for adalimumab, compared with -0.244 for placebo. Mean change in HAQ in patients not achieving a PsARC response: -0.190 for etanercept, -0.194 for infliximab, and -0.130 for adalimumab, compared with 0 for placebo. **Psoriasis Area and Severity Index (PASI) 50:** Mean probability of a PASI 50 response: 40% for etanercept, 91% for infliximab and 74% for adalimumab, compared with 13% for placebo. **PASI 75:** Mean probability of a PASI 75 response: 18% for etanercept, 77% for infliximab and 48% for adalimumab, compared with 4% for placebo. **PASI 90:** Mean probability of a PASI 90 response: 7% for etanercept, 56% for infliximab and 26% for adalimumab, compared with 2% for placebo. The results of evidence synthesis found that infliximab appears to be the most effective of the three biologics. Across all outcomes of joint and skin disease at 12 weeks, infliximab is associated with the highest probabilities of response.
ADVERSE EVENTS:	Rates of serious infection: etanercept 0.6%–13.2%, infliximab 0.8%–13.8%, adalimumab 0.4%–5.1% Rates of malignancy: etanercept 1%–5.7%, infliximab 0.16%–5.1%, adalimumab 0.1%–1.1% Rates of activation of TB for the treatment: etanercept 0%–1.4%, infliximab 0.06%–4.6%, adalimumab 0%–0.4% Rates of mortality: etanercept 0%–3.1%, infliximab 0.06%–2.0%, adalimumab 0.5%–0.9% Rates of withdrawal due to AE: etanercept 0%–13.6%, infliximab 6.4%–12.8%, adalimumab 5.8%–10.7%
LIMITATIONS OF PRIMARY STUDIES	NR

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors: Saad et al.**[84] **Year: 2010** **Study name: Part of BSRBR** **Country:** UK **Quality rating: Fair**		
FUNDING:	Restricted support from UK pharmaceutical companies, currently Abbott Laboratories, Amgen, Schering-Plough, Wyeth Pharmaceuticals, and Roche, which finances a wholly separate contract between the British Society for Rheumatology and the University of Manchester, which provide and run the British Society for Rheumatology Biologics Register data collection, management, and analysis services		
RESEARCH OBJECTIVE:	To evaluate the impact of anti–tumor necrosis factor (anti-TNF) therapies on quality of life (QOL) and functional status in psoriatic arthritis (PsA) patients and study potential predictors for QOL improvements		
DESIGN & SIZE:	**Study design:** Observational - registry **Setting:** Multi-center **Number screened: 596** **Number eligible: NR** **Number enrolled: 596 - 510 analyzed at baseline** **Run-in/Wash-out period: NA**		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Etanercept** NR 6 months 333	**Infliximab** NR 6 months 171	**Adalimumab** NR 6 months 92
INCLUSION CRITERIA:	Physician diagnosis of PsA starting 1 of 3 available anti-TNF agents (etanercept, infliximab, and adalimumab).		
EXCLUSION CRITERIA:	NA		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

Authors: Saad et al. **Year: 2010**				
POPULATION CHARACTERISTICS:	**Overall**	**Etanercept**	**Infliximab**	**Adalimumab**
Mean age (years):	45.7	45.8	44.8	47.0
Sex (% female):	52.5	51.1	55.0	53.3
Ethnicity:	NR	NR	NR	NR
Class naïve:				
Other germane population qualities:				
• **DAS - 28**	6.4	6.1	7.3	6.0
• **SF-36 PCS**	19.14	18.99	18.11	21.19
• **SF-36 MCS**	41.73	41.76	40.33	44.43
• **HAQ median**	1.9	1.8	2.0	1.8
•				
RESULTS:	**Primary Outcome Measures:** SF-36 scores (physical component scale [PCS] and mental component scale [MSC]) at 6 months SF-36 PCS (SD) etanercept 29.4 (13.7), infliximab 27.7 (14.1), adalimumab 31.6 (12.8) SF-36 MCS (SD) etanercept 48.7 (12.2), infliximab 48.6 (10.9), adalimumab 49.2 (11.4) No significant differences between groups **Secondary Outcome Measures:** Median HAQ at 6 months etanercept 1.38 (0.50-1.88), infliximab 1.25 (0.63-2.00), adalimumab 1.19 (0.63-1.88), No significant differences between groups			

Authors: Saad et al. **Year: 2010**			
METHOD OF ADVERSE EVENTS REPORTING:	None reported		
ADVERSE EVENTS (%):	**Etanercept**	**Infliximab**	**Adalimumab**
Overall adverse effects reported: • infections • URTI • abnormal LFT • herpes simplex • pneumonia • tb • ISR		NR	
ATTRITION (*overall*):	**Overall attrition:** At 6 months 110/510 **Attrition differential high:** NR		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**		NR	

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 4. Targeted Immune Modulators – Psoriatic Arthritis

STUDY:	**Authors:** Saad et al.[85] **Year:** 2008 **Country:UK**
FUNDING:	None
DESIGN:	**Study design:** SR, MetaAnalysis **Number of patients:** 982
AIMS OF REVIEW:	efficacy and safety of tumor necrosis factor-α (TNF-α) inhibitors in the management of psoriatic arthritis (PsA), use of adalimumab, etanercept, or infliximab (used at licensed therapeutic dosages)
STUDIES INCLUDED IN META-ANALYSIS	Gladman 2007 and Mease 2005, Genovese 2007 , Mease 2000, 2001, 2004; Antoni 2005 IMPACT 2, Antoni, Kavanaugh 2005 IMPACT
TIME PERIOD COVERED:	till May 2007
CHARACTERISTICS OF INCLUDED STUDIES:	double-blind RCT that compared the use of adalimumab, etanercept, or infliximab (used at licensed therapeutic dosages) against placebo or other active treatments and reported on efficacy and/or safety outcomes.
CHARACTERISTICS OF INCLUDED POPULATIONS:	PsA with at least 3 swollen joints and 3 tender or painful joints

Authors: Saad et al. **Year:** 2008 **Country:** UK	
CHARACTERISTICS OF INTERVENTIONS:	Adalimumab 40 mg SC every other wk Etanercept 25 mg SC twice/week Infliximab 5 mg/kg at Weeks 0 2, 6, 14 then every 8 weeks
MAIN RESULTS:	**Adalimumab, etanercept, and infliximab vs. placebo at 12–16 weeks (**Gladman 2007 and Mease 2005, Genovese 2007 , Mease 2000, 2001, 2004; Antoni 2005, Antoni, Kavanaugh 2005) • ACR20 pooled RR 4.35 (95% CI 3.24, 5.84) ACR50 pooled RR 10.37 (95% CI 6.36, 16.93) ACR70 pooled RR 16.51 (95% CI 6.74, 40.40) • PsARC pooled RR 2.60 (95%CI 2.22, 3.04) • PASI 50 pooled RR 5.50 (95% CI 2.53, 11.92) PASI 75 pooled RR 16.30 (95% CI 7.33, 36.28) PASI 90 pooled RR 34.64 (95% CI 6.95, 172.57) **Adalimumab vs placebo at 12 wks (**Mease 2005, Genovese 2007) • HAQ DI mean percentage change 26.67 (95% CI 20.13, 33.20) **infliximab vs. placebo at 14–16 weeks** (Antoni 2005, Antoni, Kavanaugh 2005) • HAQ DI mean percentage change 56.06 (95% CI 42.07,70.05) **Adalimumab vs placebo at 12 wks (**Gladman 2007 and Mease 2005, Genovese 2007) • SF-36 PCS WMD 5.54 (95% CI 0.64, 10.43) • SF-36 MCS WMD 0.88 (95% CI –0.99, 2.75) **Adalimumab vs placebo at 24 wks (**Gladman 2007 and Mease 2005, Genovese 2007) • SF-36 PCS WMD 7.90 (95% CI 5.63,10.17) SF-36 MCS WMD 1.20 (95% CI –1.06, 3.46) **infliximab vs. placebo at 14 weeks** (Antoni, Kavanaugh 2005) • SF-36 PCS WMD 8.00 (95% CI 5.27, 10.73), SF-36 MCS WMD 5.00 (95% CI 2.16, 7.84) **In direct comparisons** RR (95% CI) Efficacy ACR 20 Adalimumab vs etanercept 0.63 (0.22, 1.81) Adalimumab vs infliximab 0.60 (0.30, 1.20) Etanercept vs infliximab 0.96 (0.33, 2.76) PsARC Adalimumab vs etanercept 1.35 (0.67, 2.73) Adalimumab vs infliximab 0.77 (0.53, 1.13) Etanercept vs infliximab 0.57 (0.28, 1.17) Safety Serious AE Adalimumab vs etanercept 0.61 (0.12, 3.03) Adalimumab vs infliximab 0.52 (0.14, 2.01) Etanercept vs infliximab 0.64 (0.14, 2.96)
ADVERSE EVENTS:	Withdrawal for any reason • Adalimumab vs placebo RR0.83 (0.39, 1.74) Gladman 2007 and Mease 2005, Genovese 2007

	• Etanercept vs placebo RR 0.24 (0.12, 0.49) Mease 2000, 2001, 2004 • Infliximab RR1.50 (0.26, 8.61)Antoni 2005 • Pooled RR 0.48 (0.20, 1.18) Withdrawal due to AE • Pooled RR 2.14 (0.73, 6.27) Gladman 2007 and Mease 2005, Genovese 2007 , Mease 2004; Antoni 2005, Antoni, Kavanaugh 2005 Serious AE • Pooled RR 0.98 (0.55, 1.77) Gladman 2007 and Mease 2005, Genovese 2007 , Mease 2000, 2001, 2004; Antoni 2005, Antoni, Kavanaugh 2005 Upper respiratory tract infections • Pooled 0.91 (0.65, 1.28)Gladman 2007 and Mease 2005, Genovese 2007 , Mease 2000, 2001, 2004; Antoni 2005, Antoni, Kavanaugh 2005 Injection site reactions • Etanercept vs placebo RR 4.27 (2.25, 8.13)*RR Mease 2000, 2001, 2004 • Adalimumab vs placebo) RR 1.44 (0.65, 3.17)Gladman 2007 and Mease 2005, Genovese 2007 • Pooled RR 2.48 (1.16, 5.29)Gladman 2007 and Mease 2005, Genovese 2007 , Mease 2000, 2001, 2004;
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	Good

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Colombel et al.[86,87] and Feagan et al.[88] and Loftus et al.[89] and Kamm et al.[90]** **Year: 2007, 2008, 2009, 2011** **Country:** Multinational		
FUNDING:	Abbott Laboratories		
RESEARCH OBJECTIVE:	Efficacy and safety of ADA, administered subcutaneously, in the maintenance of response and remission in patients with moderate to severe Crohn's disease (CD), ADA maintenance treatment on the risks of hospitalization and surgery. And on health-related quality of life (HQL).		
DESIGN:	**Study design:** RCT **Setting:** Multinational **Sample size:** 854 enrolled and had active run-in, 778 remaining at week 4 then randomized to three groups. The patients were stratified into "responders" and "non-responders" at week 4 (decrease in CDAI ≥70). All end-points except fistula and safety are reported for the "responders" population.		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 56 weeks 261 (170 responders, 91 non-responders)	**ADA** 40mg/every second week 56 weeks 260 (172 responders, 88 non-responders)	**ADA** 40mg/week 56 weeks 257 (157 responders, 100 non-responders)
INCLUSION CRITERIA:	Men and women 18–75 years of age with known CD of at least 4 months' duration (radiologic/endoscopic confirmation required) that at the screening visits was moderately to severely active, as defined by a baseline Crohn's Disease Activity Index (CDAI) score of 220–450 points.		
EXCLUSION CRITERIA:	ulcerative colitis, symptomatic obstructive disease, bowel resection within the past 6 months, an ostomy, extensive small bowel resection or short bowel syndrome; were currently receiving total parenteral nutrition; had a history of cancer, *Listeria*, human immunodeficiency virus, central nervous system demyelinating disease, or untreated tuberculosis; had received investigational chemical agents within 30 days or investigational biologic therapy within 3 months; had received antibiotic treatment for non-CD–related infections within 3 weeks before screening; were pregnant or breast-feeding; had a history of significant drug or alcohol abuse within the past year; had poorly controlled medical conditions; had received treatment with ADA or participated in an ADA clinical study; had received enema therapy within 2 weeks before screening; had received cyclosporine, mycophenolate mofetil, or tacrolimus within 8 weeks of screening; had a positive *Clostridium difficile* stool assay; or had clinically significant deviations in prespecified laboratory parameters.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concurrent therapies for CD, including stable dosages (for at least 4 weeks before screening) of azathioprine, 6-mercaptopurine, MTX, 5-aminosalicylates, sulfasalazine, oral mesalamine, and CD-related antibiotics, were permitted, as were stable dosages (for at least 2 weeks before screening) of		

	prednisone (≤30 mg/day or equivalent) or budesonide (≤9 mg/day) (patients could not be on both prednisone and budesonide). Patients who had received INF or any TNF antagonist other than ADA more than 12 weeks before screening could be enrolled provided that they did not exhibit initial nonresponse to the agent (i.e., no clinical response to first injection as judged by the investigator).

Authors: Colombel et al., Feagan et al., Loftus et al., Kamm et al. **Year: 2007, 2008, 2009, 2011**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No (ADA 40mg/2nd week less severe- 6.5% fewer with fistulae) **Disease severity:** moderate to severe		
	Placebo	**ADA 40mg/2ND week**	**ADA 40mg/week**
Mean age (years):	36.9	36.8	37.8
Sex (% female):	62.1	62.7%	61.1%
Ethnicity:	94.3% white 3.1% black	94.2% white 2.7% black	89.9% white 4.7% black
Other germane population qualities:			
• Previous surgery for CD (%)	NR	NR	NR
• Patients with fistulae (%)	18.0%	11.5%	15.6%
• Mean baseline CDAI (after 4 week active lead-in)	209	195	209
• Mercaptopurine/Azathioprine use (%)	NR	NR	NR
• Corticosteroids use (%)	41.0%	38.1%	41.6%
• HAQ score	NR	NR	NR
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** The percentage who achieved clinical remission (CDAI score <150) at weeks 26 and 56. NB: trial included 4 week open-label induction, "responders" (defined as a decrease in CDAI scores ≥70 points at week 4 compared with baseline) were randomized into the three groups as above. HQL: Zung Self-Rating Depression Scale, FACIT-F, IBDQ, SF-36, VAS (abdominal pain) 12-month risk of hospitalization and rate of surgery. **Secondary Outcome Measures:** (1) percentage of patients with a clinical response (decrease in CDAI score from baseline by ≥70 points and by ≥100 points) at weeks 26 and 56; (2) changes from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) total scores at weeks 26 and 56; (3) percentage of patients in clinical remission at weeks 26 and 56 who were able to discontinue corticosteroid use; (4) percentage of patients in clinical remission at weeks 26 and 56 who were able to discontinue corticosteroid use for ≥90 days; (5) percentage of patients with fistula remission (closure of all fistulas that were draining at screening and baseline visits);		

	(6) previous/concomitant use of immunosuppressants (with vs. without), and previous use of TNF antagonists (experienced vs. naive); and (7) median time in clinical remission among randomized responders achieving remission. Post-hoc analyses were conducted to evaluate the sustainability of response and the response in certain subgroups: (1) percentage of patients with fistula closure at 26 weeks who continued to have fistula closure at 56 weeks and (2) clinical remission rates stratified by baseline C-reactive protein (CRP) concentration (<1 vs. ≥1 mg/dL). **Timing of assessments:** weeks 0, 2, 4, 6, 8, 12, 16, 20, 26, 32, 40, 48, 56, and 60 (4-week follow-up period).
RESULTS:	**Health Outcome Measures:** • clinical remission (CDAI<150) week 26: ADA 40mg/2ND week 40%, ADA 40 mg/wk 47%, and placebo 17% p<0.001 • clinical remission (CDAI <150) week 56: ADA 40mg/2ND week 36%, ADA 40 mg/wk 41%, and placebo 12% $p < 0.001$ **Intermediate Outcome Measures:** • Decrease From Baseline in CDAI Score ≥100 week 56: ADA 40mg/2ND week 41.3%, ADA 40mg/wk 47.8%, placebo 16.5% • Decrease From Baseline in CDAI Score ≥70 week 56: ADA 40mg/2ND week 43.0%, ADA 40mg/wk 49.0%, placebo 17.6% • Corticosteroid-free remission at week 56: ADA 40mg/2ND week 29%, ADA 40mg/wk 23%, placebo 6% • Complete fistula closure week 56: combined ADA groups 33% vs. placebo 13% $P = .016$ • IBDQ at week 56: ADA 40mg/2ND week 177 vs. ADA 40mg/wk 171 vs. induction-only " >7 points below 170" (mean value not given) • SF-36 PCS week 56: ADA 40mg/2ND week 77% vs. placebo 61% had achieved an MCID improvement of 5 points or more($P < 0.01$) • SF-36 MCS week 56: ADA 40mg/2ND week 67% vs. placebo 54% had achieved an MCID improvement of 5 points or more($P < 0.05$) • 12-month risk of all-cause hospitalization: ADA 40mg/2ND week 13.5% vs. ADA 40mg/wk 11.7% vs. placebo 25.2% ($P < 0.01$). • Major surgery rate: ADA 40mg/2ND week 0.4% vs. ADA 40mg/wk 0.8% vs. placebo 3.8% • Subgroup analysis of patients with fistula (ADA = 70 placebo = 47) mean number of draining fistula per day during RCT, ADA 0.88 vs. placebo 1.34, $P = 0.043$.

Authors: Colombel et al., Feagan et al., Loftus et al., Kamm et al. **Year: 2007, 2008, 2009, 2011**			
ADVERSE EVENTS:	**Placebo**	**ADA 40mg/2ND week**	**ADA 40mg/week**
Overall adverse effects reported:	84.7%	88.8%	85.6%
• AEs leading to discontinuation	13.4	6.9	4.7
• infections	36.8	46.2	44.4
• arthralgia	8.8	10.4	13.2
• headache	5.7	9.6	11.7
• injection site reaction	0.4	4.2	5.8
• urinary tract infection	1.5	4.2	5.8
Significant differences in adverse events:	Yes: discontinuation, arthalgia, headache, injection site reaction, urinary tract infection		
ANALYSIS:	**ITT:** modified ITT with NRI **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 41% (of original population) 35% of randomized population **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**Placebo**	**ADA 40mg/2ND week**	**ADA 40mg/week**
Attrition overall:	44%	36%	25%
Attrition due to adverse events:	13.4%	6.9%	4.7%
QUALITY RATING:	**Fair**		

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors:** Ford et al.[91] **Year:** 2011 **Country:** **Quality rating:** Good
FUNDING:	American College of Gastroenterology
DESIGN & SIZE:	**Study design:** Systematic review with meta-analysis **Number of patients:** 4,526 **Trials:** 27
OBJECTIVE OF REVIEW:	To conduct a systematic review and meta-analysis of RCTs to estimate the efficacy and safety of biologic therapies in inflammatory bowel disease.
ELIGIBILITY CRITERIA:	RCTs examining the effect of biological therapies, restricted to those approved for use by the US Food and Drug Administration (FDA), in adult patients (> 90 % of participants over the age of 16 years) with active or quiescent IBD were eligible for inclusion.
STUDIES INCLUDED IN REVIEW:	For Ulcerative Colitis: Rutgeerts, 2005; Jarnerot, 2005; Probert, 2003; Sands, 2001 For Crohn's Disease: Hanauer, 2006; Sandborn, 2007; Hibi, 2002, Colombel, 2007, Sandborn, 2007b, Colombel, 2009, Schreiber, 2005, Sandborn, 2007c, Sandborn, 2010, Schreiber, 2007, Targan, 1997, Lemann, 2006, Colombel, 2010, Rutgeerts, 1999, Hanauer, 2002, Present, 1999, Sands, 2004, Gordon, 2001, Ghosh, 2003, Sandborn, 2005, Sands, 2007, Targan, 2007, Sandborn, 2005
LITERATURE SEARCH DATES:	MEDLINE (1966 to December 2010), EMBASE (1984 to December 2010), the Cochrane central register of controlled trials (Issue 4, October 2010), and the Cochrane IBD Group Specialized Trials Register.
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	For Ulcerative Colitis: Five RCTs, reported in four separate articles that reported efficacy of biological therapies in inducing remission in patients with moderately to severely active UC who had failed, or were receiving, therapy with corticosteroids. All trials used infliximab, and none were at low risk of bias. Three RCTs recruited hospitalized inpatients and two recruited ambulatory outpatients. Study duration ranged from 6 to 12 weeks

	For Crohn's Disease: The review included 27 randomized controlled trials: eight on adalimumab, seven on certolizumab pegol, seven on infliximab, and six on natalizumab. The review assessed two outcomes, failure of remission and relapse of disease activity, and analyzed the subgroup of patients with fistulizing disease separately. Most of the included efficacy studies were conducted in narrowly defined populations and/or were limited to less than one year of follow-up. Patients were allowed to remain on stable doses of corticosteroids in all trials. All patients suffered from active Crohn's disease of at least three months' duration.

Authors: Ford et al. **Year: 2011**	
DATA SYNTHESIS METHODS:	Meta-analysis (random effects model)
MAIN RESULTS: (RESULTS IN SUBGROUPS)	For Ulcerative Colitis: Remission was not achieved in 231 (42.9 %) of 539 patients randomized to infliximab at 6 weeks to 3 months, compared with 201 (69.8 %) of 288 assigned to placebo. RR = 0.72 (95% CI, 0.57 to 0.91) for a failure to achieve remission (infliximab vs. placebo) [I-squared = 70%, P = 0.009, 5 studies (827 patients)] For Crohn's Disease: *Adalimumab (vs. placebo):* The relative risk of not achieving remission for adalimumab-treated patients compared with placebo was 0.85 (95% CI, 0.79 to 0.91). The relative risk of failing to prevent relapse was not statistically significant 0.54 (95% CI, 0.27 to 1.07). The relative risk of not achieving healing of fistulizing Crohn's disease was 0.94 (95% CI, 0.76 to 1.17). *Certolizumab Pegol (vs. placebo):* The relative risk of not achieving remission for certolizumab pegol-treated patients compared with placebo was 0.95 (95% CI, 0.9 to 1.01). By week 26, the relative risk of failure in preventing relapse in certolizumab pegol-treated patients compared with placebo was 0.73 (95% CI, 0.63 to 0.85). The calculated risk ratio of not healing fistulizing Crohn's disease was 0.97 (95% CI, 0.77 to 1.22). *Infliximab (vs. placebo):* The relative risk of not achieving remission for infliximab-treated patients compared with placebo-treated patients was 0.68 (95% CI, 0.52 to 0.9). The relative risk of not preventing relapse was statistically significantly lower in infliximab compared with placebo (relative risk, 0.72; 95% CI, 0.63 to 0.83). The risk of not healing of fistulizing Crohn's disease for infliximab-treated patients compared with placebo-treated patients was 0.62 (95% CI, 0.48 to 0.81). The relative risk of loss of response of fistulizing Crohn's disease was 0.81 (95% CI, 0.68 to 0.96). *Natalizumab (vs. placebo):*

	The reviewers calculated a relative risk of natalizumab failing to induce remission in active luminal Crohn's disease of 0.88 (95% CI, 0.83 to 0.94). The reviewers calculated a relative risk of preventing relapse in quiescent luminal Crohn's disease of 0.71 (95% CI, 0.61 to 0.84).
ADVERSE EVENTS:	Ulcerative Colitis: The RR of any adverse event was no higher with infliximab, and serious adverse events were lower (RR = 0.64; 95 % CI 0.41 – 1.00, P = 0.05, 4 studies (515 patients)). No statistically significant differences were detected in numbers of patients experiencing infusion reactions, headache, rash, or arthralgia with infliximab compared with placebo. Crohn's disease: Eight trials of anti-TNFα antibodies (Adalimumab, Certolizumab pegol, infliximab) provided data on adverse events. No statistically signifi cant difference in the incidence of adverse events was detected with anti-TNFα antibodies compared with placebo. The relative risk of experiencing any adverse event was 0.99 (95% CI, 0.90 to 1.08). Five trials of natalizumab provided data on adverse events. There were significantly more patients allocated to natalizumab reporting headache, compared with placebo. The relative risk was 1.23 (95 % CI, 1.03 to 1.47).
LIMITATIONS OF PRIMARY STUDIES	Attrition

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Ghosh et al.**[92] **Year: 2003** **Country:** Multinational			
FUNDING:	Elan Pharmaceuticals and Biogen			
RESEARCH OBJECTIVE:	To determine the efficacy of Natalizumab for Active Crohn's Disease			
DESIGN:	**Study design:** RCT **Setting:** Multicenter (35) **Sample size:** 248			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo & placebo** 2 infusions 4 weeks apart 12 weeks 63	**NAT 3mg/kg & placebo** 2 infusions 4 weeks apart 12 weeks 68	**NAT 3mg/kg & NAT 3mg/kg** 2 infusions 4 weeks apart 12 weeks 66	**NAT 6mg/kg & NAT 6mg/kg** 2 infusions 4 weeks apart 12 weeks 51
INCLUSION CRITERIA:	Male and female patients at least 18 years of age who had clinical evidence of moderate-to-severe Crohn's disease, CDAI score between 220 and 450.			
EXCLUSION CRITERIA:	Patients who had received MTX, cyclosporine, or any investigational agents within three months before randomization were excluded; patients who were receiving azathioprine or mercaptopurine were required to have been taking a stable dose for at least four months before randomization. Other criteria for exclusion included prior treatment with any antibody agent, current use of oral prednisolone at a dose of more than 25 mg per day or another corticosteroid at an equivalent dose, current use of an elemental diet or parenteral nutrition, infectious or neoplastic diseases of the bowel, bowel surgery within three months before randomization, the presence of an ostomy, the presence of symptoms due mainly to fibrotic strictures, and a clinical impression that the patient was likely to require abdominal surgery soon.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	See above (prednisolone<25mg/day)			

Authors: Ghosh et al.
Year: 2003

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: moderate to severe

	Placebo &placebo	NAT 3mg/kg & placebo	NAT 3mg/kg & NAT 3mg/kg	NAT 6mg/kg & NAT 6mg/kg
Mean age (years):	34	36	36	35
Sex (% female):	52	60	55	51
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• Previous surgery for CD (%)	NR	NR	NR	NR
• Patients with fistulae (%)	10	16	12	25
• Mean baseline CDAI	300	288	300	298
• Mercaptopurine /Azathioprine use (%)	35	38	26	18
• Corticosteroids use (%)	49	46	56	63
• HAQ score	NR	NR	NR	NR

OUTCOME ASSESSMENT:

Primary Outcome Measures: clinical remission: CDAI < 150 at 6 weeks; clinical response: a decrease of least 70 points from baseline.
Secondary Outcome Measures: serum level of CRP; HR-QOL (IBDQ)
Timing of assessments:
Week 2, 4, 6, 8, 12

RESULTS:

Health Outcome Measures:

- Week 12 remission: placebo 27% vs. 1 infusion of NAT 3mg/kg 28% vs. 2 infusions of NAT 3mg/kg 42% vs. 2 infusions of NAT 6mg/kg 39% ($P = 0.042$ for 2 infusions of 3mg/kg vs. placebo only)
- Week 12 response: placebo 43% vs. 1 infusion of NAT 3mg/kg 50% vs. 2 infusions of NAT 3mg/kg 61% vs. 2 infusions of NAT 6mg/kg 65% ($P = 0.033$ for 2 infusions of 3mg/kg vs. placebo and $P = 0.018$ for 2 infusions of 6mg/kg)
- IBDQ week 12 scores: placebo 145 vs. 1 infusion of NAT 3mg/kg 149 vs. 2 infusions of NAT 3mg/kg 161 vs. 2 infusions of NAT 6mg/kg 155 ($P = 0.021$ for 2 infusions of 3mg/kg vs. placebo and $P = 0.014$ for 2 infusions of 6mg/kg)
- Patients used rescue medication during study: placebo 17% vs. 1 infusion of NAT 3mg/kg 21% vs. 2 infusions of NAT 3 mg/kg 15% vs. 2 infusions of Nat 6 mg/kg 12% (P = NS, data NR)

Authors: Ghosh et al. **Year: 2003**				
ADVERSE EVENTS:	**Placebo & placebo**	**NAT 3mg/kg & placebo**	**NAT 3mg/kg & NAT 3mg/kg**	**NAT 6mg/kg & NAT 6mg/kg**
Overall adverse effects reported(%):	81	77	88	78
• Infections (%)	13	11	12	8
• abdominal pain (%)	17	12	15	18
• influenza syndrome (%)	8	14	11	20
• pain (%)	8	6	6	18
• infusion reaction (%)	0	0	2	2
• serious adverse events (%)	11	11	9	12
Significant differences in adverse events:	No			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes			
ADEQUATE RANDOMIZATION:	Yes			
ADEQUATE ALLOCATION CONCEALMENT:	Yes			
BLINDING OF OUTCOME ASSESSORS:	Yes			
ATTRITION (*overall*):	**Overall attrition:** 11% **Attrition differential high:** No			
ATTRITION (*treatment specific*):	**Placebo & placebo**	**NAT 3mg/kg & placebo**	**NAT 3mg/kg & NAT 3mg/kg**	**NAT 6mg/kg & NAT 6mg/kg**
Attrition overall:	15.9%	8.8%	9.1%	11.8%
Attrition due to adverse events :	3%	1%	3%	6%
QUALITY RATING:	**Good**			

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Hanauer et al.,[93] Lichtenstein et al.,[94] Feagan et al.[95] Geboes et al.,[96] and Rutgeerts et al.[97]** **Year: 2002, 2003, 2005, 2006** **Country:** Multinational		
FUNDING:	Centocor, Malvern PA		
RESEARCH OBJECTIVE:	To assess the benefit of maintenance infliximab therapy in patients with active Crohn's disease who respond to a single infusion of infliximab, the impact of remission on patients' employment, quality of life, and hospitalization to validate clinical remission and health related quality of life and effect of infliximab on endoscopic and histologic disease activity and expression of inflammatory markers		
DESIGN:	**Study design:** RCT **Setting:** Multicenter (55 sites) **Sample size:** 573 (48 mucosal biopsy substudy)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF dose 1** 5 mg/kg at weeks 2,6 & every 8 weeks thereafter 54 weeks 192 (18)	**INF dose 2** 5 mg/kg injections at weeks 2, 6, then 10 mg/kg every 8 weeks 54 weeks 193 (15)	**Placebo** N/A (responded to one initial dose of INF) 54 weeks 188 (15)
INCLUSION CRITERIA:	Crohn's disease of at least 3 months duration; CDAI score between 220 and 400		
EXCLUSION CRITERIA:	Previous treatment with INF or another agent targeted at TNF; pregnancy		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	5-aminosalicylates or antibiotics; corticosteroids; azathioprine or 6-mercatopurine; MTX		

Authors: Hanauer et al., Lichtenstein et al., Feagan et al., Geboes et al., and Rutgeerts et al. **Year: 2002, 2003, 2005, 2006**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR; characterized week 2 responders and non-responders **Disease severity:** Moderate to severe
	All patients
Median age (years):	35
Sex (% female):	58
Ethnicity (White):	96%
Other germane population qualities:	
• Previous surgery for CD (%)	51%
• Median baseline CDAI	297
• Median baseline IBDQ	127
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Time to loss of response (CDAI score $\geq$ 175) up to and including week 54 among week 2 responders; proportion of week 2 responders in remission at week 30 (CDAI score < 150); Employment status; PCS and MCS of SF-36; IBDQ **Secondary Outcome Measures:** Employment status; hospitalizations, surgeries, and work loss; PCS and MCS of SF-36; IBDQ, Corticosteroid discontinuation; endoscopic healing **Timing of assessments:** Weeks 0,2,6,10,14,22,30,38,46,54; SF-36 taken at wk 10, 30, and 54

Authors: Hanauer et al., Lichtenstein et al., Feagan et al., Geboes et al., and Rutgeerts et al. **Year: 2002, 2003, 2005, 2006**	
RESULTS:	**Health Outcome Measures: At 54 weeks** • Among patients unemployed at baseline, significantly more patients who achieved remission were employed (31%) than patients who did not achieve remission (16%) ($P < 0.05$) • Hospitalization rate, # of surgeries, and work loss were lower for responding patients ($P < 0.05$) • Patients in remission had significantly better MCS and PCS scores. ($P < 0.0001$) • Total IBDQ score was more significantly improved in the INF 5mg/kg group ($P < 0.05$) and the INF 10mg/kg group ($P < 0.001$) than the placebo group. • Significantly more patients discontinued corticosteroids in Active vs. Placebo OR: 4.2 (CI 1.5-11.5) **Intermediate Outcome Measures:** • Patients on active treatment were more likely to be in clinical remission at 30 weeks than patients taking placebo; OR: 2.7 (CI 1.6-4.6) • Patients on active treatment had a significantly longer time to loss of response than placebo patients; median 46 weeks for INF compared to 19 weeks for placebo ($P = 0.0002$) • Higher proportion of 2 week responders in combined scheduled maintenance group had complete mucosal healing at week 54 compared with episodic group (50% vs. 7%, $P=0.007$) • Significantly greater improvement in CDEIS occurred with scheduled maintenance compared with episodic treatment at week 54 ($P = 0.026$) • No strong relationship found between clinical remission and complete mucosal healing

Authors: Hanauer et al., Lichtenstein et al., Feagan et al., Geboes et al., and Rutgeerts et al. **Year: 2002, 2003, 2005, 2006**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Infections • Intestinal Stenosis • Infusion reactions • Serum sickness like reactions	**INF 5mg/kg** 72 (37%) 3 (2%) 44 (23%) 5 (3%)	**INF 10mg/kg** 58 (30%) 5 (3%) 36 (19%) 6 (3%)	**Placebo** 78 (41%) 6 (3%) 17 (9%) 3 (2%)
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 124 (22%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**INF dose 1** 49 (26%) 29 (15%)	**INF dose 2** 37 (19%) 16 (8%)	**Placebo** 38 (20%) 5 (3%)
QUALITY RATING:	**Fair**		

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Sands et al.[98-100] and Lichtenstein et al.[101]** **Year: 2004, 2005, 2006** **Country:** Multinational	
FUNDING:	Centocor and NIH	
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of infliximab in maintaining closure of draining fistulas among patients who had a response to a three dose induction regimen of infliximab	
DESIGN:	**Study design:** RCT **Setting:** 45 sites **Sample size:** 282	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 54 weeks 144	**INF** 5mg/kg of body weight 54 weeks 138
INCLUSION CRITERIA:	Men and women, 18 or older, with Crohn's disease with single or multiple draining fistulas, including perianal and enterocutaneous fistulas, for at least 3 months; women with rectovaginal fistulas were included if they had at least one other enterocutaneous draining fistula.	
EXCLUSION CRITERIA:	Patients with rectovaginal fistulas but no enterocutaneous fistula; patients that had a stricture or abscess for which surgery might be indicated; previous treatment with INF	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concurrent stable doses of 5-aminosalicylates, oral corticosteroids, azathioprine, mercaptopurine, mycophenolate mofetil, MTX, and antibiotics were permitted	

<table>
<tr><td colspan="4">Authors: Sands et al.
Year: 2004 and 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: Moderate</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>INF</u></td><td></td></tr>
<tr><td>Median age (years):</td><td>36</td><td>37</td><td></td></tr>
<tr><td>Sex (% female):</td><td>52</td><td>45</td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Previous surgery for CD (%)</td><td>55</td><td>57</td><td></td></tr>
<tr><td>• CDAI (%) ≥150</td><td>59</td><td>59</td><td></td></tr>
<tr><td>• CDAI (%) ≥220</td><td>32</td><td>34</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Time to loss of response defined by change in the number of draining fistulas
Secondary Outcome Measures: Crohn’s disease activity index (CDAI); Inflammatory bowel disease questionnaire (IBDQ), hospitalizations, hospitalization days, number of surgeries; new abscess
Timing of assessments: weeks 0, 2, 6, 10, 14, 22, 30, 38, 46,54</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Time to loss was significantly longer for patients with received INF maintenance therapy than for those who received placebo maintenance (more than 40 weeks vs. 14 weeks, $P < 0.001$).
• 62% of patients in placebo group had a loss of response vs. 42% in INF group ($P < 0.001$)
• At week 54, 19% of patients in placebo group had a complete absence of draining fistulas, as compared with 36% of INF patients ($P = 0.009$).
• Compared to placebo, INF patients had fewer hospitalizations (11 vs. 31; $P < 0.05$), fewer mean hospitalization days (0.5 vs. 2.5 days/100; $P < 0.05$), and fewer surgeries (65 vs. 126; $P < 0.05$)
Intermediate Outcome Measures:
• Median decrease in CDAI at week 54 was 15 for placebo and 40 for INF ($P = 0.04$)
• Median increase for IBDQ at week 54 was 5 for placebo and 10 for INF ($P = 0.03$)
2nd Year Safety Analysis:
• 15% (95%CI: 9-21%)of patients in INF maintenance group had at least one newly developed fistula-related abscess compared with 19% (95%CI: 12-25%) in placebo group ($P = 0.526$)
• Proportion of patients with a new fistula-related abscess was similar regardless of whether or not patients crossed over to a 5 mg/kg higher INF dose
• Number of fistula-related abscesses diagnosed over time did not differ between groups</td></tr>
</table>

Authors: Sands et al. **Year:2004**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Infections • New fistula related abscesses • Infusion reactions • Developed antinuclear antibodies	**Placebo** 132 (92%) 48 (33%) 25 (17%) 24 (17%) 24 (18%)	**INF** 123 (89%) 22 (16%) 17 (12%) 22 (16%) 56 (46%)	
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Method NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** Unable to assess; assume no loss to follow-up		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Placebo** NR 12 (8%)	**INF** NR 5 (4%)	
QUALITY RATING:	**Good**		

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Schreiber et al.[102] and Rutgeerts et al.[103]** **Year: 2005 and 2008** **Country:** Multinational			
FUNDING:	Celltech (now UCB)			
RESEARCH OBJECTIVE:	To investigate the safety and efficacy of certolizumab in Crohn's disease			
DESIGN:	**Study design:** RCT **Setting:** Multicenter (58) **Sample size:** 292 (291 ITT)			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 20 weeks 73	**Certolizumab100** 100 mg wks 0,4,8 20 weeks 74	**Certolizumab200** 200 mg wks 0,4,8 20 weeks 72	**Certolizumab400** 400 mg wks 0,4,8 20 weeks 72
INCLUSION CRITERIA:	At least 18 years old with a clinical diagnosis of Crohn's disease as confirmed by radiologic, endoscopic, or histologic evidence following established diagnostic criteria; moderate to severe disease, defined by a CDAI score of 220–450 points over a 7-day screening period.			
EXCLUSION CRITERIA:	Suspected or diagnosed abscess at screening, a bowel perforation or evidence of noninflammatory obstruction during the 6 months before, extensive bowel resection, a functional colostomy or ileostomy, a positive stool culture for enteric pathogens, or a known history of tuberculosis; treatment for Crohn's disease with sodium cromoglycate, mycophenolate, or cyclosporine within 4 weeks, or receipt of other anti-TNF therapy with a biologic agent within 12 weeks; treated previously with any anti-TNF agent and either had experienced an infusion reaction that was suspected or confirmed to be associated with an immune response, or had showed a lack of clinical response to the first dose; participated in another clinical trial with certolizumab; involved in any other clinical drug trial within the 4 weeks			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Permitted if the patient was on a stable dose that could be continued throughout the 12-week duration			

Authors: Schreiber et al. and Rutgeerts et al.
Year: 2005 and 2008

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: moderate-to-severe

	Placebo	Certolizumab100	Certolizumab200	Certolizumab400
Mean age (years):	35.8	33.5	40.1	35.9
Sex (% female):	67.1	52.7	69.4	55.6
Ethnicity (% white):	96.6	96.6	96.6	96.6
Other germane population qualities:				
• Disease duration (yrs)	7.95	7.73	8.84	8.43
• IBDQ	122.9	132.2	122.9	126.5

OUTCOME ASSESSMENT:

Primary Outcome Measures: CDAI response (≥ 100 point decrease) or remission (CDAI score ≤ 150) at week 12

Secondary Outcome Measures: Remission (CDAI score ≤ 150), HRQOL at 12 weeks using IBDQ

Timing of assessments: Weeks 0,2,4,6,8,10,12

RESULTS:

Health Outcome Measures:

- Week 12 response or remission: placebo 35.6% CER100 36.5% CER200 36.1% CER400 26.4%
- Week 12 remission placebo 23.3% CER100 27.0% CER200 19.4% CER400 44.4%
- Week 12 remission on IBDQ (>170) placebo 23.36%, CER100 38.4%, CER200 23.6%, CER400 38.9%: CER400 vs. placebo $P < 0.05$

Authors: Schreiber et al. and Rutgeerts et al. **Year: 2005 and 2008**				
ADVERSE EVENTS: **Overall adverse effects reported:** • Serious AE • ISR	**Placebo** 69.9 8.2 2.7	**Certolizumab100** 77.0 9.5 6.8	**Certolizumab200** 76.4 13.9 5.6	**Certolizumab400** 65.8 8.2 2.7
Significant differences in adverse events:	No			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 1			
ADEQUATE RANDOMIZATION:	Yes			
ADEQUATE ALLOCATION CONCEALMENT:	Yes			
BLINDING OF OUTCOME ASSESSORS:	Yes but method NR			
ATTRITION (*overall*):	**Overall attrition:** 29% (85 withdrawals) **Attrition differential high:** No			
ATTRITION (*treatment specific*):	**Placebo**	**Certolizumab100**	**Certolizumab200**	**Certolizumab400**
Attrition overall:	27%	32%	26%	29%
Attrition due to adverse events:	11%	12%	10%	10%
QUALITY RATING:	**Fair**			

Evidence Table 5. Targeted Immune Modulators – Crohn's Disease

STUDY:	**Authors: Targan et al.[104] and Lichtenstein et al.[105]** **Year: 1997 and 2002** **Country:** North America and Europe			
FUNDING:	Centocor and an Orphan drug grant from the FDA			
RESEARCH OBJECTIVE:	To assess the efficacy of infliximab in Crohn's disease; patients not responding at 4 weeks were given open label infliximab at 10mg/kg			
DESIGN:	**Study design:** RCT **Setting:** Multi-center (18 sites) **Sample size:** 108			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** Single infusion at 5 mg/kg 12 weeks 27	**INF** Single infusion at 10 mg/kg 12 weeks 28	**INF** Single infusion at 20 mg/kg 12 weeks 28	**Placebo** N/A 12 weeks 25
INCLUSION CRITERIA:	Crohn's disease for six months, with scores on the CDAI between 220 and 400			
EXCLUSION CRITERIA:	Cyclosporine, MTX, or experimental agents within three months before screening; symptomatic stenosis or ileal strictures; proctocolectomy or total colectomy; stoma; history of allergy to murine proteins; prior treatment with murine, chimeric, or humanized monoclonal antibodies; treatment with parenteral corticosteroids or corticotropin within four weeks before screening.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Mesalamine for 8 or more weeks; mercaptopurine or azathioprine for 6 or more months; coticosteroids			

Authors: Targan et al. and Lichtenstein et al.
Year: 1997 and 2002

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: Moderate - severe

	INF 5	INF10	INF20	Placebo
Mean age (years):	37.0	39.3	36.0	38.5
Sex (% female):	48	54	54	40
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• Previous surgery for CD (%)	44	50	50	52
• Mean baseline CDAI	312	318	307	288

OUTCOME ASSESSMENT:

Primary Outcome Measures: CDAI response of reduction of 70 or more points at 4 weeks

Secondary Outcome Measures: IBDQ and CRP(mg/liter)

Timing of assessments: 2, 4, and 12 weeks; patients not responding at 4 weeks were given an open-label dose of INF 10mg/kg

RESULTS:

Health Outcome Measures:

- At 4 weeks, the end of the blinded portion, the CDAI response was significantly better in the active treatment groups (INF 5mg/kg 81% ($P < 0.001$ vs. placebo); INF 10mg/kg 50% ($P = 0.003$ vs. placebo); INF 20mg/kg 64% ($P < 0.001$ vs. placebo); placebo 17%
- IBDQ score increase was significantly better for active treatment (INF 5mg/kg 46 ($P < 0.001$ vs. placebo); INF 10mg/kg 30 ($P = 0.02$ vs. placebo); INF 20 ($P = 0.03$ vs. placebo); placebo 5

Intermediate Health Outcome Measure:

- CRP decreased significantly compared to placebo ($P < 0.01$)
- At 4 weeks, 48 non-responders were given a10mg/kg dose; 57% of persons initially on placebo responded and 34% of persons with 2nd INF dose responded

Authors: Targan et al. and Lichtenstein et al. **Year: 1997 and 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Headache • Nausea • URTI • Fatigue	**<u>One dose (n = 102)</u>** 76 (75%) 19 (19% 11 (11%) 8 (8%) 6 (6%)	**<u>Two doses (n = 29)</u>** 23 (79%) 3 (10%) 5 (17%) 4 (14%) 3 (10%)	**<u>Placebo (n = 25)</u>** 15 (60%) 5 (20%) 2 (8%) 3 (12%) 1 (4%)
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**<u>One dose</u>** NR NR	**<u>Two doses</u>** NR 2 (7%)	**<u>Placebo</u>** 0 NR
QUALITY RATING:	**Fair**		

Evidence Table 6. Targeted Immune Modulators – Ulcerative Colitis

STUDY:	**Authors:** Ford et al.[91] **Year:** 2011 **Country:** **Quality rating:** Good
FUNDING:	American College of Gastroenterology
DESIGN & SIZE:	**Study design:** Systematic review with meta-analysis **Number of patients: 4526** (827 Ulcerative Colitis) **Trials: 27** (5 Ulcerative Colitis)
OBJECTIVE OF REVIEW:	To conduct a systematic review and meta-analysis of RCTs to estimate the efficacy and safety of biologic therapies in inflammatory bowel disease.
ELIGIBILITY CRITERIA:	RCTs examining the effect of biological therapies, restricted to those approved for use by the US Food and Drug Administration (FDA), in adult patients (> 90 % of participants over the age of 16 years) with active or quiescent IBD were eligible for inclusion.
STUDIES INCLUDED IN REVIEW:	For Ulcerative Colitis: Rutgeerts, 2005; Jarnerot, 2005; Probert, 2003; Sands, 2001 For Crohn's Disease: Hanauer, 2006; Sandborn, 2007; Hibi, 2002, Colombel, 2007, Sandborn, 2007b, Colombel, 2009, Schreiber, 2005, Sandborn, 2007c, Sandborn, 2010, Schreiber, 2007, Targan, 1997, Lemann, 2006, Colombel, 2010, Rutgeerts, 1999, Hanauer, 2002, Present, 1999, Sands, 2004, Gordon, 2001, Ghosh, 2003, Sandborn, 2005, Sands, 2007, Targan, 2007, Sandborn, 2005
LITERATURE SEARCH DATES:	MEDLINE (1966 to December 2010), EMBASE (1984 to December 2010), the Cochrane central register of controlled trials (Issue 4, October 2010), and the Cochrane IBD Group Specialized Trials Register.
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	For Ulcerative Colitis: Five RCTs, reported in four separate articles that reported efficacy of biological therapies in inducing remission in patients with moderately to severely active UC who had failed, or were receiving, therapy with corticosteroids. All trials used infliximab, and none were at low risk of bias. Three RCTs recruited hospitalized inpatients and two recruited ambulatory outpatients. Study duration ranged from 6 to 12 weeks

	For Crohn's Disease: The review included 27 randomized controlled trials: eight on adalimumab, seven on certolizumab pegol, seven on infliximab, and six on natalizumab. The review assessed two outcomes, failure of remission and relapse of disease activity, and analyzed the subgroup of patients with fistulizing disease separately. Most of the included efficacy studies were conducted in narrowly defined populations and/or were limited to less than one year of follow-up. Patients were allowed to remain on stable doses of corticosteroids in all trials. All patients suffered from active Crohn's disease of at least three months' duration.

Authors: Ford et al. **Year: 2011**	
DATA SYNTHESIS METHODS:	Meta-analysis (random effects model)
MAIN RESULTS: (RESULTS IN SUBGROUPS)	For Ulcerative Colitis: Remission was not achieved in 231 (42.9 %) of 539 patients randomized to infliximab at 6 weeks to 3 months, compared with 201 (69.8 %) of 288 assigned to placebo. RR = 0.72 (95% CI, 0.57 to 0.91) for a failure to achieve remission (infliximab vs. placebo) [I-squared = 70%, P = 0.009, 5 studies (827 patients)] For Crohn's Disease: *Adalimumab (vs. placebo):* The relative risk of not achieving remission for adalimumab-treated patients compared with placebo was 0.85 (95% CI, 0.79 to 0.91). The relative risk of failing to prevent relapse was not statistically significant 0.54 (95% CI, 0.27 to 1.07). The relative risk of not achieving healing of fistulizing Crohn's disease was 0.94 (95% CI, 0.76 to 1.17). *Certolizumab Pegol (vs. placebo):* The relative risk of not achieving remission for certolizumab pegol-treated patients compared with placebo was 0.95 (95% CI, 0.9 to 1.01). By week 26, the relative risk of failure in preventing relapse in certolizumab pegol-treated patients compared with placebo was 0.73 (95% CI, 0.63 to 0.85). The calculated risk ratio of not healing fistulizing Crohn's disease was 0.97 (95% CI, 0.77 to 1.22). *Infliximab (vs. placebo):* The relative risk of not achieving remission for infliximab-treated patients compared with placebo-treated patients was 0.68 (95% CI, 0.52 to 0.9). The relative risk of not preventing relapse was statistically significantly lower in infliximab compared with placebo (relative risk, 0.72; 95% CI, 0.63 to 0.83). The risk of not healing of fistulizing Crohn's disease for infliximab-treated patients compared with placebo-treated patients was 0.62 (95% CI, 0.48 to 0.81). The relative risk of loss of response of fistulizing Crohn's disease was 0.81 (95% CI, 0.68 to 0.96).

	Natalizumab (vs. placebo): The reviewers calculated a relative risk of natalizumab failing to induce remission in active luminal Crohn's disease of 0.88 (95% CI, 0.83 to 0.94). The reviewers calculated a relative risk of preventing relapse in quiescent luminal Crohn's disease of 0.71 (95% CI, 0.61 to 0.84).
ADVERSE EVENTS:	Ulcerative Colitis: The RR of any adverse event was no higher with infliximab, and serious adverse events were lower (RR = 0.64; 95 % CI 0.41 – 1.00, P = 0.05, 4 studies (515 patients)). No statistically significant differences were detected in numbers of patients experiencing infusion reactions, headache, rash, or arthralgia with infliximab compared with placebo. Crohn's disease: Eight trials of anti-TNFα antibodies (Adalimumab, Certolizumab pegol, Infliximab) provided data on adverse events. No statistically signifi cant difference in the incidence of adverse events was detected with anti-TNFα antibodies compared with placebo. The relative risk of experiencing any adverse event was 0.99 (95% CI, 0.90 to 1.08). Five trials of natalizumab provided data on adverse events. There were significantly more patients allocated to natalizumab reporting headache, compared with placebo. The relative risk was 1.23 (95 % CI, 1.03 to 1.47).
LIMITATIONS OF PRIMARY STUDIES	Attrition

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Asahina et al.**[106] **Year: 2010** **Study name:** The Adalimumab M04-688 Study Group **Country:** Japan **Quality rating:** Fair			
FUNDING:	Sponsored by Abbott Japan, Tokyo, Japan, and Eisai, Tokyo, Japan; Abbot Laboratories provided medical writing support.			
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of three different dosing regimens of adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis.			
DESIGN & SIZE:	**Study design:** Phase II/III RCT **Setting:** multicenter (42 sites in Japan) **Number screened:** Not Reported **Number eligible:** 235 consented **Number enrolled:** 169 **Run-in/Wash-out period:** 14 days for topical therapies and phototherapy, 28 days for systemic therapy and PUVA.			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Drug 1** Adalimumab 40mg every other week 24 weeks 38	**Drug 2** Adalimumab 40mg every other wk starting wk 2, after loading dose of 80mg at wk 0 24 weeks 43	**Drug 3** Adalimumab 80mg every other week 24 weeks 42	**Drug 4** Placebo every other week 24 weeks 46
INCLUSION CRITERIA:	≥20 years of age, a clinical diagnosis of moderate to severe chronic plaque psoriasis, defined by a score of 12 or greater on the Psoriasis Area and Severity Index (PASI) and body surface area (BSA) involvement of 10% or greater, for at least 6 months, during which time plaque psoriasis was stable for at least the recent two months			
EXCLUSION CRITERIA:	previous exposure to anti-TNF therapy, other active skin diseases or skin infections, diagnosis of systemic lupus erythematosus, scleroderma, or rheumatoid arthritis, history of central nervous system demyelinating disease, cancer, lymphoma, leukemia, tuberculosis, or lymphoproliferative disease, positive serology for anti-HIV antibody, hepatitis B surface antigen, anti-hepatitis C antibody, active infectious disease, immunosuppressive disease, or abnormal hematological, hepatic, or renal values			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	weak or medium-potency topical corticosteroids to palms, soles, face, scalp, and groin			

Authors: Asahina et al. **Year: 2010**				
POPULATION CHARACTERISTICS:	**Adalimumab 40mg**	**Adalimumab 40mg with 80mg loading dose**	**Adalimumab 80mg**	**Placebo**
Mean age (years):	47.8±12.81	44.2±14.32	43.5±12.40	43.9±10.75
Sex (% female):	6 (15.8%)	8 (18.6%)	7 (16.7%)	5 (10.9%)
Ethnicity:	Japanese	Japanese	Japanese	Japanese
Class naïve:	100%	100%	100%	100%
Other germane population qualities:				
• **Mean PASI**	25.44±8.977	30.24±10.946	28.27±11.029	29.10±11.767
• **Mean body surface area involvement**	43.3%	48.3%	46.1%	46.7%
• **Mean duration of psoriasis**	14.2 yrs ±9.29 yrs	14.0 yrs ±7.36 yrs	11.6 yrs ±7.45 yrs	15.5 yrs ±8.83 yrs
• **Received prior systemic therapy of nonbiologics within 6 mo prior to screening (%)**	47.4%	41.9%	42.9%	37.0%
• **Phototherapy received within 6 months prior to screening (%)**	18.4%	23.3%	16.7%	41.3%
RESULTS:	**Primary Outcome Measures:** %of patients achieving a 75% or greater improvement in Psoriasis Area and Severity Index (PASI 75) score at week 16: Drug 1: 57.9%; Drug 2: 62.8%; Drug 3: 81.0%; Placebo 4.3% ($p<0.001$). **Secondary Outcome Measures:** % of patients achieving PASI 50, PASI 90 and Physicians Global Assessment of "clear" or "minimal", changes in health-related QOL were assessed by the Dermatology Life Quality Index (DLQI) and Short Form 36 (SF-36) Health Survey at week 16; PASI 50: Drug 1: 73.7%; Drug 2: 81.4%; Drug 3: 90.5%; Placebo 19.6%; PASI 90: Drug 1: 36.8%; Drug 2: 39.5%; Drug 3: 61.9%; Placebo: 0%; PGA "Clear" or "Minimal": Drug 1: 44.7%; Drug 2: 60.5%; Drug 3: 78.6%; Placebo: 4: 8.7%; DLQI change from baseline to week 16: Drug 1: -3.9; Drug 2: -5.1; Drug 3: -6.8; Placebo:+1.0 ($p<0.001$ for PASI, PGA, and DLQI); SF-36change from baseline to week 16: Drug 1: 3.7 ($p<0.05$); Drug 2: 4.6 ($p<0.01$); Drug 3: 4.9 ($p<0.001$); Placebo: -0.4($p>0.05$).			

Authors: Asahina et al. **Year: 2010**				
METHOD OF ADVERSE EVENTS REPORTING:	**Adverse events were assessed at each, every other week, visit. Laboratory evaluations and vital signs were conducted at baseline and at weeks 2, 4, 8, 12, 16, 20, and 24.**			
ADVERSE EVENTS (%):	**Drug 1**	**Drug 2**	**Drug 3**	**Drug 4**
Overall adverse effects reported:	37 (97.4%)	39 (90.7%)	38 (90.5%)	41 (89.1)
• Infections	55.3%	41.9%	50.0%	50.0%
• URTI				
• abnormal LFT	see below	see below	see below	see below
• herpes simplex				
• pneumonia				
• tb	0%	0%	0%	not stated: assume 0%
• ISR	15.8%	18.6%	14.3%	6.5%
• ALT	15.8%	16.3%	4.8%	6.5%
• AST	7.9%	9.3%	2.4%	4.3%
• GGT	13.2%	2.3%	2.4%	0%
• Hepatic event	39.5%	30.2%	23.8%	8.7%
• Hepatobiliary disorders	7.9%	7.0%	11.9%	0%
ATTRITION (*overall*):	**Overall attrition:** 22 (13.0%) **Attrition differential high:** Possibly, for comparisons of Drug 1 and 3 vs Drug 2			
ATTRITION (*treatment specific*):	**Drug 1**	**Drug 2**	**Drug 3**	**Drug 4**
Attrition overall:	4 (10.5%)	8 (18.6%)	4 (9.5%)	6 (13.0%)
Attrition due to adverse events:	2 (5.3%)	5 (11.6%)	3 (7.1%)	5 (10.9%)

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Brimhall et al.**[107] **Year: 2008** **Country:**
FUNDING:	None
DESIGN:	**Study design:** Systematic review **Number of patients:** 7,931
AIMS OF REVIEW:	To evaluate and compare the efficacy and safety of biological agents in the treatment of plaque psoriasis
STUDIES INCLUDED IN META-ANALYSIS	**ALE (three trials)** n=1289 **EFA (five trials)** n=3130 **ETA (four trials)** n=2017 **INF (four trials)** n=1495
TIME PERIOD COVERED:	MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. were searched from inception to June 2005; an updating search was conducted in July 2006 to capture reports from the interim period
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized, controlled, double-blind, monotherapy trials
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients with psoriasis

Authors: Brimhall et al. **Year: 2008**				
CHARACTERISTICS OF INTERVENTIONS:	ALE vs. placebo EFA vs. placebo ETA vs. placebo INF vs. placebo			
MAIN RESULTS:	NNT (95% CI)	PASI 50	PASI 75	PASI 90
	ALE	4(3.07–4.48)	8 (5.05–12.20)	N/A
	EFA	3(3.26–4.48)	4(3.36–5.24)	N/A
	ETA	N/A	3(2.07–2.49)	5(4.29–5.88)
	INF	N/A	2(1.24–1.38)	2(1.67–2.31)
ADVERSE EVENTS:			NNH (95%CI)	
	ALE		15(7.63–142.86)	
	EFA		9(7.30–13.88)	
	ETA		46(–48–14)	
	INF		9(5.99–19.61)	
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes			
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes			
QUALITY RATING:	**Fair**			

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Gordon et al.[108] and Shikiar et al.[109]** **Year: 2006** **Country:** US and Canada		
FUNDING:	Abbott Labs		
RESEARCH OBJECTIVE:	Efficacy and safety of ADA in patients with moderate to severe plaque psoriasis. After 12 week all patients were switched to active arms.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 147		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 12 weeks 52	**ADA EOW** 80 mg at week 0 and 40 mg EOW 12 weeks 45	**ADA Weekly** 80 mg at week 0 and 40 mg weekly 12 weeks 50
INCLUSION CRITERIA:	Men and women age 18 years and older with plaque psoriasis of at least 1-year duration and involving 5% or more of their body surface area.		
EXCLUSION CRITERIA:	History of neurologic symptoms suggestive of central nervous system demyelinating disease, or with a history of cancer or lymphoproliferative disease (other than successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Low to mid dose topical corticosteroids		

<table>
<tr><td colspan="4">Authors: Gordon et al. and Shikiar et al.
Year: 2006</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline:</td></tr>
<tr><td><u>Placebo</u></td><td><u>ADA EOW</u></td><td><u>ADA Weekly</u></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Ethnicity (% Caucasian):
Other germane population qualities:
• Mean PASI
• Mean body surface area involvement
• Mean duration of psoriasis -yrs
• Received prior systemic therapy (%)</td><td>43
35
92

16.0
28

19
NR</td><td>46
29
89

16.7
29

21
NR</td><td>44
34
90

14.5
25

18
NR</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: PASI 75% and DLQI at 12 weeks
Secondary Outcome Measures: PASI 75 at 24 weeks and PGA, SF-36 Health Survey, and Euro QoL-5D (EQ-5D)
Timing of assessments: weeks 0, 1, 2, and 4, and then every 4 or 8 weeks thereafter.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• PASI 75% at 12 weeks Placebo 4% ADA EOW 53% ADA WK 80%
• PASI 100% at 12 weeks Placebo 0% ADA EOW 11% ADA WK 26%
• DLQI change at 12 weeks Placebo 1.3% (3.3, 0.7) ADA EOW 10.8 (13.1, 8.5) ADA WK 11.5 (13.6, 9.4) ADA(both) vs. placebo $P < 0.001$
• EQ-5D Index score change at 12 weeks Placebo 0.01 (0.07, 0.1) ADA EOW 0.21 (0.11, 0.31) ADA WK 0.19 (0.09, 0.28) ADA(both) vs. placebo $P < 0.001$
• EQ-5D VAS change at 12 weeks Placebo 0.5 (5.7, 6.8) ADA EOW 17.9 (10.5, 25.2) ADA WK 10.7 (4.1, 17.4) ADA EOW vs. placebo $P < 0.001$ and ADA WK vs. placebo $P = 0.013$
• SF-36 PCS change at 12 weeks Placebo 0.5 (2.4, 3.5) ADA EOW 3.6 (0.2, 7.0) ADA WK 5.5 (2.4, 8.6) ADA EOW vs. placebo $P = 0.118$ and ADA WK vs. placebo $P = 0.010$
• SF-36 MCS change at 12 weeks Placebo 0.1 (3.5, 3.3) ADA EOW 7.8 (3.9, 11.8) ADA WK 5.2 (1.6, 8.9) ADA EOW vs. placebo $P < 0.001$ and ADA WK vs. placebo $P = 0.017$</td></tr>
</table>

Authors: Gordon et al. and Shikiar et al. **Year: 2006**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Dyspepsia • Nausea • Injection site pain	**Placebo** 67.3% 0 0 5.8% 5.8%	**ADA EOW** 62.2% 0 0 6.7% 6.7%	**ADA Weekly** 78.0% 2.0% 8.0% 2.0% 12.0%
Significant differences in adverse events:	None reported		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 1		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall attrition:** 7 (5%) **Attrition differential high:** No		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**Placebo** 3.8% 1.9%	**ADA EOW** 4.4% 4.4%	**ADA Weekly** 6.0% 6.0%
QUALITY RATING:	**Fair**		

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Griffiths et al.**[110] **Year: 2010** **Study name: -** **Country: Worldwide** **Quality rating: FAIR**		
FUNDING:	Centocor Research and Development (pharmaceutical industry)		
RESEARCH OBJECTIVE:	To compare two biologic agents, ustekinumab and etanercept, for the treatment of psoriasis		
DESIGN & SIZE:	**Study design:** head-to-head RCT **Setting:** multi-center **Number screened:** 1,175 **Number eligible:** not reported **Number enrolled:** 903 **Run-in/Wash-out period:** no		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 50 mg twice weekly 12 weeks 347	**UST** 45 mg at weeks 0 and 4 12 weeks 209	**UST** 90 mg at weeks 0 and 4 12 weeks 347
INCLUSION CRITERIA:	≥18 years of age, diagnosis of plaque psoriasis at least 6 months earlier, candidates for phototherapy or systemic treatment, score ≥12 on PASI, score ≥3 on physician's global assessment; involvement of ≥10% of body-surface area; inadequate response, intolerance or contraindication to ≥1 conventional systemic agent (i.e., methotrexate, cyclosporine, or psoralen plus UVA), and no previous treatment with UST or ETA.		
EXCLUSION CRITERIA:	Nonplaque or drug-induced forms of psoriasis, recent serious infection, history of chronic or recurrent infectious disease, known malignant condition (other than treated basal- or squamous-cell skin cancer or cervical cancer in situ with no evidence of recurrence for ≥5 years), receipt of conventional systemic therapy or phototherapy within 4 weeks before enrollment, topical psoriasis agents within 2 weeks, investigational drugs within 4 weeks or 5 half-lives, biologic agents within 3 months or 5 half-lives.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	None reported		

Authors: Griffiths et al. **Year: 2010**			
POPULATION CHARACTERISTICS:	**ETA**	**UST 45 mg**	**UST 90 mg**
Mean age (years):	45.7	45.1	44.8
Sex (% female):	29.1%	36.4%	32.6%
Ethnicity:	91.1% white	92.3% white	89.0% white
Class naïve:	88.2%	87.6%	89.6%
Other germane population qualities:			
• **Mean PASI**	18.6	20.5	19.9
• **Mean body surface area involvement**	23.8%	26.7%	26.1%
• **Mean duration of psoriasis**	18.8 years	18.9 years	18.7 years
• **Received prior systemic therapy (%)**	57.3%	61.7%	52.4%
RESULTS:	**Primary Outcome Measures:** 56.8% of ETA group had ≥75% improvement in PASI score compared with 67.5% of UST 45 mg group (P=0.01 vs. ETA)and 73.8% of UST 90 mg group (P<0.001 vs. ETA). **Secondary Outcome Measures:** 23.1% of ETA group had ≥90% improvement in PASI score compared with 36.4% of UST 45 mg group (P<0.001 vs. ETA) and 44.7% of UST 90 mg group (P<0.001 vs. ETA). 49.0% of ETA group had cleared or minimal disease (physician's global assessment score=0 or 1) compared with 65.1% of UST 45 mg group (P<0.001 vs. ETA) and 70.6% of UST 90 mg group (P<0.001 vs. ETA). 8.6% of ETA group had cleared disease (physician's global assessment score=0) compared with 16.3% of UST 45 mg group (P=0.006 vs. ETA) and 26.2% of UST 90 mg group (P<0.001 vs. ETA).		

Authors: Griffiths et al. **Year: 2010**			
METHOD OF ADVERSE EVENTS REPORTING:	Safety was evaluated by assessing adverse events and routine hematologic and laboratory values. Possible major cardiovascular events were adjudicated by an independent panel of academic cardiologists. Serum samples were evaluated for antibodies to UST.		
ADVERSE EVENTS (%):	**ETA**	**UST 45 mg**	**UST 90 mg**
Overall adverse effects reported:	70.0%	66.0%	69.2%
• Infections	29.1%	30.6%	29.7%
• URTI	5.8%	6.2%	6.3%
• abnormal LFT	NR	NR	NR
• herpes simplex	NR	NR	NR
• pneumonia	NR	NR	NR
• tb	NR	NR	NR
• ISR	24.8%	4.3%	3.7%
• nonmelanoma skin cancer	0.0%	1.0%	0.3%
• back pain	2.0%	6.7%	4.3%
• ≥ serious adverse event	1.2%	1.9%	1.2%
ATTRITION (*overall*):	**Overall attrition:** 2.7% **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**ETA**	**UST 45 mg**	**UST 90 mg**
Attrition overall:	3.2%	3.8%	1.4%
Attrition due to adverse events:	2.3%	1.9%	1.2%

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Krueger et al.**[111] **Year: 2007** **Study name:** CNTO 1275 Psoriasis Study Group **Country:** Multinational **Quality rating: Fair**				
FUNDING:	Centocor				
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of a human interleukin-12/23 monoclonal antibody in treating psoriasis				
DESIGN & SIZE:	**Study design:** RCT – phase 2 **Setting:** Multi-center **Number screened: 487** **Number eligible: NR** **Number enrolled: 320** **Run-in/Wash-out period: None**				
INTERVENTION:	**Placebo**	**Interleukin-12/23 Monoclonal Antibody**			
Dose: **Duration:** **Sample size:**	NA 36 weeks 64	45 mg 36 weeks 64	90 mg 36 weeks 64	4 x 45 mg 36 weeks 64	4 x 90 mg 36 weeks 64
INCLUSION CRITERIA:	Men and women (age, ≥18 years); a diagnosis of plaque psoriasis for at least 6 months, candidates for phototherapy or systemic therapy, a baseline score on the psoriasis area-and-severity index of 12 or higher (on a scale of 0 to 72, with higher scores indicating more severe disease), and involvement of at least 10% body-surface area				
EXCLUSION CRITERIA:	Nonplaque forms of psoriasis; recent serious systemic or local infection; active or latent tuberculosis, asthma, or a known malignancy within the previous 5 years (except treated basal-cell skin cancer); previous treatment with any agent specifically targeting interleukin-12 or interleukin-23; biologic or investigational agents within the previous month or five drug half-lives; conventional systemic psoriasis therapy or phototherapy within the previous 4 weeks; or topical psoriasis treatment within the previous 2 weeks.				
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	See above				

Authors: Krueger et al. **Year: 2007**					
	Placebo	**Interleukin-12/23 Monoclonal Antibody**			
POPULATION CHARACTERISTICS:	NA	45 mg	90 mg	4 x 45 mg	4 x 90 mg
Mean age (years):	44	46	46	45	44
Sex (% female):	28	41	27	39	19
Ethnicity:	NR	NR	NR	NR	NR
Class naïve:	NR	NR	NR	NR	NR
Other germane population qualities:					
• **Mean PASI**	19.9	19.0	18.8	18.9	19.0
• **Mean body surface area involvement**	26.6	28.5	26.3	27.4	27.4
• **Mean duration of psoriasis**	16.9	19.1	17.9	19.8	17.3
• **Received prior systemic therapy (%)**	61	61	58	72	55

RESULTS:	**12 week change**		**Placebo**		**Interleukin-12/23 Monoclonal Antibody**	
		NA	45 mg	90 mg	4 x 45 mg	4 x 90 mg
	Mean PASI (SD)	16.4 (8.1)	6.5 (6.6)*	5.7 (7.0)*	3.6 (4.2)*	3.0 (3.7)*
	50% improved n (%)	7 (11)	48 (75)*	52 (81)*	59 (92)*	59 (92)*
	75% improved n (%)	**1 (2)**	**33 (52)***	**38 (59)***	**43 (67)***	**52 (81)***
	90% improved n (%)	1 (2)	15 (23)	19(30)	28 (44)*	33 (52)*
	Physician – clear or excellent	0	32 (50)*	34 (53)*	46 (72)*	53 (83)*
	Clear	0	4 (6)**	11 (17)*	10 (16)*	15 (23)*
	Change in DLQI	**-2.2 (4.2)**	**-7.4 (6.2)***	**-9.8 (7.0)***	**-10.2 (6.8)***	**-8.4 (6.2)***
	DLQI score	1 (2)	13 (20)*	19 (30)*	27 (42)*	26 (41)*
		* P < 0.001	** P not calculated			

Authors: Krueger et al. **Year: 2007**					
METHOD OF ADVERSE EVENTS REPORTING: NR					
ADVERSE EVENTS (%): at 20 weeks	**Placebo**	**Interleukin-12/23 Monoclonal Antibody**			
Overall adverse effects reported: • Infections • Serious AEs	**72%** **39** **1**	**79%** **43** **4**			
	Placebo	**Interleukin-12/23 Monoclonal Antibody**			
	NA	45 mg	90 mg	4 x 45 mg	4 x 90 mg
At least 1 AE	72	90	81	78	68
URTI	21	25	31	14	18
Headache	16	19	19	3	15
Fatigue	1	5	5	3	5
ATTRITION (*overall*):	**Overall attrition:** 10% **Attrition differential high:** Yes				
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**Placebo** 13/64 (20%) 4%	**Interleukin-12/23 Monoclonal Antibody** 19/256 (7.4%) 3%			

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Leonardi et al.[112] and Lebwohl et al.[113]** **Year: 2008 and 2009** **Study name: PHOENIX 1** **Country:** Multinational **Quality rating: Fair**		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	Assess the efficacy, quality of life and safety of ustekinumab in patients with moderate-to-severe psoriasis with up to 76 weeks of treatment (cross-over to active treatment at 72 weeks)		
DESIGN & SIZE:	**Study design:** RCT **Setting:** Multicenter **Number screened: 984** **Number eligible: NR** **Number enrolled: 766** **Run-in/Wash-out period:**		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Ustekinumab 45** 45 mg weeks 0 and 4, then every 12 weeks 12 weeks 255	**Ustekinumab 90** 90 mg weeks 0 and 4, then every 12 weeks 12 weeks 256	**Placebo** NA 12 weeks 255
INCLUSION CRITERIA:	18 years or older; a diagnosis of plaque psoriasis for 6 months or longer, a baseline psoriasis area and severity index (PASI) score of 12 or higher, at least 10% body surface area involvement, and candidates for phototherapy or systemic therapy.		
EXCLUSION CRITERIA:	History or symptoms of active tuberculosis; non-plaque forms of psoriasis, recent serious systemic or local infection, known malignancy (except treated basal cell skin cancer or squamous cell skin cancer of at least5 years' duration), treatment with any agent that specifically targeted interleukins 12 or 23, received biological or investigational agents within the previous 3 months or five drug half-lives, conventional systemic psoriasis treatment or phototherapy within the previous 4 weeks, or topical psoriasis treatment within 2 weeks.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	See above		

Authors: Leonardi et al. and Lebwohl et al. **Year: 2008 and 2009**			
POPULATION CHARACTERISTICS:	**Ustekinumab 45**	**Ustekinumab 90**	**Placebo**
Mean age (years):	44.8	46.2	44.8
Sex (% female):	31.4	32.4	28.2
Ethnicity:	NR	NR	NR
Class naïve:	NR	NR	NR
Other germane population qualities:			
• **Mean PASI**	20.5	19.7	20.4
• **Mean body surface area involvement**	27.2	25.2	27.7
• **Mean duration of psoriasis**	19.7	19.6	20.4
• **Received prior systemic therapy (%)**	55.3	55.2	55.7
RESULTS:	**Primary Outcome Measures:** PASI 75 Secondary outcomes: PGA, DLQI		
At 12 weeks	**Ustekinumab 45**	**Ustekinumab 90**	**Placebo**
PASI 50 n (%)	213 (83.5%)*	220 (85.9%)*	26 (10.2%)
PASI 75 n (%)	**171 (67.1%)***	**170 (66.4%)***	**8 (3.1%)**
PASI 90 n (%)	106 (41.6%)*	94 (36.7%)*	5 (2.0%)
PASI 100 n (%)	32 (12.5%)*	28 (10.9%)*	0
Physicians assessment			
Cleared	47 (18.4%)*`	45 (17.6%)*	1 (0.4%)
Cleared or Minimal	154 (60.4%)*	158 (61.7%)*	10 (3.9%)
Change in DLQI (SD)	-8.0 (6.87)*	-8.7 (6.47)*	-0.6 (5.97)
Change SF-36 PCS (SD)	2.0 (7.4)*	3.2 (7.6)*	-0.51 (7.5)
Change SF-36 MCS (SD)	2.1 (9.3)*	2.5 (9.5)*	-1.3 (7.5)

* vs. placebo $P < 0.001$

Authors: Leonardi et al. and Lebwohl et al. **Year: 2008 and 2009**			
METHOD OF ADVERSE EVENTS REPORTING: at visits			
ADVERSE EVENTS (%): at 12 weeks	**Ustekinumab 45**	**Ustekinumab 90**	**Placebo**
Overall adverse effects reported: • Infections • URTI • Headache • herpes simplex •	57.6 31.4 7.1 5.5	51.4 25.9 6.3 5.1	48.2 26.7 6.3 2.4
ATTRITION (*overall*):	**Overall attrition:** 3% **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**Ustekinumab 45**	**Ustekinumab 90**	**Placebo**
Attrition overall:	0.3%	4.3%	4.7%
Attrition due to adverse events:	0	0.8%	2.4%

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors:** Leonardi, et al.[114] **Year:** 2011 **Study name:** Randomized Controlled Evaluation of Adalimumab in Treatment of Chronic Plaque Psoriasis of the Hands and Feet (REACH) **Country:** US and Canada **Quality rating: FAIR**		
FUNDING:	Abbott Laboratories (pharmaceutical industry)		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of adalimumab in psoriasis of the hands and/or feet		
DESIGN & SIZE:	**Study design:** placebo-controlled RCT **Setting:** multicenter **Number screened:** NR **Number eligible:** NR **Number enrolled:** 81 **Run-in/Wash-out period:** Washout periods of 30 days or 5 half-lives (whichever was longer) were required for biological, systemic, and investigational agents prior to baseline.		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Adalimumab (ADA)** 40mg every other week 16 weeks 49	**Placebo** NA 16 weeks 23	
INCLUSION CRITERIA:	Adults 18 years and older diagnosed as having moderate to severe chronic plaque psoriasis of the hands and/or feet for at least 6 months with a Physician's Global Assessment of the hands and/or feet (hfPGA) score of 3 or higher at baseline and with evidence of psoriatic disease on at least 1 other area of skin outside the hands and/or feet.		
EXCLUSION CRITERIA:	Receipt of prior treatment with adalimumab, diagnosis of palmoplantar pustulosis		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Psoralen and UV-A phototherapy was not allowed within 4 weeks of baseline; topical therapies on the hands and/or feet (except low- to mid-potency corticosteroids [classes VI and VII]), UV-B phototherapy, and excessive sun exposure or tanning bed use were not allowed within 2 weeks of baseline.		

Authors: Leonardi, et al. **Year:** 2011			
POPULATION CHARACTERISTICS:	**ADA**	**Placebo**	
Mean age (years): **Sex (% female):** **Ethnicity:** **Class naïve:** Other germane population qualities: • **Mean PASI** • **Mean body surface area involvement** • **Mean duration of psoriasis** • **Received prior systemic therapy (%)**	49.0 57% 92% white NR 8.8 8.9% 14.9 years NR	54.8 65% 87% white NR 5.7 5.1% 11.5 years NR	
RESULTS:	**Primary Outcome Measure:** 31% of ADA patients achieved hfPGA score of clear (0) or almost clear (1) compared with 4% of placebo (p=0.01). **Secondary Outcome Measures:** 51% of ADA patients achieved hfPGA score of clear (0), almost clear (1), or mild (2) compared with 26% of placebo (p=NR). 29% of ADA patients achieved >75% improvement in ESIF (ESIF 75) relative to baseline compared with 4% of placebo (p=0.03). 43% of ADA patients achieved >50% improvement in ESIF (ESIF 50) relative to baseline compared with 17% of placebo (p=0.04). Mean % improvement in total ESIF score relative to baseline was 41% for ADA patients, compared with 21% for placebo (p=NR). In patients with palmar involvement, mean % improvement in total ESIF score relative to baseline was 47% for ADA patients, compared with 20% for placebo (p=0.01). In patients with plantar involvement, mean % improvement in total ESIF score relative to baseline was 41% for ADA patients, compared with 35% for placebo (p=0.67). In patients with psoriatic nail disease, mean % improvement in total NAPSI relative to baselime was 50% for ADA patients, compared with 8% for placebo (p=0.02) Mean pain score was 26.6 for ADA patients, compared with 43.4 for placebo (p=0.048). In patients with pain score >0 at baseline, mean % improvement in pain score was 31% for ADA patients, compared with 9% for placebo (p=0.39).		

Authors: Leonardi, et al. **Year:** 2011			
METHOD OF ADVERSE EVENTS REPORTING:	Laboratory data, physical examinations, and vital signs (and, presumably, patient self-report).		
ADVERSE EVENTS (%):	**ADA**	**Placebo**	
Overall adverse effects reported: • Infections	63% reported any AE 0% reported a serious AE 35% reported an infectious AE Opportunistic only: 2% (oral candidiasis)	70% reported any AE 4% reported a serious AE 44% reported an infectious AE Opportunistic only: 0%	
• URTI	NR	NR	
• abnormal LFT	NR	NR	
• herpes simplex	NR	NR	
• pneumonia	NR	NR	
• tb	NR	NR	
• ISR	NR	NR	
• malignant diseases	0%	4% (N=1, breast cancer)	
• serious hepatic events	2%	0%	
• psoriasis	4%	9%	
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall attrition:** 19.7% **Attrition differential high:** ? (10%) **ADA**	**Placebo**	
Attrition overall:	16%	26%	
Attrition due to adverse events:	6%	9%	

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Menter et al.[115] and Revicki et al.[116,117]** **Year: 2008 and 2007** **Country:** United States and Canada		
FUNDING:	Abbott Labs		
RESEARCH OBJECTIVE:	Clinical efficacy and safety of adalimumab for moderate to severe psoriasis and investigate continuous versus interrupted therapy		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 1212		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 16 weeks 398	**Adalimumab** 80 mg at wk 0 then 40 mg eow 16 weeks 814	**drug 3**
INCLUSION CRITERIA:	18 years or older, clinical diagnosis of psoriasis for at least 6 months, stable plaque psoriasis for at least 2 months before screening, moderate to severe plaque psoriasis defined as 10% or more of body surface area affected, a PASI score of 12 or greater, and PGA of at least moderate severity at the baseline.		
EXCLUSION CRITERIA:	history of neurologic symptoms suggestive of central nervous system demyelinating disease or with a history of cancer or lymphoproliferative disease (other than successfully treated nonmelanoma skin cancer or localized carcinoma in situ of the cervix)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Low- to mid-potency topical corticosteroids applied to the palms, soles, face, and intertriginous areas		

Authors: Menter et al. and Revicki et al.
Year: 2008, 2007

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes

	Placebo	Adalimumab
Mean age (years):	45.4	44.1
Sex (% female):	35.4	32.9
Ethnicity (% Caucasian):	90.2	91.2
Other germane population qualities:		
• Mean PASI	18.8	19.0
• Mean body surface area involvement	25.6	25.8
• Mean duration of psoriasis	18.4 yrs	18.1 yrs
• Prior Systemic therapy: Non-biologic/Biologic (%)	22.1/13.3	23.1/11.9

OUTCOME ASSESSMENT:

Primary Outcome Measures: PASI 75 at 16 weeks, % of patients losing an adequate response after week 33 to week 52 and DLQI
Secondary Outcome Measures: PGA, SF-36
Timing of assessments: Baseline and weeks 4,8,12,16,24,33,36,40,44,48,and 52

RESULTS:

Health Outcome Measures:

- PASI 75 at 16 weeks Placebo 7% vs. ADA 71% P < 0.001
- PASI 90 and 100 at 16 weeks Placebo 2% and 1% vs. ADA 45% and 20% P < 0.001
- PGA, clear or minimal at week 12, Placebo 4% vs. ADA 60% P < 0.001
- From weeks 33 to 52, patients rerandomized to placebo (28%; 68 of 240) compared with patients rerandomized to adalimumab (5%; 12 of 250) P < 0.001.

Measure	Placebo change from baseline at 16 weeks	ADA change from baseline at 16 weeks	
DLQI	1.9 (2.6, 1.3)	8.4 (8.8, 7.9)	P < 0.001
SF 36 PCS	0.4 (0.5, 1.2)	3.7 (3.1, 4.3)	P < 0.001
SF 36 MCS	0.3 (0.7, 1.4)	3.8 (3.1, 4.5)	P < 0.001
Patients global assessment	0.4 (0.5, 0.3)	1.7 (1.8, 1.6)	P < 0.001

Authors: Menter et al. and Revicki et al. **Year: 2008 and 2007**		
ADVERSE EVENTS %: **Overall adverse effects reported:** • Serious AE • Serious infection • Infection • Malignincies (not NMSC) • NMSC • URTI • Nasopharyngitis • Headache	**Placebo** 55.5 1.8 1.0 22.4 0.3 0.3 3.5 6.5 3.8	**Adalimumab** 62.2 1.8 0.6 28.9 P = 0.019 0.2 0.5 7.2 P = 0.01 5.3 4.9
Significant differences in adverse events:	In infections and URTI – see above	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No	
ADEQUATE RANDOMIZATION:	**Yes**	
ADEQUATE ALLOCATION CONCEALMENT:	Yes	
BLINDING OF OUTCOME ASSESSORS:	Yes	
ATTRITION (*overall*):	**Overall attrition:** 74/1212 or 6.1% **Attrition differential high:** No	
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**Placebo** 10.8% 1%	**Adalimumab** 3.8% 1%
QUALITY RATING:	**Good**	

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Paller et al.[118] and Siegfried et al.[119] and Langley et al.[120]** **Year: 2008, 2010, 2011** **Country:** US and Canada **Quality rating:** Fair	
FUNDING:	Immunex, a wholly owned subsidiary of Amgen, and by Wyeth Pharmaceuticals.	
RESEARCH OBJECTIVE:	Assess the efficacy and safety of etanercept in children and adolescents with moderate-to-severe plaque psoriasis.	
DESIGN & SIZE:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 211; 138 in withdrawal-retreatment phase	
INTERVENTION: **Dose:** **Duration:** **Sample size:** *Withdrawal-retreatment period:* **Dose:** **Duration:** **Sample size:**	**Etanercept** 0.8 mg per kg 12 weeks 106 **Etanercept** Max 50 mg for weights ≥62 kg 12 weeks 69	**Placebo** NA 12 weeks 105 **Placebo** NA 12 weeks 69
INCLUSION CRITERIA:	4 to 17 years; stable, moderate-to-severe plaque psoriasis at screening, defined as a psoriasis area-and-severity index (PASI) score of at least 12), a static physician's global assessment of at least 3 (where 0 indicates clear and 5 severe psoriasis), and psoriasis involvement of at least 10% of the BSA; a history of psoriasis for at least 6 months; and previous or current treatment with phototherapy or systemic psoriasis therapy (e.g., methotrexate, cyclosporine, or retinoids) or psoriasis considered by the investigator as poorly controlled with topical therapy.	
EXCLUSION CRITERIA:	Pregnancy or lactation (sexually active patients were required to use contraception); guttate, erythrodermic, or pustular psoriasis; other skin conditions that would interfere with study evaluations; previous treatment with anti-TNF agents; major concurrent medical conditions; treatment with psoralen and ultraviolet A (PUVA), ultraviolet A, ultraviolet B, systemic psoriasis medications, oral or parenteral corticosteroids, topical corticosteroids, topical vitamin A or D analogue preparations, anthralin, or calcineurin inhibitor within a 14-day washout period before the study; and treatment with biologic agents within a 30-day washout period	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Low-to-moderate-potency topical steroids on the scalp, axillae, or groin.	

Authors: Paller et al. and Siegfried et al. and Langley et al. **Year: 2008, 2010, 2011**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline**		
	Etanercept	**Placebo**	**Withdrawal-Retreatment Period**
Mean age (years):	14	13	13 (median)
Sex (% female):	48	50	51
Ethnicity:	78% white	71% white	78% white
Other germane population qualities:			
• **Mean PASI**	16.7	16.4	16.7 (median)
• **Mean body surface area involvement**	21.0	20.0	20.5 (median)
• **Mean duration of psoriasis**	6.8 years	5.8 years	5.8 years (median)
• **Received prior systemic therapy (%)**	55	59	57
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PASI 75 at week 12 **Secondary Outcome Measures:** PASI 50 and 90, physicians global assessment of clear or almost clear, Children's Dermatology Life Quality Index **Timing of assessments:** Baseline weeks 2 ,4, 6, 8, 12, 16 and every 4 weeks Following the 12 week double-blind period, all patients received open-label etanercept for 24 weeks. At the end of this period, patients who received 75% improvement in PASI response from baseline (PASI 75) were re-randomized to a 12-week, double-blind withdrawal-treatment period. During this phase, patients received either placebo or etanercept as long as they maintained a clinical response, defined as PASI 75. Patients whose response fell below PASI 75 were retreated with etanercept in an open-label fashion until study completion. PASI 75 was assessed every 4 weeks during the 12-week, double-blind withdrawal-retreatment period.		
RESULTS:	**Health Outcome Measures at 12 weeks:** • PASI 75: etanercept 57% vs. placebo 11%, p<0.001 • PASI 50: etanercept 75% vs. placebo 23%, p<0.001 • PASI 90: etanercept 27% vs. placebo 7%, p<0.001		

	• Physicians global assessment of clear or almost clear: etanercept 53% vs. placebo 13%, p<0.001 • CDLQI mean improvement: etanercept 52% vs. placebo 18% **Withdrawal-Retreatment period:** Etanercept (received etanercept throughout withdrawal-retreatment) vs. Placebo (received placebo in withdrawal phase) vs. Placebo (received etanercept in retreatment phase) • Percentage of patients who achieved PASI 75 at: Week 40: 81% vs. 75% vs. N/A Week 44: 82% vs. 76% vs. 27% Week 48: 80% vs. 85% vs. 36% • Percentage of patients who achieved PGA clear/almost clear at: Week 40: 69% vs. 60% vs N/A Week 44: 65% vs. 57% vs 33% Week 48: 58% vs. 68% vs 29% • In the group treated with blinded or open-label etanercept, 80% patients maintained or regained PASI 75 at the end of the 12-week period. In all, 70% patients on blinded etanercept maintained PASI 75 at every study visit during the 12-week period, compared with 54% patients who did so on blinded placebo. • At the time the 29 patients on placebo began receiving etanercept retreatment, their mean improvement from baseline in the PASI response had decreased to 47.4%. After 4 to 8 weeks of retreatment, their mean improvement from baseline in the PASI response was 64.4%. • Of the 137 patients who completed the 12-week period, 95 (69%) remained on blinded placebo or blinded etanercept for the 12-week period. In the placebo group, 40/69 (58%) patients remained on blinded placebo throughout the period, and 29/69 (42%) received etanercept retreatment. In the etanercept group, 55/68 (81%) patients remained on blinded etanercept. The remaining 13 (19%) patients on etanercept entered the open-label retreatment phase, although one patient entered without losing PASI 75.

Authors: Paller et al. and Siegfried et al. and Langley et al. **Year: 2008, 2010, 2011**			
ADVERSE EVENTS:	**Etanercept**	**Placebo**	
Overall adverse effects reported (event rates per 100 pt/yrs:	554.5	765.4	
• URTI	54.6	69.1	
• Headache	32.8	95.7	
• Nasophyrantgitis	31.5	53.2	
• Influenza	14.0	15.9	
• Streprococcal pharygitis	13.3	5.3	
• Cough	12.1	10.6	
• Pharyngolaryneal pain	12.1	31.9	
• Vomiting	12.1	10.6	
• Nasal congestion	10.3	15.9	
• Skin papilloma	9.7	0	
Overall adverse effects reported:	Double-blind withdrawal phase:	Double-blind withdrawal phase:	Open-label retreatment phase: **Etanercept**
• Overall adverse effects	52.9%	46.4%	42.9%
• At least 1 serious AE	0%	0%	0%
• Headache	8.8%	2.9%	NR
• Nasophyrantgitis	10.3%	2.9%	NR
• URTI	NR	NR	14.3%
• Sinitius	NR	NR	7.1%
• Injection site reaction	1.5%	1.4%	2.4%
ATTRITION (*overall*):	**Overall attrition:** 3 (plus 1 in withdrawal-retreatment phase) **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**Etanercept**	**Placebo**	
Attrition overall:	2%	1%	
Attrition due to adverse events:	0%	1%	

URTI: upper respiratory tract infection.

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Papp et al.**[121] **Year: 2008** **Study name: PHOENIX 2** **Country:** Multinational **Quality rating: Good**		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	Assess the efficacy and safety of ustekinumab in patients with moderate-to-severe psoriasis with up to 52 weeks of treatment.		
DESIGN & SIZE:	**Study design:** RCT **Setting:** Multicenter **Number screened: 1568** **Number eligible: NR** **Number enrolled: 1230** **Run-in/Wash-out period: No**		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Ustekinumab 45** 45 mg weeks 0 and 4, then every 12 weeks 12 weeks 409	**Ustekinumab 90** 90 mg weeks 0 and 4, then every 12 weeks 12 weeks 411	**Placebo** NA 12 weeks 410
INCLUSION CRITERIA:	18 years or older; a diagnosis of plaque psoriasis for 6 months or longer, a baseline psoriasis area and severity index (PASI) score of 12 or higher, at least 10% body surface area involvement, and candidates for phototherapy or systemic therapy.		
EXCLUSION CRITERIA:	History or symptoms of active tuberculosis; non-plaque forms of psoriasis, recent serious systemic or local infection, known malignancy (except treated basal cell skin cancer or squamous cell skin cancer of at least5 years' duration), treatment with any agent that specifically targeted interleukins 12 or 23, received biological or investigational agents within the previous 3 months or fi ve drug half-lives, conventional systemic psoriasis treatment or phototherapy within the previous 4 weeks, or topical psoriasis treatment within 2 weeks		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	See above		

Authors: Papp et al. **Year: 2008**			
POPULATION CHARACTERISTICS:	**Ustekinumab 45**	**Ustekinumab 90**	**Placebo**
Mean age (years):	45.1	46.6	47.0
Sex (% female):	30.8	32.3	31.0
Ethnicity:	NR	NR	NR
Class naïve:	61.6	63.5	61.2
Other germane population qualities:			
• **Mean PASI**	19.4	20.1	19.4
• **Mean body surface area involvement**	25.9	27.1	26.1
• **Mean duration of psoriasis**	19.3	20.3	20.8
• **Received prior systemic therapy (%)**	54.5	54.5	58.8
RESULTS:	**Primary Outcome Measures:** PASI 75 Secondary outcomes: PGA, DLQI		
At 12 weeks	Ustekinumab 45	Ustekinumab 90	Placebo
PASI 50 n (%)	342 (83.6%)*	367 (89.3%)*	41 (10.0%)
PASI 75 n (%)	273 (66.7%)*	311 (75.7%)*	15 (3.7%)
PASI 90 n (%)	173 (42.3%)*	209 (50.9%)*	3 (0.7%)
PASI 100 n (%)	74 (18.1%)*	75 (18.2%)*	0
Physicians assessment			
Cleared	93 (22.7%)*	115 (28.0%)*	0
Cleared or Minimal	278 (68.0%)*	302 (73.5%)*	20 (4.9%)
Change in DLQI	-9.3 (7.12)*	-10.0 (6.67)*	-0.5 (5.66)
	*** vs placebo *P* < 0.001**		

Authors: Papp et al. **Year: 2008**			
METHOD OF ADVERSE EVENTS REPORTING: at visits			
ADVERSE EVENTS (%):	**Ustekinumab 45**	**Ustekinumab 90**	**Placebo**
Overall adverse effects reported:	53.1	47.9	49.8
• infections	21.5	22.4	20.0
• Arthralgia	3.4	2.4	2.9
• Cough	0.7	1.0	1.7
• Headache	4.6	4.6	4.1
• URTI	4.4	2.9	3.4
• Nasopharyngitis	7.3	6.8	7.1
• ISR	1.5	1.5	0.2
ATTRITION (*overall*):	**Overall attrition:** 2.6% **Attrition differential high:** no		
ATTRITION (*treatment specific*):	**Ustekinumab 45**	**Ustekinumab 90**	**Placebo**
Attrition overall:	1.4%	2.2%	4.3%
Attrition due to adverse events:	0.5%	1.2%	2.0%

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Reich et al.**[122-124] **Year: 2005 and 2006 and 2007** **Country:** NR		
FUNDING:	Centocor and Schering-Plough		
RESEARCH OBJECTIVE:	To present the results of a phase III study, addressing the long-term safety, efficacy and productivity of infliximab for the treatment of skin and nail lesions in patients with psoriasis		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 378		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo / INF** N/A, then 5 mg/kg (wk 0,2,6,14,22) 22 weeks, then 24 weeks (total 46) 77	**INF** 5 mg/kg (wk 0,2,6, then every 8 wks) 46 weeks 301	
INCLUSION CRITERIA:	Patients diagnosed with moderate to severe plaque psoriasis for ≥ 6 months; candidates for phototherapy or systemic therapy; PASI of ≥ 12 and ≥ 10% of their total body surface area affected by psoriasis.		
EXCLUSION CRITERIA:	History or risk of serious infection, lymphoproliferative disease, or active TB; previous treatment with INF or any other TNFα-antagonist was allowed.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	2.5% hydrocortisone, or equivalent, applied topically to face, groin, or both, after week 10.		

<table>
<tr><td colspan="3">Authors: Reich et al.
Year: 2005 and 2006 and 2007</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: Yes
Disease severity: Moderate-to-severe</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>INF</u></td></tr>
<tr><td>Mean age (years):</td><td>43.8</td><td>42.6</td></tr>
<tr><td>Sex (% female):</td><td>21</td><td>31</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td></tr>
<tr><td>• Psoriasis duration (yrs)</td><td>17.3</td><td>19.1</td></tr>
<tr><td>• Body surface area (%)</td><td>18</td><td>19</td></tr>
<tr><td>• PASI</td><td>22.8</td><td>22.9</td></tr>
<tr><td>• Patients with nail psoriasis (%)</td><td>86</td><td>81</td></tr>
<tr><td>• MTX use (%)</td><td>46</td><td>42</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: PASI 75 (≥ 75% improvement in baseline PASI) at week 10 and Quality of life DLQI and SF-36, 10-cm productivity visual analog scale (VAS), role-physical and role-emotional domain scores of the Short Form 36-Item questionnaire (SF-36).
Secondary Outcome Measures: PASI 75 at week 24; PGA of cleared or minimal at week 10, 24, and 50; PASI 50; PASI 90; NAPSI at weeks 10, 24, and 50.
Timing of assessments: NR</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
• At week 24, PASI 75 achieved by 82% (INF) vs. 4% (placebo) ($P < 0.0001$)
• The % improvement in the NAPSI was significantly greater in INF-treated patients than placebo at weeks 10 and 24.
Improvement from baseline
• At week 24, DLQI INF 10.0 vs. placebo 0.2 ($P < 0.001$)
• At week 24, SF-36 PCS INF 4.9 vs. placebo -1.4 ($P < 0.001$)
• At week 24, SF-MCS INF 5.3 vs. placebo -0.5 ($P < 0.001$)
• At week 24, Productivity VAS, INF – 0.2 ± 3.2 vs. placebo 2.5 ± 3.5 ($P < 0.001$)
• At week 24, PGA response INF 74 vs. placebo 3%, ($P < 0.0001$)
Intermediate Outcome Measures:
• 6% and 2% of patients in INF group had asymptomatic increases in alanine aminotransferase and aspartate aminotransferase, respectively.
• Fewer antibody-positive patients achieved PASI 75.</td></tr>
</table>

Authors: Reich et al. **Year: 2005 and 2006 and 2007**		
ADVERSE EVENTS: **Overall adverse effects reported (%)**	**Placebo/INF**	**INF**
• URTI	16	15
• Headache	12	14
• Pain	5	6
• Psoriasis	13	3
• Severe adverse event	3	6
• Infections	40	42
• Neoplasms	0	1
Significant differences in adverse events:	No	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR	
ADEQUATE RANDOMIZATION:	Yes	
ADEQUATE ALLOCATION CONCEALMENT:	Yes	
BLINDING OF OUTCOME ASSESSORS:	Yes	
ATTRITION %(*overall*):	**Overall loss to follow-up:** 17.5% (24 weeks) **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*):	**Placebo/INF**	**INF**
Loss to follow-up:	31.2	30.1
Withdrawals due to adverse events:	NR	NR
QUALITY RATING:	**Good**	

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors:** Reich et al[125] and van de Kerkhof et al., 2008[126] **Year:** 2009, 2008 **Study name: -** **Country:** Europe (9 countries) **Quality rating: FAIR**	
FUNDING:	Wyeth Research (pharmaceutical industry)	
RESEARCH OBJECTIVE:	To assess baseline patient-reported outcomes (PROs) and PRO improvement in patients with psoriasis administered 50 mg once weekly.	
DESIGN & SIZE:	**Study design:** placebo-controlled RCT **Setting:** unclear **Number screened:** 161 **Number eligible:** 143 **Number enrolled:** 142 **Run-in/Wash-out period:** none	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 50mg once a week (QW) 12 weeks 96	**Placebo** N/A 12 weeks 46
INCLUSION CRITERIA:	Clinically stable plaque psoriasis involving ≥10% of body surface area; minimum PASI score of 10 (moderate-to-severe); failed to respond to, had a contradiction for or were intolerant of ≥1 systemic treatment or phototherapy at an adequate dose of sufficient duration.	
EXCLUSION CRITERIA:	Patients with active guttate, erythrodermic or pustular psoriasis at the time of screening, or other active skin conditions that would interfere with study evaluations, were excluded. Patients were also ineligible if they had a serious infection within 1 month of study screening or the baseline visit or a body mass index (BMI) greater than 38 kg m2. Patients were not to have received etanercept, an antibody to TNF, or other TNF inhibitors at any time; alefacept, efalizumab, anti-CD4 agents, or diphtheria interleukin-2 fusion protein within the previous 6 months; ultraviolet A or B phototherapy, psoralen and ultraviolet A phototherapy, systemic psoriasis therapy (methotrexate, ciclosporin, acitretin or fumarates), or oral or parenteral corticosteroids within the previous month; or topical corticosteroids in high strengths, topical vitamin A or D analogue preparations, dithranol or topical calcineurin inhibitors (pimecrolimus or tacrolimus) within the previous 2 weeks.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Patients were permitted to use only topical corticosteroids of low to moderate strength on the scalp, axillae and groin during the study. Topical corticosteroids were not allowed on other areas, including the hands and feet. Doses of topical corticosteroids were to remain stable for at least 2 weeks before the baseline visit until the end of the double-blind period.	

Authors: Reich et al. and van de Kerkhof et al. **Year: 2009, 2008**			
POPULATION CHARACTERISTICS:	**ETA**	**Placebo**	**Full Sample**
Mean age (years):	45.9	43.6	44.7
Sex (% female):	38.5%	45.6%	42%
Ethnicity:	NR	NR	NR
Class naïve:	100%	100%	100%
Other germane population qualities:			
• **Mean PASI**	21.4	21.0	21.2
• **Mean body surface area involvement**	26.5%	30.3%	28.4
• **Mean duration of psoriasis**	19.3 years	17.3 years	18.3 years
• **Received prior systemic therapy (%)**	49.0% (failed ≥1)	47.8% (failed ≥1)	NR
RESULTS:	**Primary Outcome Measures:** 37.5% of ETA patients had ≥75% improvement on the PASI, compared with 2.2% of placebo (p<0.0001); ETA patients had a mean decrease in DLQI of 7.4 compared with placebo (-1.2); P<0.0001; ETA patients had a mean increase in EQ-5D utility score of 0.12 compared with placebo (+0.02); P<0.05; ETA patients had a mean change in EQ-5D VAS score of +6.8 compared with placebo (-4.9); P<0.01; **Secondary Outcome Measures:** 19.8% of ETA patients and 50.0% of placebo patients had DLQI ≥11; 29.2% of ETA patients and 15.2% of placebo patients achieved DLQI of 0 or 1; 74.7% of ETA patients and 28.6% of placebo patients achieved improvement of ≥5 points on DLQI; P<0.0001; Mean DLQI score: ETA = 5.8 vs. placebo = 12.3; P<0.0001; Mean EQ-5D utility score: ETA = 0.81 vs. placebo = 0.69; Mean FACIT-F score (change from baseline): ETA = 40.7 (+1.3) vs. placebo = 39.5 (+0.3); no significant difference; 9.4% fewer ETA patients reported mobility problems, compared with no fewer placebo patients (P<0.05); 10.4% fewer ETA patients reported anxiety/depression, compared with 4.4% fewer placebo patients (P<0.05);		

	26% fewer ETA patients reported pain discomfort, compared with 13% fewer placebo patients (P<0.05); 14.5% fewer ETA patients reported problems with usual activities, compared with 2.1% more placebo patients, NSD; 7.2% fewer ETA patients reported problems with self-care, compared with 4.4% fewer placebo patients, NSD.

Authors: Reich et al. and van de Kerkhof et al. **Year: 2009, 2008**			
METHOD OF ADVERSE EVENTS REPORTING:	NR		
ADVERSE EVENTS (%):	**ETA**	**Placebo**	
Overall adverse effects reported: • Infections • URTI • abnormal LFT • herpes simplex • pneumonia • tb • ISR • • •	NR NR NR NR NR NR NR NR	NR NR NR NR NR NR NR NR	
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Attrition overall:** **Attrition due to adverse events:**	**Overall attrition:** 11% **Attrition differential high:** Yes **ETA** 6% 3.1%	 **Placebo** 22% 6.5%	

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 7. Targeted Immune Modulators – Plaque Psoriasis

STUDY:	**Authors: Saurat et al.[127] and Revicki et al.[128]** **Year: 2007, 2008** **Country:** Multinational		
FUNDING:	Abbott Labs		
RESEARCH OBJECTIVE:	Compare a biologic agent ADA with MTX, a traditional systemic agent, to define clearly the role of biologics in psoriasis		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 271		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 16 weeks 53	**Methotrexate** 7.5 to 25 mg weekly 16 weeks 110	**Adalimumab** 80 mg load then 40 mg eow 16 weeks 108
INCLUSION CRITERIA:	≥18 years of age with moderate to severe psoriasis, plaque psoriasis for at least 1 year and stable plaque psoriasis for at least 2 months, candidates for systemic therapy or phototherapy and to have had active psoriasis despite treatment with topical agents, naive to both TNF-antagonist therapy and methotrexate.		
EXCLUSION CRITERIA:	History of clinically significant haematological, renal or liver disease⁄abnormal laboratory values; with a history of demyelinating disease, cancer, or other lymphoproliferative disease (other than successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and⁄or localized carcinoma in situ of the cervix); or who were immunocompromised.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Shampoos free of corticosteroids; bland emollients; and low-potency topical corticosteroids for the palms, soles, face, inframammary areas and groin only, not used within 24 h of a study visit		

Authors: Saurat et al. and Revicki et al. **Year: 2007, 2007**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes		
	Placebo	**Methotrexate**	**Adalimumab**
Mean age (years):	40.7	41.6	42.9
Sex (% female):	34	33.6	35.2
Ethnicity (% Caucasian):	92.5	95.5	95.4
Other germane population qualities:			
• Mean PASI	19.2	19.4	20.2
• Mean body surface area involvement	28.4	32.4	33.6
• Mean duration of psoriasis	18.8	18.9	17.9
• Received prior systemic therapy and/or phototherapy (%)	90.4	87.2	82.2
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PASI 75 at week 16 and DLQI **Secondary Outcome Measures:** PASI 50, 90 and 100, and PGA and EuroQOL5D **Timing of assessments:** baseline and at weeks 1, 2, 4, 8, 12 and 16.		
RESULTS:	**Health Outcome Measures at 16 weeks:** PASI 75 ADA 79.6% vs. 35.5% MTX vs. Placebo 18.9% PASI 100 ADA 16.7% vs. MTX 7.3% vs. placebo 1.9 P = .004 DLQI change from baseline (95% CI) ADA 9.1 (-10.4 to -7.8) vs. MTX-5.7 (-6.8 to -4.5) vs. placebo -3.4 (-5.2 to -1.6) ADA vs. placebo P < 0.001 EQ 5D Index Score change from baseline (95% CI) ADA 0.2 (0.2 to 0.3) vs. MTX 0.1 (0.1 to 0.2) vs. placebo 0.1 (0.0 to 0.2) EQ-5D VAS change from baseline (95% CI) ADA 21.4 (16.6 to 26.3) vs. MTX 11.5 (6.5 to 16.5) vs5.7 (-1.4 to 12.8) PGA ADA -1.6 vs. placebo -0.5 P < 0.001		

Authors: Saurat et al. and Revicki et al. **Year: 2007, 2008**			
ADVERSE EVENTS %:	**Placebo**	**Methotrexate**	**Adalimumab**
Overall adverse effects reported:	79.2	81.8	73.8
• Serious AEs	1.9	0.9	1.9
• Infections (non-serious)	43.4	41.8	47.7
• Serious infections	0	0	0
• Nasopharyngitis	20.8	23.6	28.0
• Headache	9.4	10.9	13.1
• Pruritus	11.3	1.8	3.7
• Rhinitis	7.5	3.6	2.8
• Nausea	7.5	7.3	3.7
• Rhinorrhea	5.7	0	2.8
• Viral Infection	1.9	5.5	0
• Arthralgia	1.9	4.5	5.6
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	**Yes**		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 15 (5.5%) **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**Placebo**	**Methotrexate**	**Adalimumab**
Attrition overall:	9.4%	5.5%	3.7%
Attrition due to adverse events:	<1%	5.5%	1%
QUALITY RATING:	**Good**		

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Askling et al.**[129] **Year: 2005** **Country:** Sweden		
FUNDING:	Swedish Cancer Society; the insurance company AFA; Wyeth Ayerst, Schering-Plough, Abbott Immunology, and Bristol Myer Squibb; Swedish National Board of Health and Welfare		
RESEARCH OBJECTIVE:	To depict the cancer pattern of contemporary patients with RA and to understand the risk of solid cancer after TNF treatment by obtaining cancer data from cohorts treated in routine care rather than trials.		
DESIGN:	**Study design:** retrospective cohort **Setting:** small outpatient clinics and larger population based centers **Sample size:** 60,930		
INTERVENTION:	N/A **Inpatient RA cohort**	N/A **Early Arthritis RA cohort**	N/A **TNF antagonist cohort**
Dose:	N/A	N/A	N/A
Duration:	N/A	N/A	N/A
Sample size:	53,067	3,703	4,160
INCLUSION CRITERIA:	Inpatient Register RA cohort: inpatients above 16 years of age ever discharged with an RA diagnosis between January 1990 & December 31 2003. Early Arthritis RA cohort: patients with RA diagnosed from 1999 through 2003. TNF antagonist cohort: patients with RA treated with ETA, INF, or ADA.		
EXCLUSION CRITERIA:	Inpatient Register RA cohort: Patients who were also discharged with systemic lupus erythematosus, AS, or PsA; observed and expected cancers during the 1st year of follow up.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Askling et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No
Disease severity: NR</td></tr>
<tr><td></td><td><u>Inpatient RA cohort</u></td><td><u>Early Arthritis RA cohort</u></td><td><u>TNF antagonist cohort</u></td></tr>
<tr><td>Mean age (years):</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>% age 45-74 years:</td><td>56.3</td><td>65.4</td><td>71.8</td></tr>
<tr><td>Sex (% female):</td><td>71.4</td><td>69.9</td><td>74.8</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• DAS28 score (mean)</td><td>NR</td><td>3.5</td><td>5.5</td></tr>
<tr><td>• HAQ score (mean)</td><td>NR</td><td>0.6</td><td>1.4</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: observed cancers
Secondary Outcome Measures: NR
Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
<u>Inpatient RA cohort</u>
• Based on 3379 observed solid cancers, this cohort had minimally increased overall risk of solid cancer (SIR = 1.05, 95% CI 1.01 to 1.08)
• Overall RR was 1.19 (95% CI 1.13 to 1.26, n = 1311) among men and 0.97 (95% CI 0.93 to 1.02, n = 2068) among women.
<u>Early Arthritis cohort</u>
• Overall, 138 solid cancers (SIR = 1.1, 95% CI 0.9 to 1.3), with a non-increased risk in women (SIR = 0.87, 95% CI 0.67 to 1.11, n=64) and an increased risk among men (SIR = 1.42, 95% CI 1.12 to 1.79, n=74)
<u>TNF antagonist cohort</u>
• 67 solid cancers observed (SIR = 0.9, 95% CI 0.7 to 1.2)
• RR of solid cancer was non-significantly reduced among women (SIR = 0.87, 95% CI 0.63 to 1.16, n = 45) but 1.06 (95% CI 0.67 to 1.61, n = 22) among men.</td></tr>
</table>

<table>
<tr><td colspan="4">Authors: Askling et al.
Year: 2005</td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
• infections</td><td colspan="3">N/A</td></tr>
<tr><td>Significant differences in adverse events:</td><td colspan="3">N/A</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ADEQUATE RANDOMIZATION:</td><td colspan="3">N/A</td></tr>
<tr><td>ADEQUATE ALLOCATION CONCEALMENT:</td><td colspan="3">N/A</td></tr>
<tr><td>BLINDING OF OUTCOME ASSESSORS:</td><td colspan="3">N/A</td></tr>
<tr><td rowspan="2">ATTRITION (overall):

ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:</td><td colspan="3">Overall loss to follow-up: NR
Loss to follow-up differential high: NR</td></tr>
<tr><td><u>Inpatient RA cohort</u>
NR</td><td><u>Early Arthritis RA cohort</u>
NR</td><td><u>TNF antagonist cohort</u>
NR</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">N/A</td></tr>
</table>

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Askling et al.**[130] **Year: 2005** **Country:** Sweden		
FUNDING:	Swedish National Board of Health and Welfare		
RESEARCH OBJECTIVE:	To assess expected rates and relative risks of haematopoietic malignancies, especially those associated with TNF antagonists, in large population based cohorts of patients with RA.		
DESIGN:	**Study design:** Observational - cohort **Setting:** Inpatient **Sample size:** 60930		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Inpatient register** N/A various	**Early Arthritis** N/A	**TNF antagonist** ETA, INF or ADA various
INCLUSION CRITERIA:	Patients with RA in Sweden		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A		

Authors: Askling et al. **Year: 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NA **Disease severity:** Mild-moderate-severe		
	Inpatient register	**Early Arthritis**	**TNF antagonist**
Mean age (years):	NR	NR	NR
Sex (% female):	71.3%	70%	75%
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• DAS score	N/A	3.5	5.5
• HAQ score	N/A	0.6	1.4
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** risk of malignant lymphomas, and maybe also of leukemia and multiple myeloma		

RESULTS:	# SIR (95% CI)	**Inpatient register**	**Early Arthritis**	**TNF antagonist**
	All haematopoietic malignancies	481 1.7 (1.5 to 1.8)	15 1.6 (0.9 to 2.6)	11 2.1 (1.1 to 3.8)
	Malignant lymphoma(CLL also)	319 1.9 (1.7 to 2.1)	11 2.0 (1.0 to 3.5)	9 2.9 (1.3 to 5.5)
	After adjustment for sex, age, and disease duration, the lymphoma risk after exposure to TNF antagonists was no higher than in the other RA cohorts.(data not shown)			

Authors: Askling et al. **Year: 2005**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** **Post randomization exclusions:**
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Askling et al.**[131] **Year: 2007** **Country:** Sweden		
FUNDING:	NR		
RESEARCH OBJECTIVE:	The degree to which treatment with tumor necrosis factor (TNF) antagonists may be associated with increased risks for serious infections		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Swedish registers **Sample size:** 44 946		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**All anti-TNF** various NR 4167	**Anti-TNF 1998-2003** various NR 2692	**Controls from RA inpatient** various NR 10 295
INCLUSION CRITERIA:	The ARTIS, 4167 rheumatoid arthritis (RA) patients starting TNF antagonist treatment 1999 and 2003 were identified. Secondly, in the Swedish Inpatient Register, all individuals hospitalized for any reason and who also carried a diagnosis of RA, between 1964 and 2003 (n = 44 946 of whom 2692 also occurred in ARTIS), were identified. Thirdly, in the Swedish Inpatient Register, all hospitalizations listing an infection between 1999 and 2003 were identified		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A		

<table>
<tr><td colspan="3">Authors: Askling et al.
Year: 2007</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline:
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• Mean disease duration
• DAS score
• HAQ score</td><td><u>All anti-TNF 1998–2003</u>
75%
NR

12.1 yrs
5.63
1.43</td><td><u>Anti-TNF 1998–2003, also in Inpatient Register RA cohort</u>
78%
NR

15.0 yrs
5.74
1.57</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: infection</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
Within the cohort of 44 496 RA patients, the risk ratio (RR (95% CI)) for infection associated with TNF antagonists –
1st year 1.43 (95% CI 1.18 to 1.73)
2nd year 1.15 (95% CI 0.88 to 1.51)
3rd year 0.82 (95% CI 0.62 to 1.08)

Age, duration of RA, HAQ, DMARD use other than MTX, and pre-treatment co-morbidity all predicted infection risk</td></tr>
</table>

Authors: Askling et al. **Year: 2007**	
ADVERSE EVENTS: **Overall adverse effects reported:**	See Results
Significant differences in adverse events:	Yes
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:**
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Good**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Askling et al.** [132] **Year: 2009** **Study name: NA** **Country: Sweden** **Quality rating: Good**		
FUNDING:	Government (Swedish Cancer Society and the Stockholm County Council)		
RESEARCH OBJECTIVE:	To determine the short-term and medium-term risks of cancer in patients receiving anti-TNFα therapies		
DESIGN & SIZE:	**Study design:** Prospective cohort **Setting:** Population-based **Sample size:** 6,604		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Drug 1** Etanercept, dose NR NA (reported by person-years) 2287	**Drug 2** Adalimumab, dose NR NA (reported by person-years) 937	**Drug 3** Infliximab, dose NR NA (reported by person-years) 3380
INCLUSION CRITERIA:	Patients with rheumatoid arthritis who were alive in 1998 and started therapy with their first TNF antagonist between February 1998 and July 31, 2006.		
EXCLUSION CRITERIA:	No additional criteria.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Reported patients taking Methotrexate or other DMARDs, steroids, NSAIDs, and analgesics.		

Author: Askling et al. **Year: 2009**	
POPULATION CHARACTERISTICS:	
Mean age (years): **Sex (% female):** **Ethnicity:** **Class naïve:** Other germane population qualities: • **Tender joint count** • **Swollen joint count** • **Mean disease duration** • **DMARD use (%)** • **MTX use (%)** • **Corticosteroids use (%)** • **DAS score** • **HAQ score**	55 25% NR 100% 8.7 9.5 10.6 years 16% no DMARD use, 69% MTX, 11% other than MTX, 4% no information NR 51% oral steroids, 33% no steroids, 15% no information 5.5 1.4
RESULTS:	**Primary Outcome Measures:** Occurrence of cancer

Authors: Askling et al. **Year: 2009**			
METHOD OF ADVERSE EVENTS REPORTING:	Linked individuals to the Swedish Cancer Register (to which reporting of all incident malignancies has been mandatory, both for the treating physician and for the pathologist, since 1958, and resulting in a near-complete coverage of all diagnosed cancers in Sweden)		
ADVERSE EVENTS	**Etanercept**	**Adalimumab**	**Infliximab**
Occurrence of cancer following start of anti-TNF therapy			
• Person-years of followup	9,413	2,160	14,120
• Number of first cancers	70	26	144
• Crude incidence (range per 100,000)	743 (580-939)	1204 (786-1763)	1020 (860-1201)
Relative risk (95% CI); number of events of a first primary cancer vs cohort of unselected, biologics-naïve patients with RA			
• Overall	0.78 (0.61-1.00); 70	1.09 (0.91-1.30); 144	1.32 (0.87-1.98); 26
• <1 year since start of anti-TNF	0.43 (0.22-0.84); 10	1.23 (0.85-1.77); 31	1.91 (1.11-3.31); 15
• ≥ 1-2 years	0.80 (0.46-1.40); 13	0.83 (0.53-1.28); 21	0.84 (0.37-1.92); 6
• ≥ 2 years	0.92 (0.68-1.24); 47	1.13 (0.91-1.41); 92	1.08 (0.43-2.67); 5

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Atteno et al.**[133] **Year: 2010** **Study name:** **Country:** Italy **Quality rating:**		
FUNDING:	Under Disclosures, article reports "None"		
RESEARCH OBJECTIVE:	To compare the effectiveness and safety of Infliximab (INF), Etanercept (ETN), and Adalimumab (ADA) in patients with established psoriatic arthritis (PsA) who experienced an inadequate response to a previous disease-modifying antirheumatic drug (DMARD) therapy.		
DESIGN & SIZE:	**Study design:** Longitudinal, enrolling consecutive patients **Setting:** Single-center, outpatient clinic **Number screened:** 1240 **Number eligible:** 100 **Number enrolled:** 100 **Run-in/Wash-out period:** none reported		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Drug 1** Etanercept 25mg twice weekly 12 months 36	**Drug 2** Adalimumab 40mg every other week 12 months 34	**Drug 3** Infliximab 5mg/Kg every 6-8 wks (changing dose as needed) 12 months 30
INCLUSION CRITERIA:	>18 years with psoriatic arthritis based on the CASPAR classification criteria, regardless of disease duration, with inadequate response to a previous disease modifying antirheumatic drug (DMARD)		
EXCLUSION CRITERIA:	previous usage of anti-TNF-α inhibitor; usage of DMARDs other than sulfasalazine, methotrexate, azathioprine, and leflunomide within 4 weeks of enrollment; the usage of more than 10mg of prednisone daily; and variation of dosage of NSAIDs or prednisone within 2 weeks of enrollment.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	none stated		

Authors: Atteno et al. **Year: 2010**			
POPULATION CHARACTERISTICS (%):	**Drug 1** Etanercept	**Drug 2** Adalimumab	**Drug 3** Infliximab
Mean age (years): **Sex (% female):** **Ethnicity:** **Class naïve:** Other germane population qualities: • **Polyarticular arthritis** • **DIP joints of hand/feet** • **Asymmetric peripheral arthritis** • **NSAID use (%)** • **MTX use (%)** • **Corticosteroids use (%)** • **DAS score** **Values below are median (interquartile range)** • **HAQ score** • **PASI** • **Tender joints** • **Swollen joints**	**49.3±13.4** **21 (58%)** **Not Reported** **100%** **1.2 (0.4)** **26 (18.5)** **13 (5)** **4 (3.2)**	**47.5±11.5** **20 (59%)** **Not Reported** **100%** **1.2 (0.3)** **18 (16.5)** **13 (7)** **5 (3.8)**	**48.5±12.9** **19 (63%)** **Not Reported** **100%** **1.5 (0.5)** **15 (14.8)** **12 (4.8)** **3 (3)**
RESULTS:	**Primary/Secondary Outcome Measures:** (unable to determine primary from secondary outcomes) Outcomes listed include: PASI (measure of the extension of psoriasis), tender joints count (TJC), swollen joint count (SJC), health assessment questionnaire (HAQ) score; ACR20 response rates; PASI: Drug 1: 1: 2; Drug 2: 0.1; Drug 3: 0 ($p<0.01$); HAQ: Drug 1: 0.1; Drug 2: 0.1; Drug 3: 0.1 ($p=0.60$); Tender joints: Drug 1: 1; Drug 2: 1; Drug 3: 1 ($p=0.12$); Swollen joints: Drug 1: 0; Drug 2: 0.5; Drug 3: 1 ($p=0.23$); ACR20 response rate: Drug 1: 72%; Drug 2: 70%; Drug 3: 75%		

Authors: Atteno et al. **Year: 2010**			
METHOD OF ADVERSE EVENTS REPORTING:	**Not Specified; patients were followed up every 3 months with clinical and laboratory assessment**		
ADVERSE EVENTS (%):	**Drug 1**	**Drug 2**	**Drug 3**
Overall adverse effects reported:	**17%**	**6% (p<0.001)**	**23%**
• infections			
• URTI			
• abnormal LFT			
• herpes simplex			
• pneumonia			
• tb	**0**	**0**	**0**
• ISR			
• Pneumonitis	**0**	**0**	**1 (3%)**
• Thrombocytopenia	**0**	**0**	**1 (3%)**
ATTRITION (*overall*):	**Overall attrition:** no attrition reported **Attrition differential high:** no attrition reported		
ATTRITION (*treatment specific*):	**Drug 1**	**Drug 2**	**Drug 3**
Attrition overall:	no attrition reported	no attrition reported	no attrition reported
Attrition due to adverse events:	no attrition reported	no attrition reported	no attrition reported

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Bongartz et al.**[134] **Year:** 2006 **Country:** Multinational
FUNDING:	Mayo Foundation; Abbott & Centocor
DESIGN:	**Study design:** systematic literature review with meta-analysis **Number of patients:** 5,005 patients randomized (9 trials)
AIMS OF REVIEW:	To assess extent to which anti-TNF antibody therapy may increase risk of serious infection and malignancies in patients with RA; to derive estimates of sparse harmful events occurring in randomized trials of anti-TNF therapy.
STUDIES INCLUDED IN META-ANALYSIS	Keystone (2004), St Clair (2004), Furst (2003), Lipsky (2000), van de Putte (2003), Weinblatt (2003), Maini (1998), van de Putte (2004), and Westhovens (2004)
TIME PERIOD COVERED:	N/A
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized controlled trials of INF & ADA in which patients had ACR-diagnosed RA and were randomized to anti-TNF vs. placebo (or anti-TNF antibody + traditional DMARD vs. placebo + traditional DMARD). Both the patient and observer were masked. Trial had to be at least 12 weeks in duration (all trials were 3 to 12 months).
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients with an ACR diagnosis of RA who were randomized to receive Anti-TNF or placebo

Authors: Bongartz et al. **Year: 2006**		
CHARACTERISTICS OF INTERVENTIONS:	Anti-TNF (INF or ETA), doses varied	
MAIN RESULTS:	• In patients with RA, anti-TNF treatment leads to increased risk of serious infection and a dose-dependent increased risk of malignancies. • Malignancies reported in 24 / 3493 (0.8%) patients who received ≥ 1 dose of anti-TNF vs. 2 / 1512 (0.2%) patients on control. • Pooled OR for malignancies in anti-TNF group vs. placebo group = 3.3 (95% CI, 1.2 – 9.1); NNH was 154 (95% CI 91 – 500) within a treatment period of 3 to 12 months • Serious infections reported in 126 anti-TNF- treated patients vs. 26 control group patients (OR, 2.0; 95% CI, 1.3 – 3.1); NNH was 59 (95% CI 39 – 125) within a treatment period of 3 to 12 months	
ADVERSE EVENTS (%): • Malignancy[1] • Serious infections[2] [1] OR = 3.29 (1.19 – 9.08) [2] OR = 2.01 (1.31 – 3.09)	**Anti-TNF** 23 / 3192 126 / 3493	**Control** 3 / 1428 26 / 1512
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes: EMBASE, MEDLINE, Cochrane Library, and electronic abstracts of the annual scientific meetings both the EULAR and the American College of Rheumatology – through December 2005	
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes	
QUALITY RATING:	**Good**	

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Bongartz et al.[135]** **Year: 2009** **Country: US, UK** **Quality rating: Good**
FUNDING:	Wyeth
DESIGN & SIZE:	**Study design:** Systematic review/Individual patient data meta-analysis **Number of patients:** 3316 **Trials:** 9 (reported in 8 publications and 5 poster abstracts and 1 unpublished study)
OBJECTIVE OF REVIEW:	To assess the risk of malignancy with etanercept.
ELIGIBILITY CRITERIA:	Trials with study participants diagnosed with RA according to American College of Rheumatology criteria, were randomly assigned to etanercept or control treatment, and the study duration was at least 12 weeks.
STUDIES INCLUDED IN REVIEW: **(Author, Year, refID)**	TNR 00102 Unpublished Moreland 1997 Moreland 1999 Bathon 2000 Genovese 2002 Weinblatt 1999 Baumgartner 2004 (abstract); Ericson and Wadjula,1999 (abstract) Klareskog 2004 van der Heijde 2006; van der Heijde 2006 (abstract); Mola 2006 (abstract); Combe 2006; Combe 2005 (abstract)
LITERATURE SEARCH DATES:	Inception of databases to December 2006
INCLUDED STUDIES: **(Study design, characteristics of included population, characteristics of included interventions)**	− TNR 00102 Unpublished: N=158; Active RA with inadequate response to MTX; Etanercept 10 mg twice weekly vs Etanercept 25 mg twice weekly vs Placebo; 12 weeks − Moreland 1997: N=180; Active RA with inadequate response to ≥1 DMARD; Etanercept 0.25 mg/m^2 twice weekly vs Etanercept 2.0 mg/m^2 twice weekly vs Etanercept 16.0 mg/m^2 twice weekly vs Placebo; 12 weeks − Moreland 1999: N=246; Active RA with inadequate response to ≥1 DMARD; Etanercept 10 mg twice weekly vs Etanercept 25 mg twice weekly vs Placebo; 26 weeks (with extension up to 52 weeks) − Bathon 2000: N=654; Active early RA <3 years (no previous MTX); Etanercept 10 mg twice weekly vs Etanercept 25 mg twice weekly vs Placebo+Methotrexate; 104 weeks − Genovese 2002: N=89; Active RA with inadequate response to MTX; Etanercept 25 mg twice weekly +Methotrexate vs Placebo+Methotrexate; 24 weeks − Weinblatt 1999: N=564; Active RA and at least one comorbidity that increases the likelihood of infection;

	Etanercept 25 mg twice weekly vs Placebo; 16 weeks − Baumgartner 2004 (abstract); Ericson and Wadjula,1999 (abstract): N=559; Active RA with inadequate response to ≥1 DMARD; Etanercept 10 mg weekly vs Etanercept 25 mg weekly vs Etanercept 10 mg twice weekly 25 mg twice weekly vs Placebo; 12 weeks − Klareskog 2004: N=686; Active RA with inadequate response to DMARD other than MTX; Etanercept 25 mg twice weekly vs Etanercept 25 mg twice weekly+Methotrexate vs Methotrexate+Placebo; Approximately 180 weeks − van der Heijde 2006; van der Heijde 2006 (abstract); Mola 2006 (abstract); Combe 2006; Combe 2005 (abstract): N=260; Active RA with inadequate response to sulfasalazine; Etanercept 25 mg twice weekly+Sulfasalazine vs Etanercept 25 mg twice weekly+Placebo vs Sulfasalazine+Placebo; 104 weeks

Authors: Bongartz et al.
Year: 2009

DATA SYNTHESIS METHODS:

All patients from eligible trials who were randomly assigned and received at least one dose of the study drug were included in the analysis. A survival analysis of time-to-first-event using a Cox's proportional hazards model stratified by trial and assuming a fixed treatment effect was performed. A meta-analysis of study-level HRs based on a random effects model was conducted. Sensitivity analyses, and potential duration response analysis, were also conducted.

MAIN RESULTS: (RESULTS IN SUBGROUPS)

Dataset	Model	Events in Etanercept group	Events in Control group	HR (95% CI)	p Value
Full	Fixed effects survival model stratified by trial	26	7	1.84 (0.79 to 4.28)	0.16
Full	Random effects survival model stratified by trial	26	7	1.82 (0.78 to 4.22)	0.17
Non-melanoma skin cancer excluded	Fixed effects survival model stratified by trial	17	4	1.86 (0.62 to 5.59)	0.27
Cancers diagnosed within first 42 days excluded	Fixed effects survival model stratified by trial	23	6	1.87 (0.75 to 4.62)	0.18
<6 Months	Fixed effects survival model stratified by trial	8	3	1.52 (0.35 to 6.55)	0.99
6–12 Months	Fixed effects survival model stratified by trial	12	1	5.81 (0.73 to 46.16)	0.17
>12 Months	Fixed effects survival model stratified by trial	6	3	0.88 (0.21 to 3.66)	0.86
Full	Fixed effects survival model, treatment varying with ln(time)	26	7	0.97 (0.47 to 2.01)	0.93
Aggregate data	Fixed effects Mantel–Haenszel model	26	7	1.93 (0.85 to 4.38)	0.12
Aggregate data	Random effects DerSimonian and Laird model	26	7	1.71 (0.73 to 4.01)	0.21

	Malignancies identified: Twenty-six patients with incident malignancies in the treatment groups (incidence rate 10.47/1000 person-years) and seven patients in the control groups (IR 6.66/1000 person-years) Withdrawals: 574 of 2244 (25.6%) in the etanercept arms vs 455 of 1072 (42.4%) in the control arms
ADVERSE EVENTS:	See Main Results
LIMITATIONS OF PRIMARY STUDIES	NR

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Brassard**[136] **Year: 2006** **Country:** USA	
FUNDING:	Sanofi -Aventis	
RESEARCH OBJECTIVE:	To quantify the rate of *Mycobacterium tuberculosis* disease (TB) among a cohort of patients with rheumatoid arthritis (RA) and to assess whether the independent use of DMARDs is associated with the risk of developing TB.	
DESIGN:	**Study design:** Nested cohort **Setting:** Pharmaceutical database **Sample size:** 112,300- 386 cases of TB	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Case** varied 363 days 386	**Control** varied 364 days 38600
INCLUSION CRITERIA:	Age 18 or more years; diagnosis of RA during inpatient or outpatient visit; dispensed one or more anti-RA drug from 09/1998 to 12/2003	
EXCLUSION CRITERIA:	Prior history of TB	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

Authors: Brassard **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe		
	Case	**Control**	***P* =**
Mean age (years):	54	56	0.01
Sex (% female):	77.2	73.7	0.12
Ethnicity:	NR	NR	N/A
Other germane population qualities:			
• Biological DMARDs	17.4	11.8	0.008
• Infliximab	4.9	2.8	0.01
• Etanercept	8.3	6.1	0.07
• Anakinra	4.9	3.6	0.17
• DMARD use	50.8	44.1	0.008
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** TB **Timing of assessments:** time of diagnosis		
RESULTS:	**Health Outcome Measures:** Overall rate of 2.19 (95% CI, 1.97–2.41) cases per 1000 person-years of follow-up. Exposed to TNF blocking agents the rate was 2.57 (95% CI, 1.89–3.26) cases per 1000 person-years. Biological DMARDs RR (95% CI) 1.5 (1.1-1.9) INF RR (95% CI) 1.6 (1.0–2.6) ETA RR (95% CI) 1.2 (0.9–1.8) AKA RR (95% CI) 1.3 (0.8–2.1)		

Authors: Brassard **Year: 2006**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** No **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	**No but they are not suppose to be.**
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Braun et al.**[137,138,139,140] **and Listing et al.**[141] **Year: 2002, 2003, 2004, 2005** **Country:** Multinational	
FUNDING:	Schering-Plough	
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of infliximab treatment of AS	
DESIGN:	**Study design:** RCT **Setting:** Multi-center **Sample size:** 70	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 5 mg/kg 12 weeks 35	**Placebo** N/A 12 weeks 35
INCLUSION CRITERIA:	AS that was clinically classified as active based on a score of ≥4 on the BASDAI and a score of ≥4 on a 10-cm visual analog scale for pain in the spine	
EXCLUSION CRITERIA:	Comorbidity; insufficient disease activity; complete ankylosis; incorrect diagnosis; DMARD therapy; active TB within the previous 3 years; specific changes in the radiograph of the chest at baseline; serious infections within the previous 2 months or a history of lymphoproliferative disease or other malignant diseases in the past 5 years; signs or symptoms of severe renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs, but the dosage could not be increased over the baseline level during the course of the trial	

<table>
<tr><td colspan="3">Authors: Braun et al. and Listing et al.
Year: 2002, 2003, 2004, 2005</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: Yes
Disease severity: Severe (mean disease duration 15.6 years)</td></tr>
<tr><td><u>INF</u></td><td><u>Placebo</u></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• Mean disease duration (years)
• BASDAI score (mean)
• BASFI score (mean)</td><td>40.6
32
NR

16.4
6.5
5.4</td><td>39.0
37
NR

14.9
6.3
5.1</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: BASDAI
Secondary Outcome Measures: BASFI, BASMI, SF-36, CRP
Timing of assessments: 0, 2, 12 weeks</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
• More patients given INF (53%, 95% CI: 37-69) achieved a 50% improvement in BASDAI at week 12 than did controls (9%, 3-22)
• Function and quality of life improved significantly on INF but not on placebo ($P < 0.0001$ and $P < 0.0001$, respectively)
• BASDAI improved significantly to 3.3 at 12 weeks in the INF group, whereas little change was recorded in controls (5.7; difference 2.1 (1.6-3.7); $P < 0.0001$)
• The BASFI changed to 3.4 in the INF group ($P < 0.0001$) and to 5.0 in the placebo group ($P = 0.54$)
• In a 2 year open-label extension hospital admissions for INF patients were significantly reduced compared to the 12 months before the start of the trial (10% vs. 41%). A reduction of the mean inpatient days from 11.1 days before INF treatment to 2.9 days after 2 years of treatment
• Treatment effects could be sustained in the third year of extension
• Overall 16% of participants discontinued treatment because of adverse events during 3 years
Intermediate Outcome Measures:
• CRP and ESR dropped significantly from baseline to endpoint in the INF group ($P < 0.001$); no significant changes were seen in the placebo group ($P = 0.77$)</td></tr>
</table>

Authors: Braun et al. and Listing et al. **Year: 2002, 2003, 2004, 2005**		
ADVERSE EVENTS: **Overall adverse effects reported:** • Infections • Serious events	**INF** NR 18 3	**Placebo** NR 12 0
Significant differences in adverse events:	Yes-three patients on INF had serious events and were withdrawn from the study, compared with one on placebo ($P = 0.239$)	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No	
ADEQUATE RANDOMIZATION:	Yes	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	NR	
ATTRITION (*overall*):	**Overall loss to follow-up:** 4.2% **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**INF** 0 3	**Placebo** 2 0
QUALITY RATING:	**Fair**	

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Burmester et al.**[142] **Year: 2007** **Country:** Multinational
FUNDING:	Abbott
RESEARCH OBJECTIVE:	Safety and efficacy of ADA in patients with RA
DESIGN:	**Study design:** Uncontrolled, open-label trial **Setting:** Multicenter **Sample size:** 6610
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA** 40 mg eow 12 weeks to 5 years 6610
INCLUSION CRITERIA:	Men and women >18 years of age with active, adult-onset RA; a disease duration of >3 months, a DAS28 of >3.2, and treatment failure with at least one traditional DMARD.
EXCLUSION CRITERIA:	Current pregnancy or breast feeding; any persistent or severe infection within 30 days of baseline; previous treatment with other TNF antagonists up to 2 months before enrolment; treatment with alkylating agents, total lymphoid irradiation, intravenous immunoglobulin or any investigational biologic agent; a history of active arthritis other than RA; any uncontrolled medical condition; a history or signs of demyelinating disease; active tuberculosis (TB) or histoplasmosis; malignancy (except for completely treated squamous or basal cell carcinoma).
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	DMARDs (defined as MTX, leflunomide (LEF), sulfasalazine (SSZ), chloroquine or hydroxychloroquine (antimalarials, AM), azathioprine (AZA), and parenteral or oral gold) or any combination of DMARDs, glucocorticoids (prednisone equivalent (10 mg/day), and NSAIDs

Authors: Burmester **Year: 2007**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe
	ADA
Mean age (years):	54
Sex (% female):	81
Ethnicity:	NR
Other germane population qualities:	
• Tender joint count	14
• Swollen joint count	10
• Mean disease duration	11
• DMARD use (%)	74
• MTX use (%)	53
• Corticosteroids use (%)	71
• DAS score	6.0
• HAQ score	1.64
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 at week 12 and safety **Secondary Outcome Measures:** EULAR **Timing of assessments:** weeks 2, 6, 12, and every 8 weeks thereafter
RESULTS:	**Health Outcome Measures:** • Week 12, 69% of patients achieved an ACR20 response, 83% a moderate, and 33% a good EULAR response • AEs 72.4% of patients (4783/6610), RA-related events (9.7% (641/6610)), headache (4.8% (317/6610)) and nasopharyngitis (4.4% (293/6610)), and 9% were considered severe. Serious AEs (SAEs) occurred in 13% (882/6610) of patients (equivalent to 28.4 SAEs/100 PYs) three most commonly reported SAEs were RA-related events (2.0% (135/6610)), pyrexia (0.4% (25/6610)) and osteoarthritis (0.3% (20/66100). • Standardized mortality ratio 1.07 (95% CI 0.75 to 1.49), with 35 deaths observed compared with 32.6 deaths expected in the general population. • 10.3% discontinued because of adverse events. • 3% of patients had serious infections

Authors: Burmester **Year: 2007**			
ADVERSE EVENTS per 100 pys: **All serious AEs:** • Blood and lymphatic system disorders • Heart failure • Infections and infestations	**All** 28.4 0.5 0.4 5.5	**No DMARDs** 40.0 1.2 0.8 6.6	**Concomitant DMARDs** 24.6 0.3 0.3 5.1
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	N/A		
ATTRITION (*overall*):	**Overall attrition:** 7% **Attrition differential high:** N/A		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**ADA** 7% at 12 weeks 4.3% at 12 weeks, 10.3% at 5 years		
QUALITY RATING:	**NA**		

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Chakravarty et al.**[143] **Year: 2005** **Country:** US
FUNDING:	Bristol-Myers-Squibb
RESEARCH OBJECTIVE:	To determine the rates of reported non-melanoma skin cancer (NMSC) in a large cohort of patients with RA in comparison to patients with osteoarthritis (OA) and to determine risk factors of the development of NMSC in patients with RA
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Multi-center **Sample size:** 15,789 (RA); 3,639 (OA)
INTERVENTION: **Dose:** **Duration:** **Sample size:**	NA
INCLUSION CRITERIA:	Participants in the National Data Bank for Rheumatic Diseases (NDB); recruited from the 908 US rheumatologists; patients who returned at least 2 questionnaires between January 1999 and January 2003.
EXCLUSION CRITERIA:	NR
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR

<table>
<tr><td colspan="3">Authors: Chakravarty et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: No
Disease severity: NR</td></tr>
<tr><td></td><td><u>Patients with RA</u></td><td><u>Patients with OA</u></td></tr>
<tr><td>Mean age (years):</td><td>62</td><td>67</td></tr>
<tr><td>Sex (% female):</td><td>77</td><td>83</td></tr>
<tr><td>Ethnicity (% white):</td><td>91</td><td>94</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td></tr>
<tr><td>• HAQ-DI score</td><td>1.09</td><td>1.07</td></tr>
<tr><td>• Skin cancer before NDB (%)</td><td>3.8</td><td>5.8</td></tr>
<tr><td>• History of smoking (%)</td><td>56</td><td>46</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: Self-report of diagnosis of skin cancer; morbidity; mortality; comorbid conditions.
Timing of assessments: Semi-annual questionnaires</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
• A total of 738 patients with RA reported new cases of NMSC during followup within the NDB; crude incidence rate = 18.1 / 1000 patient-years (95% CI, 16.8 – 19.4 / 1000 person-years).
• After excluding prevalent cases of NMSC, incidence rate was 15.2 / 1000 person-years (95% CI, 14.1 – 16.5).
• Based on multivariate Cox proportional hazard analysis restricted to patients with RA:
  • Use of prednisolone was associated with an increased hazard ratio (HR) (HR = 1.28, 95% CI: NR; P = 0.014) for development of NMSC.
  • No association found with use of leflunomide or MTX alone.
  • Use of any anti-TNF (ETA, INF, & ADA) alone showed a slightly increased risk
  • An approximately 2-fold HR for development of NMSC was found among patients with RA using both MTX and any TNF inhibitor (HR 1.97, P = 0.001)</td></tr>
</table>

Authors: Chakravarty et al. **Year: 2005**	
ADVERSE EVENTS: **Overall adverse effects reported:** •	NR
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	NR
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	NR
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall loss to follow-up:** After initial assessment, ~ 8% of patients decline to participate each year. **Loss to follow-up differential high:** NR
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	NR
QUALITY RATING:	N/A

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Chung et al.**[144] **Year: 2003** **Country:** US		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To assess the effectiveness and safety of infliximab in patients with CHF		
DESIGN:	**Study design:** RCT **Study name: ATTACH (Anti-TNF Therapy Against Congestive Heart Failure) Trial** **Setting:** University clinics (32 centers) **Sample size:** 150		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 28 weeks 49	**INF** 5 mg/kg 28 weeks 50	**INF** 10 mg/kg 28 weeks 51
INCLUSION CRITERIA:	Men and women at least 18 years old with stable New York Heart Association (NYHA) class III or IV heart failure associated with a radionuclide left ventricular ejection fraction ≤35% within 14 days before randomization		
EXCLUSION CRITERIA:	Hemodynamically significant obstructive valvular disease, cor pulmonale, restrictive or hypertrophic cardiomyopathy, constrictive pericarditis, or congenital heart disease; had experienced an acute myocardial infarction or coronary revascularization procedure within 2 months; or were likely to undergo coronary revascularization or heart transplant during the anticipated duration of the study; resuscitation from sudden death or a therapeutic discharge of an implanted implantable cardioverter defibrillator within 3 months or had received within 2 weeks or were likely to receive within the following 28 weeks any of the following: A class IC or III antiarrhythmic other than amiodarone; a calcium channel blocker other than amlodipine for hypertension or angina; a positive inotrope other than digoxin; or a NSAID other than aspirin; experienced a serious infection within 2 months; had latent TB or had had TB within 3 years; had a documented HIV infection; or had any other opportunistic infection within 6 months; treatment within 3 months of INF or other therapeutic agents that could interfere with the actions of TNF (eg, ETA, pentoxifylline, thalidomide, or D2E7)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Vasodilators or nitrates		

<table>
<tr><td colspan="4">Authors: Chung et al.
Year: 2003</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: Moderate-severe</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>INF5</u></td><td><u>INF10</u></td></tr>
<tr><td>Mean age (years):</td><td>60 ± 12</td><td>62 ± 15</td><td>62 ± 13</td></tr>
<tr><td>Sex (% female):</td><td>24</td><td>14</td><td>16</td></tr>
<tr><td>Ethnicity (% white):</td><td>88</td><td>88</td><td>84</td></tr>
<tr><td>Current or prior angina (%):</td><td>29</td><td>18</td><td>24</td></tr>
<tr><td>Myocardial infarction (%):</td><td>63</td><td>50</td><td>67</td></tr>
<tr><td>Diabetes mellitus (%):</td><td>41</td><td>28</td><td>37</td></tr>
<tr><td>NYHA Class III/IV (%):</td><td>96/4</td><td>96/4</td><td>92/8</td></tr>
<tr><td>LVEF (%):</td><td>0.25 ± 0.07</td><td>0.23 ± 0.07</td><td>0.24 ± 0.06</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Change in clinical status, assessed by the clinical composite score, which categorized each patient as improved, worse, or unchanged using pre-specified criteria

Timing of assessments: 1,2,6,10,14,20,28 weeks</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• 10 mg/kg INF group were more likely to die or be hospitalized for heart failure than placebo (hazard ratio 2.84, 95% CI 1.01 to 7.97; nominal P = 0.043 using log-rank test)
• Patients in the 10 mg/kg INF group were more likely to be hospitalized for heart failure or for any reason than patients in the placebo or 5 mg/kg INF groups</td></tr>
</table>

Authors: Chung et al. **Year:2003**			
ADVERSE EVENTS: **Overall adverse effects reported (# of patients with 1 or more) n (%):** • Dizziness • Dyspnea • Hypotension • Angina • Serious AEs • Serious infections	**Placebo** 40 (83.3) 2 (4.2) 6 (12.5) 0 (0.0) 1 (2.1) (29.2) (2.1)	**INF5** 47 (92.2) 16 (31.4) 10 (19.6) 3 (5.9) 3 (5.9) (23.5) (5.9)	**INF10** 42 (84.0) 10 (20.0) 12 (24.0) 4 (8.0) 4 (8.0) (44.0) (8.0)
Significant differences in adverse events:	Yes		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high**: NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:** 6 in all, NR separately	**Placebo** 1	**INF5** 2	**INF10** 5
QUALITY RATING:	**Fair**		

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Curtis et al.**[145] **Year: 2007** **Country:** USA		
FUNDING:	Funded by FDA CBER Award #223-02-1420 Task Order #1, the Maryland chapter of the Arthritis Foundation, grant HS10389 from AHRQ, K24 AR052361-01 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and T32 AR47512-03 from the NIH.		
RESEARCH OBJECTIVE:	Investigate a possible association between TNF-antagonist use and incident heart failure,		
DESIGN:	**Study design:** Cohort study **Setting:** US claims data **Sample size:** 4018		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Exposed** ETA or INF Various 1707	**Unexposed** N/A Various 2311	
INCLUSION CRITERIA:	At least two ICD9-CM diagnosis codes for RA (714.X) or CD (555.X) during the study period and also required that each individual had received an infusion or filled a prescription for a TNF- antagonist (i.e. ETA or INF) or filled at least three prescriptions for one of several selected immunosuppressive drugs.		
EXCLUSION CRITERIA:	HIV, organ transplantation or malignancy in the 6 months prior to the index date		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

Authors: Curtis et al. **Year: 2007**					
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe				
	RA_INF	**RA_ETA**	**Unexposed**	**CD_INF**	**Unexposed**
N	330	808	983	569	1328
Mean age (years):	40	38	39	33	32
Sex (% female):	70	75	75	57	55
Ethnicity:	NR	NR	NR	NR	NR
Other germane population qualities:					
• Cases HF	4	1	1	1	2
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Heart failure				
RESULTS:	**Health Outcome Measures:** • RA treated with TNF-antagonist RR 4.3 (ns) compared with RA treated with conventional therapy • CD treated with TNF-antagonist RR 1.2 (ns) compared with CD treated with conventional therapy **"**In a cohort of more than 4000 RA and Crohn's patients younger than 50 yrs, the cumulative incidence of presumed heart failure was low (4 and 1 case per 1000 patients, respectively)."				

Authors: Curtis et al. **Year: 2007**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Curtis et al.**[146] **Year: 2007** **Country:** US	
FUNDING:	Maryland Chapter of the Arthritis Foundation, the Agency for Healthcare Research and Quality (grant HS-10389), and the NIH (grant K24-AR-052361-01 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases and grant AR-47512-03).	
RESEARCH OBJECTIVE:	To evaluate the risk of serious bacterial infections associated with tumor necrosis factor	
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Health care organization dataset **Sample size:** 5326	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**TNF antagonist** various various 2393	**MTX** various various 2933
INCLUSION CRITERIA:	between May 1998 and December 2003 RA patients >18 years old who took only MTX or anti-TNF	
EXCLUSION CRITERIA:	N/A	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	other nonbiologic DMARDs	

Authors: Curtis et al. **Year: 2007**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe	
	TNF antagonist	**MTX**
Mean age (years):	50	55
Sex (% female):	73	73
Ethnicity:	NR	NR
Other germane population qualities:		
• INF	33	0
• ETA	50	0
• ADA	3	0
• >1 antiTNF	12	0
• MTX use (%)	70	100
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Infection **Timing of assessments:** various	
RESULTS:	**Health Outcome Measures:** • No. (%) of patients with any infection anti TNF 65 (2.7%) vs. MTX only 58 (2.0%) • Hazard ratio of infection TNF-antagonists was 1.9 (95% confidence interval [95% CI] 1.3–2.8) compared with patients who received MTX only.	

Authors: Curtis et al. **Year: 2007**		
ADVERSE EVENTS: **Overall adverse effects reported:**	**TNF antagonist** see results	**MTX**
Significant differences in adverse events:	Yes	
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:**	
ARE GROUPS COMPARABLE AT BASELINE:	No	
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes	
STATISTICAL ANALYIS ADEQUATE:	Yes	
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:**	
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**TNF antagonist** N/A	**MTX**
QUALITY RATING:	**Fair**	

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Curtis, et al.**[147] **Year: 2011** **Study name: NR** **Country:** US **Quality rating: Fair**		
FUNDING:	AHRQ, Doris Duke Charitable Foundation (Government & non-profit)		
RESEARCH OBJECTIVE:	To evaluate the incidence of hospitalized infections among RA patients starting or switching various biologic agents		
DESIGN & SIZE:	**Study design:** Observational Study **Setting:** multicenter **Number screened: NR** **Number eligible: NR** **Number enrolled: 7847** **Run-in/Wash-out period: NA**		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Biologic-free** NR NR 4916	**Switcher** NR NR 2931	
INCLUSION CRITERIA:	RA diagnosis; at least one prescription or infusion for a biological agent that they had not received in the preceding 12 months; pharmacy and medical benefits in the 12 months prior to index date as well as through follow up (if older than 65 years, must be enrolled in Medicare Advantage)		
EXCLUSION CRITERIA:	Malignancy (excluding non-melanoma skin cancer)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR (although Table 1 shows that many patients were on prednisone)		

Authors: Curtis et al. **Year: 2011**			
POPULATION CHARACTERISTICS (%):	**Biologic-free**	**Switcher**	
Mean age (years):	49.5	49.2	
Sex (% female):	75.8	76.9	
Ethnicity:	NR	NR	
Class naïve:	NR (100% biologic-free for 1 year prior to index date but may have been on biologics previously)	0%	
Other germane population qualities:			
• **Polyarticular arthritis**	NR	NR	
• **DIP joints of hand/feet**	NR	NR	
• **Asymmetric peripheral arthritis**	NR	NR	
• **NSAID use (%)**	NR	NR	
• **MTX use (%)**	NR	NR	
• **Corticosteroids use (%)**	NR	NR	
• **DAS score**	NR	NR	
• **HAQ score**	NR	NR	
RESULTS:	**Primary Outcome Measures:** **Rate of Hospitalized Infection, per 100 person-years:** Biologic-free: 4.6 Switcher: 7.0 P < 0.0001 **Rate of Hospitalized Infection, Adjusted HR (95% CI)** IFX: 1.0 (ref) ABA: 0.68 (0.48 to 0.96) ADA: 0.52 (0.39 to 0.71) ETN: 0.64 (0.49 to 0.84) RTX: 0.81 (0.55 to 1.20)		

Authors: Curtis et al. **Year: 2011**		
METHOD OF ADVERSE EVENTS REPORTING:	Identified infections using a comprehensive set of ICD-9 codes developed as part of a systematic literature review and two validation studies in RA patients. The validation studies compared cases identified using these codes with cases confirmed using hospital medical records abstracted across the USA and with cases confirmed by abstracting records from a university hospital	
ADVERSE EVENTS (%):	**Overall**	
Overall adverse effects reported: • Infections • URTI • abnormal LFT • herpes simplex • pneumonia • tb • ISR • Skin and soft tissue infection • Septicaemia/bacteraemia • Benitourinary tract infection	364 (# of hospitalizations with at least one unique infection) 7.8 NR 6 (n) 23.7 5 (n) NR 17.2 16.6 15.8	
ATTRITION (*overall*):	**Overall attrition:** NA **Attrition differential high:** NA	
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**Drug 1** NA	**Drug 2** NA

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Davies et al.** **Year: 2011** **Study name: British Society for Rheumatology Biologics Register (BSRBR)** **Country: UK** **Quality rating: Fair**				
FUNDING:	British Society for Rheumatology (who receives some funding from UK pharmaceutical companies, including Abbott, Amgen, Schering Plough, and Wyeth Pharmaceuticals).				
RESEARCH OBJECTIVE:	To compare the rates of venous thrombotic events (VTEs) in patients with RA treated with anti-TNF therapy versus those treated with non-biologic DMARDs alone, and to compare the rates between each individual anti-TNF agent and non-biologic DMARDs.				
DESIGN & SIZE:	**Study design:** Cohort **Setting:** Multicenter (over 250 hospitals across the UK) **Sample size:** 15,554				
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Non-biologic DMARD** NR Mean 2.6 years 3,673	**All Anti-TNF** NR Mean 3.9 years 11,881	**Etanercept** NR NR 4,139	**Infliximab** NR NR 3,475	**Adalimumab** NR NR 4,267
INCLUSION CRITERIA:	All RA patients prescribed anti-TNF therapy within the UK, starting in 2001; comparison cohort of biologic-naïve patients from 29 centers with active RA [defined as a 28-joint DAS >4.2] despite current treatment with a non-biologic DMARD.				
EXCLUSION CRITERIA:	NR				
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Steroids; otherwise, NR				

Authors: Davies et al. **Year: 2011**		
POPULATION CHARACTERISTICS:	**Non-biologic DMARD**	**All Anti-TNF**
Mean age (years):	60	56
Sex (% female):	72	76
Ethnicity:	NR	NR
Class naïve:	NR	NR
Other germane population qualities:		
• **Tender joint count**	NR	NR
• **Swollen joint count**	NR	NR
• **Mean disease duration**	6 (median)	11 (median)
• **DMARD use (%)**	NR	NR
• **MTX use (%)**	NR	NR
• **Corticosteroids use (%)**	23	44
• **DAS score**	5.1	6.6
• **HAQ score**	1.5	2.0
RESULTS:	**Primary Outcome Measures:** Nonbiologic DMARD vs Etanercept vs Infliximab vs Adalimumab Adjusted HR of verified first VTE in non-biologic DMARD and anti-TNF-treated patients: Ref vs 0.8 (95% CI, 0.4 to 1.4) vs 1.1 (95% CI, 0.6 to 1.9) vs 0.8 (95% CI, 0.4 to 1.4), P=NS Fully adjusted OR for risk of VTE following surgery: DMARD Referent vs Anti-TNF 1.9 (95% CI, 0.5 to 7.4)	

Authors: Davies et al. **Year: 2011**			
METHOD OF ADVERSE EVENTS REPORTING:	NR		
ADVERSE EVENTS (%):	**Etanercept**	**Infliximab**	**Adalimumab**
Overall adverse effects reported:			
• infections	NR	NR	NR
• URTI	NR	NR	NR
• abnormal LFT	NR	NR	NR
• herpes simplex	NR	NR	NR
• pneumonia	NR	NR	NR
• tb	NR	NR	NR
• ISR	NR	NR	NR
• Venous thrombosis events	**See Results**	**See Results**	**See Results**
ATTRITION (*overall*):	**Overall attrition:** NA **Attrition differential high:** NA		
ATTRITION (*treatment specific*):	**Etanercept**	**Infliximab**	**Adalimumab**
Attrition overall:	NA	NA	NA
Attrition due to adverse events:	NA	NA	NA

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Dixon et al.[148]** **Year: 2010** **Study name:** **Country: UK** **Quality rating: Fair**			
FUNDING:	British Society for Rheumatology (BSR) commissioned the Biologics Register; BSR receives restricted income from UK pharmaceutical companies (Abbot, Amgen, Schering Plough, and Wyeth)			
RESEARCH OBJECTIVE:	To compare directly the risk of TB between drugs in patients with RA, to explore time to event, site of infection and the role of ethnicity.			
DESIGN & SIZE:	**Study design:** National prospective observational study **Setting:** British Society for Rheumatology Biologics Register **Sample size:** 10,712 anti-TNF cohort; 3232 DMARD cohort			
INTERVENTION:	**drug 1 (ETA)**	**drug 2 (INF)**	**drug 3(ADA)**	**DMARD**
Dose:	NR	NR	NR	NR
Duration:	2.48 yr	1.68 yr	1.26 yr	NR
Sample size:	3913	3295	3504	3232
INCLUSION CRITERIA:	Patients with a doctor's diagnosis of RA and with at least one returned consultant follow-up questionnaire before 31 March 2008. The anti-TNF cohort comprised patients starting an anti-TNF drug as their first biologic drug. A comparison cohort of biologic-naïve patients with active RA was recruited in parallel. These patients had active disease despite current treatment with a traditional DMARD and were biologic naïve.			
EXCLUSION CRITERIA:	NR			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR			

Authors: Dixon et al. **Year: 2010**				
POPULATION CHARACTERISTICS:	**Drug 1 (ETA)**	**Drug 2 (INF)**	**Drug 3 (ADA)**	**DMARD**
Mean age (years):	56	56	57	60
Sex (% female):	77	76	75	72
Ethnicity: % White	82	82	84	78
Class naïve:	100	100	100	NA
Other germane population qualities:				
• **Tender joint count**	NR	NR	NR	NR
• **Swollen joint count**	NR	NR	NR	NR
• **Mean disease duration (yr)**	12	12	10	6
• **# prior DMARDs**	4	4	3	2
• **MTX use (%)**	NR	NR	NR	NR
• **Corticosteroids use (%)**	48	46	39	23
• **DAS28 score**	6.6	6.6	6.5	5.1
• **HAQ score**	2.1	2.1	2.0	1.5
• **Prior TB**	2.5	1.5	1.5	2.3
• **Diabetes (%)**	6.1	4.8	5.9	6.6
• **COPD/Asthma (%)**	14.4	13.0	12.9	18.4
RESULTS:	**Primary Outcome Measures:** **Rate of TB**: 40 cases reported (in 39 patients; 1 patient had 2 discrete epidsodes), all in anti-TNF group; ETA=39/100,00 P-Y; INF=136/100,000P-Y; ADA=144/100,000 P-Y **After Adjustment, the incidence rate ratio compared with ETA-treated patients was**: 3.1 (95%CI 1.0 to 9.5) for INF and 4.2 (95% CI 1.4 to 12.4) for ADA **Median time to event**: ETA 13.4 months; INF 5.5 months; ADA 18.5 months **Role of Ethnicity**: "Patients of non-white ethnicity had a sixfold increased risk of TB compared with white patients treated with anti-TNF therapy." IRR 6.5 (2.8 to 15.3) **Number (and rates per 100,000P-Y) of incident TB while "on drug"**: ETA: 5, (39); INF: 11 (136); ADA: 11 (144) **Number (and rates per 100,000P-Y) incident TB "most recent drug"**: ETA: 8 (53); INF: 12 (123);			

	ADA: 20 (217) (Patients could switch between anti-TNF therapies, but all TB cases were attributable to one drug only) **Number (and rates per 100,000P-Y) of incident TB, limited to first anti-TNF drug with follow-up censored at date of starting second anti-TNF drug) while on drug**: ETA: 4 (40); INF: 11 (147); ADA: 9 (157) **Number (and rates per 100,000P-Y) of incident TB, limited to first anti-TNF drug with follow-up censored at date of starting second anti-TNF drug) most recent drug:** ETA:6 (50); INF: 12 (134); ADA: 15 (223) **Secondary Outcome Measures:** NR

Authors: Dixon et al. **Year: 2010**				
METHOD OF ADVERSE EVENTS REPORTING:	6-monthly rheumatologist questionnaire, 6-monthly patient diary, flagging with the UK Office for National Statistics which provided information on mortality, including cause of death. If active TB was reported from any source, further information, including site of infection and supporting evidence fordiagnosis was requested from the rheumatologist. Patient-reported cases of TB were only included in the analysis if later verified by a consultant.			
ADVERSE EVENTS (%):	**Drug 1 (ETA)**	**Drug 2 (INF)**	**Drug 3 (ADA)**	**DMARD**
Overall adverse effects reported:				
• infections	NR	NR	NR	NR
• URTI	NR	NR	NR	NR
• abnormal LFT	NR	NR	NR	NR
• herpes simplex	NR	NR	NR	NR
• pneumonia	NR	NR	NR	NR
• TB: Pulmonary-Lower respiratory tract (n){n on drug}	4{2}	2{2}	6{3}	0
• TB: Pulmonary-Pleural(n){n on drug}	0	2{2}	1{1}	0
• TB: Total pulmonary(n){n on drug}	4{2}	4{4}	7{4}	0
• TB: Bone and joint: (n){n on drug}	1{1}	0	0	0
• TB: Gastrointestinal: (n){n on drug}	0	3{3}	0	0
• TB: Lymph node(n){n on drug}				
• TB: CNS(n){n on drug}	2{2}	2{2}	2{2}	0
• TB: Pharyngeal wall(n){n on drug}	0	1{1}	2{1}	0
• TB: Disseminated(n){n on drug}				
• TB: Total extrapulmonary(n){n on drug}	0	0	1{1}	0

	1{0} 4{3}	2{1} 8{7}	8{3} 13{7}	0 0
• ISR	NR	NR	NR	NR
ATTRITION (*overall*):	**Overall attrition:** NR **Attrition differential high:** NR			
ATTRITION (*treatment specific*):	**Drug 1**	**Drug 2**	**Drug 3**	
Attrition overall:	NR	NR	NR	
Attrition due to adverse events:	NR	NR	NR	

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Dixon et al.**[149] **Year: 2007** **Country:** UK	
FUNDING:	The British Society for Rheumatology is indirectly funded by Schering-Plough, Whety Laboratories, Abbot Laboratories, and Amgen	
RESEARCH OBJECTIVE:	To test the hypothesis that the anti-inflammatory effect of anti–tumor necrosis-α (anti-TNFα) therapy might lead to a reduction in the incidence of myocardial infarction (MI) in RA patients	
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Data from BSRBR, a national prospective observational study **Sample size:** 10,829 (74 patients switched from comparison cohort and were included in analysis for both so actual number of patients=10,755); anti-TNF subgroup analysis: 7515	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Anti-TNFα nonresponders** N/A N/A 1638	**Anti-TNFα responders** N/A N/A 5877
INCLUSION CRITERIA:	Registered with BSRBR; diagnosed with RA; followed up for ≥ 6 months by July 31, 2006; Anti-TNFα cohort: treated with an anti-TNF drug, registered with BSRBR within 6 months of starting biologic therapy	
EXCLUSION CRITERIA:	NR	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Lipid-lowering drugs, NSAIDS	

Authors: Dixon et al. **Year: 2007**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR		
	Anti-TNFα nonresponders	**Anti-TNFα responders**	
Mean age (years):	57	56	
Sex (% female):	79	76	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Tender joint count	NR	NR	
• Swollen joint count	NR	NR	
• Median disease duration	11	7	
• DMARD use (%)	NR	100	
• MTX use (%)	NR	NR	
• Corticosteroids use (%)	45.3	42.9	
• DAS score	6.4	6.6	
• HAQ score	2.2	2.0	
• Prior MI (%)	2.9	2.6	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** MI rates **Timing of assessments:** N/A		
RESULTS:		**Nonresponders**	**Responders**
	Person-years	1815	9886
	No. of reported MIs	17	35
	Rate of MIs per 1000 person-yrs (95% CI)	9.4 (5.5-15.0)	3.5 (2.5-4.9)
	Incidence rate ratio	Referent	0.38 (0.21-0.67)
	Incidence rate ratio, adjusted for age and sex	Referent	0.38 (0.22-0.68)
	Incidence rate ratio, multivariate analysis	Referent	0.36 (0.19-0.69)
	Incidence rate ratio by sex,		

	multivariate analysis Male Female	 Referent Referent	 0.31 (0.12-0.81) 0.46 (0.20-1.06)

Authors: Dixon et al. **Year: 2007**	
ADVERSE EVENTS: **Overall adverse effects reported:**	See Above
Significant differences in adverse events:	See Results
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**NA**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Dommasch et al.**[150] **Year: 2011** **Country: U.S.** **Quality rating: Good**
FUNDING:	Grants from the National Institute of Arthritis, Musculoskeletal, and Skin Diseases, and a National Research Service Award from the National Institute of Health.
DESIGN & SIZE:	**Study design:** Systematic review/meta-analysis **Number of patients: 6810** **Trials: 20**
OBJECTIVE OF REVIEW:	To examine the risks of infection and malignancy with the use of TNF antagonists in adult patients with psoriatic disease.
ELIGIBILITY CRITERIA:	RCTs of the 4 currently licensed anti-TNF agents (etanercept, infliximab, adalimumab, golimumab), and one anti-TNF agent currently under investigation (certolizumab) for the treatment of adult patients with moderate to severe plaque psoriasis, psoriatic arthritis, or both, limited to the English language. Study participants must have been adult patients with a diagnosis of plaque psoriasis or psoriatic arthritis randomized to receive treatment with an anti-TNF agent or placebo for at least 12 weeks.
STUDIES INCLUDED IN REVIEW:	Akihiko 2010 Antoni 2005 (IMPACT) Antoni 2005 (IMPACT 2) Genovese 2007, Gordon 2006 Gottlieb 2003 Gottlieb 2004 (SPIRIT) Kavanaugh 2009 Leonardi 2003 Mease 2000 Mease 2004 Mease 2005 Menter 2007 (EXPRESS II) Menter 2008 Ortonne 2007 (unpublished conference poster) Papp 2005 Reich 2005 (EXPRESS I) Saurat 2008 (CHAMPION) Tyring 2006 van de Kerkhof 2008
LITERATURE SEARCH DATES:	Inception of databases to July 30, 2009
INCLUDED STUDIES:	All trials compared the following treatments with a placebo: 6 trials with adalimumab, 7 with etanercept, 5

	with infliximab, 1 with certolizumab, and 1 with golimumab. 7 trials specifically included patients with active psoriatic arthritis unresponsive to DMARD, NSAIDs, or both, although 5 of these trials also required that patients have active psoriatic skin lesions, a documented history of plaque psoriasis, or both. The remaining 13 trials specifically included those with moderate to severe plaque psoriasis. All psoriatic arthritis trials allowed for the use of at least one concomitant DMARD, whereas plaque psoriasis trials excluded those on concomitant immunosuppressant therapy. − Akihiko 2010: plaque psoriasis, Adalimumab (80 mg at week 0 then 40 mg every other week) vs Adalimumab (40 mg every other week) vs Adalimumab (80 mg every other week) vs placebo − Antoni 2005 (IMPACT): psoriatic arthritis, Infliximab (5 mg/kg at weeks 0, 2, 6, 14) vs placebo − Antoni 2005 (IMPACT 2): psoriatic arthritis, Infliximab (5 mg/kg at weeks 0, 2, 6, 14, 22) vs placebo − Genovese 2007: psoriatic arthritis, Adalimumab (40 mg every other week) vs placebo − Gordon 2006: plaque psoriasis, Adalimumab (40 mg every other week) vs Adalimumab (40 mg weekly) vs placebo − Gottlieb 2003: plaque psoriasis, Etanercept (25 mg twice weekly) vs placebo − Gottlieb 2004 (SPIRIT): plaque psoriasis, Infliximab (3 mg/kg at weeks 0, 2, 6) vs Infliximab (5 mg/kg at weeks 0, 2, 6) vs placebo − Kavanaugh 2009: psoriatic arthritis, Golimumab (50 mg every 4 weeks) vs Golimumab (100 mg every 4 weeks) vs placebo − Leonardi 2003: plaque psoriasis, Etanercept (25 mg weekly) vs Etanercept (25 mg twice weekly) vs Etanercept (50 mg twice weekly) vs placebo − Mease 2000: psoriatic arthritis and plaque psoriasis, Etanercept (25 mg twice weekly) vs placebo − Mease 2004: psoriatic arthritis, Etanercept (25 mg twice weekly) vs placebo − Mease 2005: psoriatic arthritis, Adalimumab (40 mg every other week) vs placebo − Menter 2007 (EXPRESS II): plaque psoriasis, Infliximab (3 mg/kg at weeks 0, 2, 6) vs Infliximab (5 mg/kg at weeks 0, 2, 6) vs placebo − Menter 2008: plaque psoriasis, Adalimumab (80 mg at week 0 then 40 mg every other week) vs placebo − Ortonne 2007 (unpublished conference poster): plaque psoriasis, Certolizumab pegol (400 mg at wk 0 then 200 mg every 2 weeks) vs Certolizumab pegol (400 mg every 2 weeks) vs placebo − Papp 2005: plaque psoriasis, Etanercept (25 mg twice weekly) vs Etanercept (50 mg twice weekly) vs

	placebo − Reich 2005 (EXPRESS I): plaque psoriasis, Infliximab (5 mg/kg at weeks 0, 2, 6, 14, 22) vs placebo − Saurat 2008 (CHAMPION): plaque psoriasis, Adalimumab (80 mg at week 0 then 40 mg every other week) vs MTX (7.5 mg – 25 mg weekly) vs placebo − Tyring 2006: plaque psoriasis, Etanercept (50 mg twice weekly) vs placebo − van de Kerkhof 2008: plaque psoriasis, Etanercept (50 mg weekly) vs placebo

Authors: Dommasch et al. **Year: 2011**	
DATA SYNTHESIS METHODS:	Used ITT method, calculated ORs, homogeneity testing performed using the I^2 test. Produced a pooled estimate of risk for each outcome, with results expressed as overall ORs with associated 95% CIs. Used a fixed effects model with Mantel-Haenszel methods. Calculated ORs across all included studies, and performed subanalyses by indication and drug. Calculated a number needed to harm based on the Mantel-Haenszel fixed effects model estimate if the OR was statistically significant. Calculated rate-adjusted estimates of risks for malignancy and infection using incidence rate ratios (IRRs), pooling the rate ratios across studies using Mantel-Haenszel weights.
MAIN RESULTS: (RESULTS IN SUBGROUPS)	***Malignancy*** Total malignancies: anti-TNF therapy 28 vs placebo 6 (including additional malignancies identified after contacting the industry sponsors) 70.6% of malignancies included in analysis were nonmelanoma skin cancer [OR 1.33 (95% CI, 0.58 to 3.04), IRR 0.72 (95% CI, 0.42 to 1.24]. OR for all malignancies excluding nonmelanoma skin cancer was 1.28 (95% CI 0.39 to 4.15), IRR 0.56 (95% CI, 0.31 to 1.01). **OR of malignancy associated with anti-TNF treatment versus control:** Adalimumab Gordon 2006: OR 1.47 (95% CI, 0.30 to 7.32) Menter 2008: OR 2.81 (95% CI, 0.13 to 59.59) Mease 2005: No events Saurat 2008: No events Genovese 2007: No events Akihiko 2010: No events **Subtotal:** I^2=0.0%, P=0.71; OR 1.73 (95% CI, 0.42 to 7.09) Certolizumab Ortonne 2007 (unpublished conference poster): No events **Subtotal:** No events Etanercept Leonardi 2003: OR 0.51 (95% CI, 0.08 to 3.07) Papp 2005: OR 4.51 (95% CI, 0.24 to 84.12)

	Tyring 2006: OR 2.96 (95% CI, 0.31 to 28.62) Mease 2000: No events Gottlieb 2003: No events Mease 2004: No events van der Kerkhof 2008: No events **Subtotal:** I^2=14.0%, P=0.31; OR 1.61 (95% CI, 0.49 to 5.35) Golimumab Kavanaugh 2009: OR 2.33 (95% CI, 0.12 to 45.52) **Subtotal:** OR 2.33 (95% CI, 0.12 to 45.52) Infliximab Gottlieb 2004: OR 1.85 (95% CI, 0.09 to 36.46) Antoni 2005 (IMPACT 2): OR 0.21 (95% CI, 0.01 to 5.30) Reich 2005: OR 1.29 (95% CI, 0.06 to 27.15) Menter 2007: OR 1.66 (95% CI, 0.08 to 34.69) Antoni 2005 (IMPACT): No events **Subtotal:** I^2=0.0%, P=0.76; OR 0.99 (95% CI, 0.25 to 3.88) **Overall:** I^2=0.0%, P=0.91; OR 1.48 (95% CI, 0.71 to 3.09) Rate adjusted analysis: IRR 0.99 (95% CI, 0.51 to 1.90) ***Infections*** Total number of patients experiencing an infectious event: anti-TNF therapy 1358 vs placebo 619 97.6% of infections were nonserious (i.e., not recorded as a serious AE), OR 1.20 (95% CI, 1.07 to 1.35) Number needed to harm for treatment with all anti-TNF agents: 29 Serious infections: anti-TNF therapy 28 (0.61%) vs placebo 19 (0.82%); OR 0.70 (95% CI, 0.40 to 1.21). When adjusting for patient-year, the IRR for overall infection was 1.01 (95% CI, 0.92 to 1.11), 0.59 (95% CI, 0.35 to 0.99) for serious infection, 1.02 (95% CI 0.93 to 1.13) for nonserious infection. **OR of overall infection associated with anti-TNF treatment versus control:** Adalimumab

	Mease 2005: OR 1.25 (95% CI, 0.80 to 1.97) Gordon 2006: OR 1.29 (95% CI, 0.52 to 3.20) Genovese 2007: OR 0.44 (95% CI, 0.17 to 1.13) Menter 2008: OR 1.41 (95% CI, 1.06 to 1.87) Saurat 2008: OR 1.13 (95% CI, 0.58 to 2.19) Akihiko 2010: OR 0.95 (95% CI, 0.48 to 1.88) **Subtotal:** I^2=18.5%, P=0.29; OR 1.23 (95% CI, 1.00 to 1.50) <u>Certolizumab</u> Ortonne 2007 (unpublished conference poster): OR 0.85 (95% CI, 0.45 to 1.61) **Subtotal:** OR 0.85 (95% CI, 0.45 to 1.61) <u>Etanercept</u> Mease 2000: OR 1.00 (95% CI, 0.36 to 2.78) Gottlieb 2003: OR 2.83 (95% CI, 1.27 to 6.28) Leonardi 2003: OR 0.64 (95% CI, 0.37 to 1.10) Mease 2004: OR 0.81 (95% CI, 0.46 to 1.44) Papp 2005: OR 1.26 (95% CI, 0.79 to 2.02) Tyring 2006: OR 1.30 (95% CI, 0.91 to 1.87) van der Kerkhof 2008: OR 1.11 (95% CI, 0.50 to 2.45) **Subtotal:** I^2=47.7%, P=0.08; OR 1.14 (95% CI, 0.92 to 1.40) <u>Golimumab</u> Kavanaugh 2009: OR 1.67 (95% CI, 1.03 to 2.72) **Subtotal:** OR 1.67 (95% CI, 1.03 to 2.72) <u>Infliximab:</u> Gottlieb 2004: OR 1.92 (95% CI, 0.92 to 3.97) Antoni 2005 (IMPACT): OR 0.61 (95% CI, 0.20 to 1.86) Antoni 2005 (IMPACT 2): OR 1.07 (95% CI, 0.61 to 1.86) Reich 2005: OR 1.11 (95% CI, 0.66 to 1.85) Menter 2007: OR 1.12 (95% CI, 0.80 to 1.58) **Subtotal:** I^2=0.0%, P=0.52; OR 1.15 (95% CI, 0.91 to 1.45)

	Overall: I^2=21.6%, P=0.19; OR 1.18 (95% CI, 1.05 to 1.33) **Withdrawals:** anti-TNF therapy 6.8% vs placebo 16.1%, P=0.005
ADVERSE EVENTS:	See Main Results.
LIMITATIONS OF PRIMARY STUDIES	Rarity of events and short duration of follow-up, making CIs wide; unable to assess risk of cancer and serious infection associated with chronic use of TNF inhibitors; unequal follow-up times, shorter durations of follow-up in placebo groups compared with treatment groups (because of higher rate of treatment failure in the former); RCTs clinically heterogeneous with respect to study drug, trial design, disease indication, previous and concomitant immunosuppressant treatment, and disease duration; some RCTs only reported number of events rather than number of subjects experiencing at least one event, so an assumption of one even per subject was made, possibly leading to an overestimation of effect.

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Du Pan et al.**[151] **Year: 2009** **Study name: None** **Country: Switzerland** **Quality rating: Fair**		
FUNDING:	Swiss Clinical Quality Management has received grants from the Swiss Health authorities, the Swiss Academy for Medical Sciences, the J.L. Warnery Foundation, the Swiss Society of Rheumatoid Arthritis Patients, and Abbott, Essex, Wyeth, Roche, Bristol-Myers Squibb, Mepha, Novartis, and Sanofi-Aventis. Dr. Dehler's work was supported by the Swiss Clinical Quality Management Foundation. Dr. Gabay's work was supported by the Swiss National Science Foundation (grant 320000-107592). Dr Finchk's work was supported by a research grant from Geneva University. See published study for additional disclosures.		
RESEARCH OBJECTIVE:	TNF inhibitors have revolutionized the treatment of severe RA, yet drug discontinuation is common. The aim of this study was to compare treatment retention rates and specific causes of anti-TNF discontinuation in a population-based RA cohort.		
DESIGN & SIZE:	**Study design**: longitudinal, observational, population-based cohort study **Setting:** Swiss Clinical quality Management RA cohort **Sample Size:** 2364		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Drug 1 (INF)** NR see time to anti-TNF discontinuation 595	**Drug 2 (ETA)** NR see time to anti-TNF discontinuation 887	**Drug 3(ADA)** NR see time to anti-TNF discontinuation 882
INCLUSION CRITERIA:	All patients in the Swiss Clinical Quality Management for Rheumatoid Arthritis registry treated with an anti-TNF between January 1997 and December 2006.		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Du Pan et al. **Year: 2009**			
POPULATION CHARACTERISTICS:	**Drug 1 (INF)**	**Drug 2 (ETA)**	**Drug 3 (ADA)**
Mean age (years):	53	54	55
Sex (% female):	76	78	79
Ethnicity: % White	NR	NR	NR
Class naïve:			
Other germane population qualities:			
• **Tender joint count**	NR	NR	NR
• **Swollen joint count**	NR	NR	NR
• **Mean disease duration (yr)**	10	10	10
• **No DMARDs ***	11	29	22
• **MTX use (%)***	74	55	61
• **Leflunomide (%)**	17	17	18
• **Other DMARD**	17	19	20
• **Corticosteroids use (%)**	52	52	49
• **DAS28 score**	4.27	4.23	4.14
• **HAQ score**	1.32	1.25	1.17
• **RADA**	4.29	4.31	4.16
• **Failure of previous anti-TNF (%)***	23	19	27
• **Rheumatoid factor + (%)**	77	74	75
• ***= p < 0.001**			
RESULTS:	**Primary Outcome Measures:** (A total of 803 anti-TNF discontinuations were reported: INF 249; ETA 309; ADA 245) **Time to anti-TNF discontinuation**: A statistically significant difference was noted in the discontinuation rates between the 3 anti-TNF agents (crude p=0.04, adjusted p<0.001). INF was associated with the highest treatment discontinuation rate (crude HR 1.19, 95% CI 1.01-1.51). Time to anti-TNF discontinuation because of an AE was significantly different between the three agents in disfavor of INF (HR 1.4, 95% CI 1.003-1.96; Cox proportional hazards model p=0.02) whereas no		

	differences existed in treatment discontinuation due to nontoxic causes (Cox proportional hazards model p=0.39). Strong confounders of the overall discontinuation rate proved to be previous failure of an anti-TNF agent and the year of treatment initiation. Median drug survival was the longest for the first anti-TNF agent (37 months) and decreased with subsequent anti-TNF agents (21 months for the second anti-TNF agent, 13 months for the third anti-TNF agent. Anti-TNF agents started before 2000 had a median survival of 43 months compared with 37 months from 2001-2004 and 26 months after 2005. Other significant predictors for treatment discontinuation included absence of concomitant glucocorticoids (HR 1.69, 95% CI 1.46-1.95) and high baseline DAS28 levels (HR 1.09, 95% CI 1.02-1.16). There was also a trend in favor of a lower risk of discontinuation of anti-TNF agents in combination with MTX (HR 0.85, 95% CI 0.70-1.02). After adjusting for these variables in the multivariate analysis, the relative risk for treatment discontinuation of ADA compared with INF was significantly modified (crude HR 0.87, 99% CI 0.70-1.10; adjusted HR 0.74, 99% CI 0.59-0.92), suggesting that previous failure of an anti-TNF agent and the year of treatment initiation particularly affected ADA treatment maintenance. After 1 year of anti-TNF initiation, 78% of the patients were still receiving INF, 82% were receiving ETA, and 84% were receiving ADA. At 2 years 58% were receiving INF, 65% were receiving ETA, and 66% were receiving ADA. **Specific causes for drug discontinuation**: Overall AEs were responsible for treatment discontinuation in 48.7% of cases (318 of 653): 16% for acute systemic reactions, 10% for a dermatologic complication, 14% for infections, 2% for malignancies, and 24% for other miscellaneous complications. Nontoxic causes were responsible for treatment discontinuation in 61% of cases (397 of 653). Treatment inefficacy represented the largest single cause for anti-TNF treatment discontinuation (50%). At the time of treatment interruption, the mean DAS28 level in this cohort was 4.37 (95% CI 3.66-3.90) for patients with other causes of treatment discontinuation (p<0.001). Other nontoxic causes included patient preference in 8.8% of cases, remission in 33%, and desire for pregnancy in 1.0%. The proportion of overall AEs causing treatment discontinuation did not differ significantly between the 3 anti-TNF agents (p=0.093). An analysis of the specific types of AEs revealed significantly more acute systemic reactions with INF (HR 2.11, 99% CI 1.23-3.62, p<0.001, adjusted p=0.018). No significant difference between the 3 anti-TNF agents for dermatologic AEs, infectious AEs or malignancies. **Secondary Outcome Measures:** NR

Authors: Du Pan et al. **Year: 2009**			
METHOD OF ADVERSE EVENTS REPORTING:	"When the reason for anti-TNF discontinuation was unclear or the dates of initiation or discontinuation were uncertain in the database, we contacted the treating physician to ascertain this information. If he or she did not answer the first request, a second was sent."		
ADVERSE EVENTS (%):	**Drug 1 (INF)**	**Drug 2 (ETA)**	**Drug 3 (ADA)**
Overall adverse effects reported:	108 (51.7%)	118 (49%)	92 (43.2%)
• infections	26 (12.4%)	41 (17%)	22 (10.3%)
• URTI	NR	NR	NR
• abnormal LFT	NR	NR	NR
• herpes simplex	NR	NR	NR
• pneumonia	NR	NR	NR
• tb	NR	NR	NR
• ISR	NR	NR	NR
• Dermatologic disease	16 (7.6%)	20 (8.4%)	29 (13.6%)
• Malignancy	8 (3.8%)	5 (2.1%)	2 (0.9%)
• Death	2 (1.0%)	0	2 (0.9%)
• Acute systemic reactions*	50 (23.9%)	24 (10%)	31 (14.6%)
• *p<0.001			
ATTRITION (*overall*):	**Overall attrition:** 803 **Attrition differential high:** Yes; INF 42%; ETA 35%; 28%		
ATTRITION (*treatment specific*):	**Drug 1 (INF)**	**Drug 2 (ETA)**	**Drug 3 (ADA)**
Attrition overall:	249 (42%)	309 (35%)	245 (28%)
Attrition due to adverse events:	108 (18%)	118 (13%)	92 (10%)

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Favalli et al.**[152] **Year: 2009** **Country:** Italy			
FUNDING:	NR- but all of the authors have received consultancy fees or Congress invitations from Schering-Plough, Wyeth, and Abbott			
RESEARCH OBJECTIVE:	To estimate the incidence of serious infections in the patients treated with anti-TNFα agents for rheumatoid arthritis recorded in the Lombardy Rheumatology Network (LORHEN) registry.			
DESIGN:	**Study design:** Cohort registry **Setting:** Population based registry **Sample size:** 1064			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**All** Various Various 1064	**INF** Various Various 519	**ADA** Various Various 303	**ETA** Various Various 242
INCLUSION CRITERIA:	RA patients receiving at least one dose of Anti-TNF			
EXCLUSION CRITERIA:	Lost to follow up in less than 6 months			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes			

Authors: Favalli **Year: 2009**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe			
	All	**INF**	**ADA**	**ETA**
Mean age (years):	55.84	55.72	56.07	55.81
Sex (% female):	83.2	81.5	85.1	84.3
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• Mean disease duration	9.44 yrs	9.28 yrs	9.56 yrs	9.63 yrs
• MTX use (%)	84.5	96.1	74.6	71.9
• Corticosteroids use (%)	84.2	88.4	76.9	84.3
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Infections-serious			
RESULTS:	**Health Outcome Measures:** • Incidence rate of infections was 35.9 per 1000 patients years			

	All	INF	ADA	ETA
Any serious infection - n (%) Incidence rate (IR): number of events per 1000 patient-yrs (95% CI).	73 (6.9%) 35.90 (27.66–44.13)	42 (8.1%) 38.91 (27.14–50.67)	20 (6.6%) 38.17 (21.44–54.90)	11 (4.5%) 25.58 (10.46–40.69)

Authors: Favalli **Year: 2009**				
ADVERSE EVENTS: **Overall adverse effects reported:**	**All** see results	**INF**	**ADA**	**ETA**
Significant differences in adverse events:	Factors that increased rate of serious infection – age at the time of starting biological drug treatment (P = 0.002), the baseline erythrocyte sedimentation rate ([ESR] P = 0.012), and the concomitant use of corticosteroids (P = 0.025).			
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A			
ARE GROUPS COMPARABLE AT BASELINE:	Yes			
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes			
STATISTICAL ANALYIS ADEQUATE:	Yes			
ATTRITION (*overall*):	**Overall attrition:** **Attrition differential high:**			
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A			
QUALITY RATING:	**Fair**			

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Feltelius et al.**[153] **Year: 2005** **Country:** Sweden
FUNDING:	Wyeth Research
RESEARCH OBJECTIVE:	To describe a nationwide system for postmarketing follow up of new antirheumatic drugs; to analyze safety & effectiveness in an etanercept-treated cohort.
DESIGN:	**Study design:** Observational (retrospective cohort) **Setting:** Swedish Society of Rheumatology database **Sample size:** 1,073
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg twice weekly ≥ 2 years 1,073
INCLUSION CRITERIA:	Active RA; previous treatment with > 1 DMARD in addition to MTX.
EXCLUSION CRITERIA:	NR
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR

Authors: Feltelius et al. **Year: 2005**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Severe (high disease activity)
	ETA
Mean age (years):	52
Sex (% female):	76.6
Ethnicity:	NR
Other germane population qualities:	
• DMARD use (%)	56.3
• MTX use (%)	40.1
• Corticosteroids use (%)	95.2
• DAS score	5.9
• HAQ score	1.62
• Mean CRP	45
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Disease activity (measured by CRP, ESR, HAQ, tender / SJC, patient & physician global assessment) . **Secondary Outcome Measures:** DAS28; EULAR; ACR20 **Timing of assessments:** Examinations at 0, 3, 6, 12, 18, & 24 months after inclusion.
RESULTS:	**Health Outcome Measures:** • In 294 patients (27%), at least 1 adverse drug reaction was reported (421 reports; mean 1.5 report per patient; median 1; rand 1 to 6). • 80 adverse drug reactions were serious and 331 were non-serious. The incidence of serious adverse events remained constant over time.

Authors: Feltelius et al . **Year: 2005**	
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Skin • Infection resistance mechanism • Respiratory system • General • Neurological • Gastrointestinal • Cardiovascular • Hematological • Musculoskeletal • Neoplasms	**ETA (n=540)** NR 24.8 16.7 13.7 13.0 5.4 5.2 4.8 3.2 2.2 2.0
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ADEQUATE RANDOMIZATION:	N/A
ADEQUATE ALLOCATION CONCEALMENT:	N/A
BLINDING OF OUTCOME ASSESSORS:	N/A
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ETA** N/A 59
QUALITY RATING:	**N/A**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Fleischmann et al.,[154,155] Schiff et al.,[156] and Tesser et al.[157]** **Year**: **2003, 2004, 2006** **Country:** Multinational	
FUNDING:	Amgen Inc., Thousand Oaks, CA	
RESEARCH OBJECTIVE:	To evaluate the safety of AKA in a large population of patients with RA, typical of those seen in clinical practice. Additionally to determine the safety in a sub-population of patients with comorbid conditions; and to examine concomitant medication's effect on adverse events.	
DESIGN:	**Study design:** RCT **Setting:** Multicenter (169 sites) **Sample size:** 1414 (1399 enrolled)	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**AKA** 100 mg/d 6 months (up to three years) 1116 (1346)	**Placebo** N/A 6 months 283
INCLUSION CRITERIA:	18 years of age or older; RA diagnosed according to ACR criteria for at least 3 months; active disease defined by a minimum of 3 swollen joints and 3 tender joints or 45 minutes of morning stiffness; stable doses of NSAIDs and corticosteroids for one month; and stable doses of DMARDs for 2 months.	
EXCLUSION CRITERIA:	Pregnant or lactating; uncontrolled medical condition (e.g., diabetes with HgbA1c > 8%); malignancy other than basal cell carcinoma of the skin or in situ carcinoma of the cervix; Felty's syndrome; leukopenia; neutropenia; thrombocytopenia; abnormal liver function test result; hepatitis B or C positive; HIV positive.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDS, corticosteroids, and DMARDs (except TNF inhibitors) either alone or in combination	

Authors: Fleischmann et al., Schiff et al., and Tesser et al. **Year: 2003, 2004, 2006**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Mild to severe	
	AKA	**Placebo**
Mean age (years):	54.6	55.7
Sex (% female):	74.7	74.6
Ethnicity (%):		
• White	87.8	90.1
• Black	6.1	5.3
• Hispanic	4.4	3.5
• Other	1.7	1.1
Other germane population qualities:		
• TJC	22.6	22.6
• SJC	18.8	18.3
• DMARD use (excluding MTX) (%)	47.7	47.7
• MTX use (%)	51.9	59.4
• Corticosteroids use (%)	57.0	60.8
• DAS score	NR	NR
• HAQ score	NR	NR
Comorbidities (Schiff 2004), %:		
• Asthma	9.8	8.1
• COPD	12.9	11.0
• Pneumonia	9.1	6.7
• DM	7.4	7.4
• CAD	5.7	5.7
• CHF	3.2	3.2

Authors: Fleischmann et al., Schiff et al., and Tesser et al. Year: 2003, 2004, 2006	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Safety (measured by adverse events, serious adverse events, infections, study discontinuation, and death; WHO adverse reaction term dictionary) **Secondary Outcome Measures:** NR **Timing of assessments:** Day 1, week 1, and months 1,3, and 6.
RESULTS:	**Health Outcome Measures:** • After 6 months, the rate of spontaneous adverse events was not different between AKA and placebo, except for ISRs, which occurred much more frequently among AKA-treated patients than placebo-treated patients (72.6% v. 32.9%) *P*-value NR • 13.4% of patients in the AKA group withdrew due to adverse event compared to 9.2% in the placebo group, but the difference was not significant ($P = 0.057$); overall discontinuation rates were similar (21.6% vs. 18.7%) • Serious infections occurred more frequently in AKA than in placebo patients (2.1% v. 0.4%), but was not statistically significantly different but may be clinically significant. ($P = 0.068$) • In patients with comorbid conditions, there were no differences between the AKA group and the placebo group in incidence of serious adverse events or overall infectious events. • In patients with comorbid conditions, the rate of serious infectious events was increased relative to placebo (2.5% vs. 0.0%; P = NR). • There is a trend towards increased risk of serious infectious events with AKA in patients with pulmonary comorbidities versus placebo (3.4% v. 1.6%), but it failed to reach statistical significance. • Neutralizing anti-ANA antibodies detected in 0.8% of AKA patients NR for patients receiving placebo. • Adverse event profiles were similar between groups taking concomitant antihypertensive, antidiabetic and statin drugs. • From 0 to 3 years the overall cumulative rate exposure adjusted rate anakinra versus placebo (3

	events per 100 pt yrs) • All AEs 689.8 vs. 1029.4 • SAEs 27.1 vs. 22.3 • Serious infections 5.4 vs. 1.6 • Deaths 0.7 vs. 0.8 • ISRs 122.26 vs. 135.6 • RA progression 67.8 vs. 122.37 • URTI 26.09 vs. 58.7 • Headache 19.05 vs. 32.25 • Arthralgia 13.77 vs. 19.02 • Sinusitis 12.8 vs. 18.19 • Nausea 12.45 vs. 19.02 • Diarrhoea 11.26 vs. 16.54 Standardised incidence ratio for cancer observed versus expected (SEER) • All sites 17 vs. 20.58 SIR 0.83 95% CI 0.48 to 1.32 • Oral cavity and pharynx 1 vs. 0.44 SIR 2.26 95% CI 0.06 to 13.00 • Digestive system 2 vs. 3.49 SIR 0.57 95% CI 0.07 to 2.07 • Respiratory system 1 vs. 3.19 SIR 0.31 95% CI 0.01 to 1.75 • Malignant melanoma 4 vs. 0.73 SIR 5.48 95% CI 1.49 to 14.00 • Breast 3 vs. 4.70 SIR 0.64 95% CI 0.13 to1.86 • Female genital system 1 vs. 1.85 SIR 0.54 95% CI 0.01 to 3.02 • Urinary system 2 vs. 1.23 SIR 1.63 95% CI 0.20 to 5.89 • Lymphoma 3 vs. 0.81 SIR 3.71 95% CI 0.77 to 11.00 • Other 0 vs. 4.13 SIR 0.00 95% CI 0.00 to 0.89

Authors: Fleischmann et al., Schiff et al., and Tesser et al. **Year: 2003, 2004, 2006**		
ADVERSE EVENTS: **Overall adverse effects reported:** • Deaths • Serious adverse events • Severe adverse events • ISRs • Infectious episode • Serious infection • URTI • Sinusitis • Influenza-like • UTI • Bronchitis	**AKA** 1,027 (92.0%) 4 (0.4%) 86 (7.7%) 15.5% 72.6% 41.2% 2.1% 13.3 6.7 5.8 4.6 3.4 2.9	**Placebo** 261 (92.2%) 1 (0.4%) 22 (7.8%) 13.1% 32.9% 43.5% 0.4% 18.4 6.0 6.4 5.3 4.6 3.2
Significant differences in adverse events:	• No significant differences reported. (No *P*-value was reported for ISRs.)	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (15/1414)	
ADEQUATE RANDOMIZATION:	NR	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	Yes	
ATTRITION (*overall*):	**Overall loss to follow-up:** 394 (21%) **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**AKA** 21.6% 13.4%	**Placebo** 18.7% 9.2%
QUALITY RATING:	**Fair**	

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Galloway et al.[158]** **Year: 2011** **Study name: British Society for Rheumatology Biologics Register (BSRBR)** **Country: UK** **Quality rating: Good**				
FUNDING:	British Society for Rheumatology Biologics Register (funded the Open Access publication charges).				
RESEARCH OBJECTIVE:	To evaluate the risk of serious infections in patients with RA treated with anti-TNF therapy, with emphasis on the risk across different ages.				
DESIGN & SIZE:	**Study design:** Observational **Setting:** Multicenter (over 250 hospitals across the UK) **Sample size:** 15,396				
INTERVENTION:	**Non-biologic DMARD**	**All Anti-TNF**	**Etanercept**	**Infliximab**	**Adalimumab**
Dose:	NR	NR	NR	NR	NR
Duration:	Mean 2.6 years	Mean 3.9 years	NR	NR	NR
Sample size:	3,598	11,798	4,129	3,467	4,202
INCLUSION CRITERIA:	All RA patients prescribed anti-TNF therapy within the UK, starting in 2001; comparison cohort of biologic-naïve patients from 29 centers with active RA [defined as a 28-joint DAS >4.2] despite current treatment with an non-biologic DMARD.				
EXCLUSION CRITERIA:	NR				
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Steroids; otherwise, NR.				

Authors: Galloway et al.
Year: 2011

POPULATION CHARACTERISTICS:	**Non-biologic DMARD**	**All Anti-TNF**
Mean age (years):	60	56
Sex (% female):	72	76
Ethnicity:	NR	NR
Class naïve:	NR	NR
Other germane population qualities:		
• **Tender joint count**	NR	NR
• **Swollen joint count**	NR	NR
• **Mean disease duration**	6 (median)	11 (median)
• **DMARD use (%)**	NR	NR
• **MTX use (%)**	NR	NR
• **Corticosteroids use (%)**	23	44
• **DAS score**	5.1	6.6
• **HAQ score**	1.5	2.0

RESULTS:

Primary Outcome Measures:

Overall and time-dependent risk of serious infection:

Results	**Non-biologic DMARD**	**Etanercept**	**Infliximab**	**Adalimumab**
Follow-up (patient-years)	9259	15874	9622	10733
Number of serious infections	296	609	441	462
Rate/1000 patient-years	32 (95% CI, 28 to 36)	38 (95% CI, 35 to 42)	46 (95% CI, 42 to 50)	43 (95% CI, 39 to 47)
Unadjusted HR	Ref.	1.4 (95% CI, 1.2 to 1.6)	1.6 (95% CI, 1.4 to 1.9)	1.4 (95% CI, 1.2 to 1.7)
Adjusted HR	Ref.	1.2 (95% CI, 1.0 to 1.4)	1.3 (95% CI, 1.1 to 1.6)	1.3 (95% CI, 1.1 to 1.5)
Follow-up				
0-6 months	Ref.	1.8 (95% CI, 1.2 to 2.7	1.7 (95% CI, 1.1 to 2.6)	1.8 (95% CI, 1.2 to 2.7)

	6-12 months	Ref.	1.3 (95% CI, 0.8 to 2.0)	1.4 (95% CI, 0.9 to 2.2)	1.4 (95% CI, 0.9 to 2.1)
	12-24 months	Ref.	1.1 (95% CI, 0.8 to 1.5)	1.1 (95% CI, 0.7 to 1.5)	1.3 (95% CI, 0.9 to 1.8)
	24-36 months	Ref.	0.8 (95% CI, 0.6 to 1.2)	1.2 (95% CI, 0.8 to 1.8)	0.8 (95% CI, 0.6 to 1.3)

Secondary Outcome Measures:

Risk of serious infection according to age – events per 1000 patient-years, DMARD vs Anti-TNF:
<55 years: 18 (95% CI, 13 to 23) vs 28 (95% CI, 25 to 31); adjusted HR 1.2 (95% CI, 0.8 to 1.6)
55–64 years: 26 (95% CI, 20 to 32) vs 46 (95% CI, 42 to 50); adjusted HR 1.4 (95% CI, 1.1 to 1.9)
65–74 years: 52 (95% CI, 43 to 62) vs 62 (95% CI, 56 to 69); adjusted HR 0.9 (95% CI, 0.7 to 1.2)
>75 years: 46 (95% CI, 33 to 62) vs 83 (95% CI, 67 to 101); adjusted HR 1.5 (95% CI, 0.9 to 2.6)

Univariate analyses to identify independent predictors of serious infection:
Age (additional hazard per year increase in age): HR 1.03 (95% CI, 1.03 to 1.04)
Female gender: HR 0.8 (95% CI, 0.7 to 0.9)
DAS28 score (additional hazard per unit increase in DAS28): HR 1.2 (95% CI, 1.1 to 1.2)
Disease duration: HR 1.02 (95% CI, 1.01 to 1.02)
HAQ score (additional hazard per unit increase in HAQ): HR 1.8 (95% CI, 1.6 to 1.9)
On steroid at baseline: HR 1.6 (95% CI, 1.5 to 1.8)
Smoking: HR 1.3 (95% CI, 1.2 to 1.4)
COPD: HR 1.9 (95% CI, 1.6 to 2.2)
Diabetes: HR 1.8 (95% CI, 1.6 to 2.1)

Comparison of outcome of serious infections, DMARD vs Anti-TNF:
Median hospital stay in days (interquartile range): 7 (3, 14) vs 6 (3, 12); P=0.1318
Deaths within 30 days of infection: 47 (16%) vs 110 (7%); P<0.001, OR 0.5 (95% CI, 0.3 to 0.8)

Authors: Galloway et al. **Year: 2011**			
METHOD OF ADVERSE EVENTS REPORTING:	3 methods: 1) 6 monthly questionnaires were sent to the treating rheumatology team for 3 years and annually thereafter; 2) questionnaires were sent to the patients every 6 months (for 3 years); 3) flagging with the UK National Health Service Information Centre, which informed the register of any deaths and the cause of death.		
ADVERSE EVENTS (%):	**Etanercept**	**Infliximab**	**Adalimumab**
Overall adverse effects reported:			
• infections	**See Results**	**See Results**	**See Results**
• URTI	NR	NR	NR
• abnormal LFT	NR	NR	NR
• herpes simplex	NR	NR	NR
• pneumonia	NR	NR	NR
• tb	NR	NR	NR
• ISR	NR	NR	NR
ATTRITION (*overall*):	**Overall attrition:** NA **Attrition differential high:** NA		
ATTRITION (*treatment specific*):	**Etanercept**	**Infliximab**	**Adalimumab**
Attrition overall:	NA	NA	NA
Attrition due to adverse events:	NA	NA	NA

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Geborek et al.**[159] **Year: 2005** **Country:** Sweden	
FUNDING:	Österlund and Kock Foundations, King Gustav V 80 year fund, and Reumatikerförbundet	
RESEARCH OBJECTIVE:	To determine whether TNF blockers increase tumour risk in patients with RA by comparing an Anti-TNF cohort to a non-TNF cohort (other).	
DESIGN:	**Study design:** retrospective cohort study **Setting:** Rheumatology practices **Sample size:** 1557 (5551 patient years)	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Anti-TNF** INF or ETA 1.7 yrs 757	**Control** N/A N/A 800
INCLUSION CRITERIA:	Patients with RA treated with ETA or INF	
EXCLUSION CRITERIA:	Tumor diagnosis prior to study	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

<table>
<tr><td colspan="3">Authors: Geborek et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: No
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>Anti-TNF</u></td><td><u>Other</u></td></tr>
<tr><td>Mean age (years):</td><td>56</td><td>64</td></tr>
<tr><td>Sex (% female):</td><td>76</td><td>73</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td></tr>
<tr><td>• Mean disease duration</td><td>12</td><td>11</td></tr>
<tr><td>• Previous DMARD use (#)</td><td>3</td><td>1</td></tr>
<tr><td>• HAQ quartile > 3</td><td>61</td><td>41</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: Cancer diagnoses in 4 categories, lymphomas, blood (leukemia + myeloma), smoking related (upper gastrointestinal tract + airway + urinary tract), and other malignancies (breast + genital + other gastrointestinal + abdominal cavity + skin + musculoskeletal).

Timing of assessments: Start of anti-TNF treatment or 1 July 1997 for the comparison cohort, until death or 31 December 2002.</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures: Anti-TNF vs. Control
• All tumors: SIR 1.1 (95% CI 0.6 to 1.8) vs. 1.4 (95% CI 1.1 to 1.8)
• Lymphomas: SIR 11.5 (95% CI 3.7 to 26.9) vs. 1.3 (95% CI 0.2 to 4.5)
• All tumors excluding lymphomas: SIR 0.79 (95% CI 0.4 to 1.42) vs. 1.39 (95% CI 1.08 to 1.76)
• The hazard ratio indicates a higher risk of lymphoma for anti-TNF drugs than for controls (RR: 4.9; 95% CI 0.9 – 26.2)</td></tr>
</table>

Authors: Geborek et al. **Year: 2005**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions: N/A**
ARE GROUPS COMPARABLE AT BASELINE:	**No**
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A
QUALITY RATING:	**N/A**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Geborek et al.**[20] **Year: 2002** **Country:** Sweden		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To assess the efficacy and safety of etanercept, infliximab, and leflunomide in a population-based setting		
DESIGN:	**Study design:** Non-randomized, open-label trial **Setting:** Primary care clinics; university clinic **Sample size:** 369 (33 patients tried two different treatments and one tried all three; 404 treatments)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** Varied 12 months 166	**INF** Varied 12 months 135	**Leflunomide** Varied 12 months 103
INCLUSION CRITERIA:	Diagnosis of RA according to the clinical judgment of the treating doctor. All patients included were required to have failed to respond to or not tolerated at least two DMARDs, including MTX. The patients were selected on the basis of current disease activity and/or unacceptable steroid requirement as judged by the treating doctor, but had different backgrounds concerning previous treatment, concomitant diseases, and functional impairment and disability		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

Authors: Geborek et al. **Year: 2002**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR **Disease severity:** Mild-moderate-severe (mean disease duration 14.5 years)		
	ETA	**INF**	**Leflunomide**
Mean age (years):	54.0	55.4	61.3
Sex (% female):	78	79	82
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• Mean disease duration	14.9	14.1	14.9
• DMARD use (%)	NR	NR	NR
• MTX use (%)	NR	NR	NR
• Corticosteroids use (%)	83	81	73
• DAS score	5.8	5.6	5.4
• HAQ score	1.55	1.47	1.46
• CRP	43.7	44.4	37.7
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR 20/50/70 **Secondary Outcome Measures:** DAS28 **Timing of assessments:** At months 0, 3 ,6, 12 and then every 3 or 6 months		
RESULTS:	**Health Outcome Measures:** • The ETA and INF performed significantly better than leflunomide • ACR 20-ETA significantly better than INF at three months ($P < 0.02$) and six months ($P < 0.05$) • ETA and INF significant decreases in prednisolone use after 2 weeks ($P < 0.001$) • ETA had a significantly higher ACR response rate than INF at 3 and 6 months (data NR; $P < 0.02$; $P < 0.05$) • ETA had a significantly higher ACR50 response rate at 3 months (data NR; $P < 0.05$) • Response rates of ETA and INF as monotherapies were not significantly better than MTX monotherapy		

Authors: Gerborek et al. **Year: 2002**			
ADVERSE EVENTS:	**ETA**	**INF**	**Leflunomide**
Overall adverse effects reported:	120	107	55
• Fatal	3	0	0
• Life threatening	0	3	0
• Serious	15	11	4
• Moderate	36	34	20
• Mild	61	59	22
• Not graded	5	0	9
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ARE GROUPS COMPARABLE AT BASELINE:	Yes		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	No, outcome assessors not blinded		
STATISTICAL ANALYSIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A		
QUALITY RATING:	**Fair**		

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Genovese et al.**[21] **Year: 2004** **Country:** US		
FUNDING:	Amgen, Inc., Thousand Oaks, CA		
RESEARCH OBJECTIVE:	To determine the potential for additive or synergistic effects of combination therapy with the selective anti-TNF-α agent etanercept and the anti-IL1 agent anakinra.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter, specialty clinic **Sample size:** 242		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg *twice* per week 24 weeks 80	**½ ETA + AKA** 25 mg *once* per week; 100 mg/day 24 weeks 81	**ETA + AKA** 25 mg *twice* per week; 100 mg/day 24 weeks 81
INCLUSION CRITERIA:	Age 18 or greater; greater than 6-month history of RA diagnosed by ACR criteria; 6+ swollen joints; 9+ tender/painful joints; at least 2 of: morning stiffness lasting 45 or more minutes, serum CRP of ≥ 1.5 mg/dl, or ESR ≥28 mm/hr; and, received MTX for at least 16 weeks, with a stable dose in the range of 10-25 mg/week for at least 8 weeks.		
EXCLUSION CRITERIA:	Any DMARD other than MTX within the past 4 weeks; treatment with AKA or any protein-based TNF-alpha inhibitor; received any intraarticular or systemic corticosteroid injections within past 4 weeks; or, had a recent history of significant infection or other important concurrent illness.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Continued treatment with stable doses of MTX and other stable medications, such as corticosteroids.		

Authors: Genovese, et al. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes, but there is a slight overall trend to more severe disease in full ETA + AKA group. **Disease severity:** Moderate		
	ETA	**½ ETA + AKA**	**ETA + AKA**
Mean age (years):	54.4	53.8	55.7
Sex (% female):	82.5	71.6	77.8
Ethnicity (% white race):	86.3	77.8	75.3
Other germane population qualities:			
• TJC	31.0	31.0	35.9
• SJC	21.4	19.8	23.4
• MTX use (%)	100	100	100
• Corticosteroids use (%)	48.8	54.3	44.4
• HAQ score	1.5	1.5	1.6
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR50 at week 24. **Secondary Outcome Measures:** ACR20 and ACR70 at week 24; sustained ACR20 response ("response for at least 4 monthly measurements, not necessarily consecutive, with 1 occurring at month 6"); good or moderate EULAR response at week 24; improvement in the ACR core criteria components; duration of morning stiffness; the DAS; and the SF-36; plasma AKA and ETA concentrations and anti-AKA and anti-ETA antibody concentrations. **Timing of assessments:** Baseline and weeks 2, 4, 8, 12, 16, 20, and 24; plasma concentrations at weeks 4, 12, and 24; antibody concentrations at weeks 12 and 24.		
RESULTS:	**Health Outcome Measures (ETA v. ½ ETA + AKA v. ETA + AKA), measure (95% CI):** • At week 24 there were no significant differences in outcomes between the treatment groups ACR50 at week 24: 41% v. 39% v. 31% (P = 0.914, by 1-tailed t-test) o OR (ETA + AKA v. ETA alone) 0.64 (90% CI: 0.37 to 1.09) o Sensitivity analysis yielded similar results. • **ACR20 at week 24:** o 68% v. 51% v. 62% Only significant difference is between ETA alone and the ½ ETA + AKA group (P = 0.037).		

	• ACR70 at week 24: 21% v. 24% v. 14% (*P*-value NR) • Sustained ACR20 response: between 43% and 54% of subjects in each group (specifics NR). • EULAR response at week 24: 79% v. 66% v. 73% (*P*-value NR) • Mean % reduction in DAS: 39% v. 41% v. 40% (*P*-value NR)

Authors: Genovese et al. **Year: 2004**			
ADVERSE EVENTS:	**ETA**	**½ ETA + AKA**	**ETA + AKA**
Overall adverse effects reported, %:	90.0	95.1	93.8
• Infections	40.0	37.0	46.9
• URTI	20.0	11.1	13.6
• ISR	40.0	67.9	70.4
• Any serious adverse event	2.5	4.9	14.8
• Serious infection	0.0	3.7	7.4
Significant differences in adverse events:	Patients receiving ETA (any dosage) + AKA experienced more ISRs and serious adverse events than patients receiving ETA alone. *P*-values NR.		
ANALYSIS:	**ITT:** YES **Post randomization exclusions:** 2		
ADEQUATE RANDOMIZATION:	**YES**		
ADEQUATE ALLOCATION CONCEALMENT:	Unknown		
BLINDING OF OUTCOME ASSESSORS:	YES		
ATTRITION (*overall*):	**Overall loss to follow-up:** 15.7% **Loss to follow-up differential high:** 15% between ETA alone and ½ ETA + AKA		
ATTRITION (*treatment specific*):	**ETA**	**½ ETA + AKA**	**ETA + AKA**
Loss to follow-up:	7%	22%	20%
Withdrawals due to adverse events:	0%	8.6%	7.4%
QUALITY RATING:	**Fair**		

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Greenwald et al.[160]** **Year: 2011** **Study name: TAME** **Country: United States** **Quality rating: Fair**	
FUNDING:	Biogen Idec, Genentech, and Roche	
RESEARCH OBJECTIVE:	To assess the safety of rituximab in combination with a tumor necrosis factor (TNF) inhibitor and methotrexate (MTX) in patients with RA.	
DESIGN & SIZE:	**Study design:** Placebo-controlled RCT **Setting:** Multicenter **Number screened:** NR **Number eligible:** NR **Number enrolled:** 54 **Run-in/Wash-out period:** Treatment with any nonbiologic or biologic DMARD (except etanercept or adalimumab and MTX) was discontinued 14 days prior to baseline, except for the following: azathioprine for 28 days, and leflunomide for 8 weeks (or 14 days after 11 days of standard cholestyramine or activated charcoal washout).	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Rituximab** 500 mg on days 1 and 15 + stable dose of MTX (10-25 mg/week) + stable dose of TNF inhibitor 24 weeks 36 (33 received medication)	**Placebo** Placebo + stable dose of MTX (10-25 mg/week) + stable dose of TNF inhibitor 24 weeks 18
INCLUSION CRITERIA:	Patients ages 18–65 years and who had active RA, in accordance with the ACR 1987 revised criteria, for ≥6 months. Patients had a swollen joint count of ≥5 and a tender joint count of ≥5, were treated with etanercept at 50 mg/week (25 mg twice per week or 50 mg once per week) or adalimumab at 40 mg every other week for at least 12 weeks immediately prior to randomization, and had used MTX for at least 12 weeks, at a stable dose of 10–25 mg/week for ≥4 weeks prior to treatment.	
EXCLUSION CRITERIA:	Patients with a rheumatic autoimmune disease (other than RA) or significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis, or Felty's syndrome), congestive heart failure, uncontrolled concomitant disease, cancer, or serious or opportunistic infections within 2 years of screening.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Corticosteroids, if the dose was stable at ≤10 mg/day (prednisone or equivalent) for ≥4 weeks prior to infusion, and was continued at this dose throughout the study.	

Authors: Greenwald et al. **Year: 2011**		
POPULATION CHARACTERISTICS:	**Rituximab**	**Placebo**
Mean age (years):	49.7	50.4
Sex (% female):	85%	94%
Ethnicity:	NR	NR
Class naïve:	NR	NR
Other germane population qualities:		
• **Tender joint count**	25.6	22.8
• **Swollen joint count**	16.9	14.2
• **Mean disease duration**	10.3	10.7
• **DMARD use (%)**	0%	0%
• **MTX use (%)**	100%	100%
• **Corticosteroids use (%)**	36%	17%
• **DAS score**	6.8	6.5
• **HAQ score**	1.3	1.5
RESULTS:	**Primary Outcome Measures:** Proportion of patients developing ≥1 serious infection through week 24, rituximab vs placebo: 1 (3%) after 14.4 patient-years of exposure (6.95 events per 100 patient-years; 95% CI, 0.98 to 49.35) vs 0 **Secondary Outcome Measures:** Rituximab vs Placebo Rate of infections (per 100 patient-years) through week 24: 215.51 (95% CI, 151.6 to 306.44) vs 316.76 (95% CI, 215.7 to 465.23) Percentage of patients achieving ACR20 improvement response at week 24: 30% vs 17% Percentage of patients achieving ACR50 improvement response at week 24: 12% vs 6% Improvement from baseline of ≥0.25 in HAQ score: 46.4% vs 22.2%	

Authors: Greenwald et al. **Year: 2011**		
METHOD OF ADVERSE EVENTS REPORTING:	AEs were collected according to system organ class and graded according to the National Cancer Institute Common Toxicity Criteria for AEs (version 3.0). Collected the following endpoints: patients developing at least 1 serious infection through week 24, incidence of all AEs, the incidence of all serious AEs, the incidence of grade 3 or 4 infections, the incidence and duration of all infections, and the proportion of patients with immunologic and laboratory assessment values outside the normal range.	
ADVERSE EVENTS (%):	**Rituximab**	**Placebo**
Overall adverse effects reported:	94%	83%
• infections	55%	61%
• URTI	18%	28%
• abnormal LFT	NR	NR
• herpes simplex	NR	NR
• pneumonia	3%	0%
• tb	0%	0%
• ISR	NR	NR
• nausea	15%	11%
• pruritus	12%	0%
• fatigue	12%	0%
• sinusitis	9%	17%
• muscle spasms	3%	11%
• grade 3 infections (requiring IV antibiotics)	9%	0%
• serious AEs	6%	0%
• infusion-related reactions	33%	11%
ATTRITION (*overall*):	**Overall attrition:** 5/51 (9.8%) **Attrition differential high:** No	
ATTRITION (*treatment specific*):	**Rituximab**	**Placebo**
Attrition overall:	5 (13.9%); 3 withdrew before treatment began	0 (0%)
Attrition due to adverse events:	2 (5.5%)	0 (0%)

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Gomez-Reino et al.**[161] **Year: 2003** **Country:** Spain
FUNDING:	Agencia Española del Medicamento (Ministerio de Sanidad y Consumo); Spanish Society of Rheumatology
RESEARCH OBJECTIVE:	To determine the long-term safety of infliximab and etanercept, in rheumatic diseases based on a national active-surveillance (BIOBADESAR: Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologia) system following the commercialization of the drugs.
DESIGN:	**Study design:** Database review **Setting:** 71 centers **Sample size:** 1540
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF and/or ETA** Various Mean 1.1 years 1540 (1578 treatments)
INCLUSION CRITERIA:	Patients with rheumatic disease being treated with biologic response modifier.
EXCLUSION CRITERIA:	N/A
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes

Authors: Gomez-Reino et al. **Year: 2003**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe
	INF and/or ETA
Mean age (years):	51
Sex (% female):	72%
Ethnicity:	NR
# of patients with:	
• RA	1265
• PsA	89
• AS	76
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Adverse events, primarily TB
RESULTS:	**Health Outcome Measures:** • Background TB incidence in Spain in the year 2000 was 21 cases per 100,000 inhabitants • 1,893 cases of TB per 100,000 patients in the year 2000 and 1,113 cases per 100,000 patients in the year 2001 in patients treated with TNF • RR of patients treated with TNF compared general population 90.1 (95% CI 58.8-146.0) in the year 2000 and 53.0 (95% CI 34.5-89.0) in the year 2001. • Estimated annual incidence of TB among RA patients not exposed to TNF inhibitors was 95 cases per 100,000 • RR in RA patients who did not receive TNF of TB (adjusted for age and sex) was 4.13 (95% CI 2.59-6.83) relative to the background rate. • RR of TB in INF-treated RA patients versus RA patients not exposed to this therapy was 19.9 (95% CI 16.2-24.8) in the year 2000 and 11.7 (95% CI 9.5-14.6) in the year 2001.

Authors: Gomez-Reino et al. **Year: 2003**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	**INF and/or ETA** NR 118 (8%)
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	NR
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYSISADEQUATE:	Yes
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**INF and/or ETA** 228 discontinued therapy (14%) 118 (8%)
QUALITY RATING:	**N/A**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Griffiths et al.**[110] **Year: 2010** **Study name: -** **Country: Worldwide** **Quality rating: FAIR**		
FUNDING:	Centocor Research and Development (pharmaceutical industry)		
RESEARCH OBJECTIVE:	To compare two biologic agents, ustekinumab and etanercept, for the treatment of psoriasis		
DESIGN & SIZE:	**Study design:** H-T-H RCT **Setting:** multi-center **Number screened:** 1,175 **Number eligible:** not reported **Number enrolled:** 903 **Run-in/Wash-out period:** no		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 50 mg twice weekly 12 weeks 347	**UST** 45 mg at weeks 0 and 4 12 weeks 209	**UST** 90 mg at weeks 0 and 4 12 weeks 347
INCLUSION CRITERIA:	≥18 years of age, diagnosis of plaque psoriasis at least 6 months earlier, candidates for phototherapy or systemic treatment, score ≥12 on PASI, score ≥3 on physician's global assessment; involvement of ≥10% of body-surface area; inadequate response, intolerance or contraindication to ≥1 conventional systemic agent (i.e., methotrexate, cyclosporine, or psoralen plus UVA), and no previous treatment with UST or ETA.		
EXCLUSION CRITERIA:	Nonplaque or drug-induced forms of psoriasis, recent serious infection, history of chronic or recurrent infectious disease, known malignant condition (other than treated basal- or squamous-cell skin cancer or cervical cancer in situ with no evidence of recurrence for ≥5 years), receipt of conventional systemic therapy or phototherapy within 4 weeks before enrollment, topical psoriasis agents within 2 weeks, investigational drugs within 4 weeks or 5 half-lives, biologic agents within 3 months or 5 half-lives.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	None reported		

Authors: Griffiths et al. **Year: 2010**			
POPULATION CHARACTERISTICS:	**ETA**	**UST 45 mg**	**UST 90 mg**
Mean age (years):	45.7	45.1	44.8
Sex (% female):	29.1%	36.4%	32.6%
Ethnicity:	91.1% white	92.3% white	89.0% white
Class naïve:	88.2%	87.6%	89.6%
Other germane population qualities:			
• **Mean PASI**	18.6	20.5	19.9
• **Mean body surface area involvement**	23.8%	26.7%	26.1%
• **Mean duration of psoriasis**	18.8 years	18.9 years	18.7 years
• **Received prior systemic therapy (%)**	57.3%	61.7%	52.4%
RESULTS:	**Primary Outcome Measures:** 56.8% of ETA group had ≥75% improvement in PASI score compared with 67.5% of UST 45 mg group (P=0.01 vs. ETA)and 73.8% of UST 90 mg group (P<0.001 vs. ETA). **Secondary Outcome Measures:** 23.1% of ETA group had ≥90% improvement in PASI score compared with 36.4% of UST 45 mg group (P<0.001 vs. ETA) and 44.7% of UST 90 mg group (P<0.001 vs. ETA). 49.0% of ETA group had cleared or minimal disease (physician's global assessment score=0 or 1) compared with 65.1% of UST 45 mg group (P<0.001 vs. ETA) and 70.6% of UST 90 mg group (P<0.001 vs. ETA). 8.6% of ETA group had cleared disease (physician's global assessment score=0) compared with 16.3% of UST 45 mg group (P=0.006 vs. ETA) and 26.2% of UST 90 mg group (P<0.001 vs. ETA).		

Authors: Griffiths et al. **Year: 2010**			
METHOD OF ADVERSE EVENTS REPORTING:	Safety was evaluated by assessing adverse events and routine hematologic and laboratory values. Possible major cardiovascular events were adjudicated by an independent panel of academic cardiologists. Serum samples were evaluated for antibodies to UST.		
ADVERSE EVENTS (%):	**ETA**	**UST 45 mg**	**UST 90 mg**
Overall adverse effects reported:	70.0%	66.0%	69.2%
• Infections	29.1%	30.6%	29.7%
• URTI	5.8%	6.2%	6.3%
• abnormal LFT	NR	NR	NR
• herpes simplex	NR	NR	NR
• pneumonia	NR	NR	NR
• tb	NR	NR	NR
• ISR	24.8%	4.3%	3.7%
• nonmelanoma skin cancer	0.0%	1.0%	0.3%
• back pain	2.0%	6.7%	4.3%
• ≥ serious adverse event	1.2%	1.9%	1.2%
ATTRITION (*overall*):	**Overall attrition:** 2.7% **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**ETA**	**UST 45 mg**	**UST 90 mg**
Attrition overall:	3.2%	3.8%	1.4%
Attrition due to adverse events:	2.3%	1.9%	1.2%

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Harrison et al.**[162] **Year: 2009** **Country:** United Kingdom	
FUNDING:	NR	
RESEARCH OBJECTIVE:	Incidence rate of psoriasis r in patients with RA treated with anti-TNFa therapy compared to those treated with traditional DMARDs	
DESIGN:	**Study design:** Cohort **Setting:** General practice **Sample size:** 12706	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Control** N/A N/A 2880	**Anti-TNF** Various N/A 9826
INCLUSION CRITERIA:	First 4000 patients with RA starting each anti-TNFa therapy were required by The National Institute for Health and Clinical Excellence (NICE) to be registered with the BSRBR and followed up for information on drug use, disease activity and adverse events	
EXCLUSION CRITERIA:	N/A	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A	

Authors: Harrison **Year: 2009**						
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe					
	Control		**Anti-TNF**			
Mean age (years):	60		56.2			
Sex (% female):	72		76			
Ethnicity:	NR		NR			
Other germane population qualities:						
• Mean disease duration	7 yrs		11			
• DAS score	5.0		6.6			
• HAQ score	1.6		2.1			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Incidence of psoriasis in RA patients					
RESULTS:		**Control (DMARD)**	**Anti TNF**	**ETA**	**INF**	**ADA**
	# psoriasis	0	25	6	6	13
	rate psoriasis/ 1000 people years	0 (0.71)	1.04 (0.67-1.54)	0.59 (0.22-1.28)	0.88 (0.32 - 1.93)	1.84 (0.98-3.15)

Authors: Harrison **Year: 2009**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	See Results
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** No **Post randomization exclusions:**
ARE GROUPS COMPARABLE AT BASELINE:	No but adjustments are made
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Hetland et al.**[22] **Year: 2010** **Study name:** DANBIO Registry **Country:** Denmark **Quality rating: Good**		
FUNDING:	Unrestricted grants from Abbott, Wyeth, and Schering-Plough (since 2004), Bristol-Myers Squibb, and Roche (since 2006), and UCB-Nordic (since 2007). The Danish Regions provided financial support for the activities related to quality improvement of biologic treatment. Dr. Hetland's work was supported by a grant from the Danish Rheumatism Association and by the Margarethe Astrid Hedvig Schaufuss Legat.		
RESEARCH OBJECTIVE:	To compare tumor necrosis factor inhibitors directly regarding the rates of treatment response, remission, and the drug survival rate in patients with rheumatoid arthritis (RA), and to identify clinical prognostic factors for response.		
DESIGN & SIZE:	**Study design:** Observational, registry **Setting:** Multicenter, outpatient **Number screened: 8074** **Number eligible: 2326** **Number enrolled: 2326** **Run-in/Wash-out period: No**		
INTERVENTION: **Dose:** **Duration (median):** **Sample size:**	**Adalimumab** 40 mg every 2 weeks 20 months 675	**Etanercept** 45 mg every week 21 months 517	**Infliximab** 229 mg every 7 weeks 16 months 1134
INCLUSION CRITERIA:	Since October 2000, Danish rheumatologists have monitored and reported details of TNF inhibitor therapy for patients with RA to the DANBIO registry.		
EXCLUSION CRITERIA:	Prior treatment with TNF inhibitor		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

Authors: Hetland et al. **Year: 2010**			
POPULATION CHARACTERISTICS:	**Adalimumab**	**Etanercept**	**Infliximab**
Mean age (years):	56	58	57
Sex (% female):	75	72	73
Ethnicity:	NR	NR	NR
Class naïve:	100%	100%	100%
Other germane population qualities:			
• **DMARD use (%)**	NR	NR	NR
• **MTX use (%)**	70	61	87
• **Corticosteroids use (%)**	40	43	50
• **DAS 28 score (mean)**	5.3	5.4	5.4
RESULTS:	**Primary Outcome Measures:** at 6 months ACR70 response 19% adalimumab, 17% etanercept, and 11% infliximab **Secondary Outcome Measures:** at 6 months EULAR good response adalimumab 41%, etanercept 34%, and infliximab 27%, DAS28 remission, adalimumab 26%, etanercept 21%, and infliximab 17% CDAI remission adalimumab 15%, etanercept 10%, and infliximab 8%, Adherence - At 48 months, the unadjusted drug adherence rates: for adalimumab, 52% (95% CI 46–57%); etanercept, 56% (95% CI 51–62%); infliximab, 41% (95% CI 37–44%) ($P < 0.0001$, by log rank test). These are the Lundex adjusted results which include all patients, crude responses are only completers at 6 months.		

Authors: Hetland et al. **Year: 2010**			
METHOD OF ADVERSE EVENTS REPORTING:	NR		
ADVERSE EVENTS (%):	**Adalimumab**	**Etanercept**	**Infliximab**
Overall adverse effects reported:	NR	NR	NR
ATTRITION (*overall*):	**Overall attrition:** 449 (23.9%) at 6 months **Attrition differential high:** NR		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**Overall at 6 months** 449 38%		

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Horneff et al.**[59] **Year: 2004** **Country:** Germany
FUNDING:	Wyeth-Pharma
RESEARCH OBJECTIVE:	To assess efficacy and safety of etanercept treatment based on a registry for children with juvenile idiopathic arthritis in Germany and Austria
DESIGN:	**Study design:** Retrospective data analysis **Setting:** 36 pediatric rheumatology centers **Sample size:** 322
INTERVENTION: **Dose:** **Duration (mean follow-up):** **Sample size:**	**ETA** 0.4 mg/kg body weight/2x weekly 13.4 months 322
INCLUSION CRITERIA:	Failure to respond to MTX; have juvenile idiopathic arthritis
EXCLUSION CRITERIA:	None
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX and corticosteroids

Authors: Horneff et al. **Year: 2004**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease characteristic:** – Polyarticular, systemic & oligoarticular
	ETA
Mean age (years):	NR
Sex (% female):	NR
Ethnicity:	NR
Other germane population qualities:	
• TJC (%)	7
• SJC (%)	11
• DMARD use (%)	NR
• MTX use (%)	NR
• Corticosteroids use (%)	NR
• DAS score	NR
• HAQ score	NR
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Gianinni's criteria of improvement **Secondary Outcome Measures:** NR **Timing of assessments:** 1, 3, 6, 12, 18, 24, and 30 months (endpoint is not clearly specified)
RESULTS:	**Health Outcome Measures:** • The mean number of tender and swollen joints decreased from 9 and 8.4 to 3.0 and 4.5 after one month, and to 2.2 and 3.3 after three months; morning stiffness decreased from 45 minutes to 12 and 7 after one and three months ($P < 0.001$ for all) • Using Gianinni's criteria of 30, 50, and 70% improvement, a therapeutic response in JIA patients was achieved by 67%, 54%, and 30%, respectively, after one month, 79%, 61%, and 38% after 3 months, 82%, 70%, and 50% after 6 months, and 80%, 71%, and 54% after 12 months

Authors: Horneff et al. **Year: 2004**	
ADVERSE EVENTS: **Overall adverse effects reported:** • Infections overall • Infection prolonged or w/fever • Herpes simplex labilas • Local skin rxn • Raised liver enzymes • Itching • Leucocytopenia • Abdominal pain	**ETA** 17% 6.2% 0.6% 1.5% 0.6% 2.8% 2.8% 1.9% 1.2% 1.9%
Significant differences in adverse events:	20% of cases were discontinued because of AEs
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** N/A
ADEQUATE RANDOMIZATION:	N/A
ADEQUATE ALLOCATION CONCEALMENT:	N/A
BLINDING OF OUTCOME ASSESSORS:	N/A
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Treatment discontinuation:** **Discontinuation due to adverse events:**	**ETA** 17.7% 3.4%
QUALITY RATING:	**N/A**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Hyams et al.**[163] **Year: 2009** **Study name: NA** **Country: France** **Quality rating:** Poor	
FUNDING:	Government and Abbott, Schering Plough, and Wyeth	
RESEARCH OBJECTIVE:	To assess the long-term outcomes of infliximab maintenance therapy in children with Crohn's Disease.	
DESIGN & SIZE:	**Study design:** Prospective cohort **Setting:** Pediatric gastroenterology centers **Sample size:** 729	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** NR NA (reported by person-years) 202	**Non-INF** NA NA 527
INCLUSION CRITERIA:	Children under age 16 newly diagnosed with IBD.	
EXCLUSION CRITERIA:	No additional criteria.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Not reported (see concomitant medications under population characteristics).	

Authors: Hyams et al. **Year: 2009**	
POPULATION CHARACTERISTICS:	
Mean age (years): **Sex (% female):** **Ethnicity:** **Class naïve:** Other germane population qualities: • **Tender joint count** • **Swollen joint count** • **Mean disease duration** • **DMARD use (%)** • **MTX use (%)** • **Corticosteroids use (%)** • **DAS score** • **HAQ score**	Mean age 12 years (SD 3 years) 41.2% Ethnicity not reported 28% mild disease, 52% moderate, 16% severe All newly diagnosed Concomitant medications within 30 days of diagnosis, INF-treated vs Non-INF-treated: Corticosteroids: 83% vs 71%; 5 aminosalicylic acid/sulfasalazine: 48% vs 67%; 6 mercaptopurine/azathioprine: 50% vs 40%; methotrexate: 1% vs 2%
RESULTS:	**Primary Outcome Measures:** Sustained clinical response

Authors: Hyams et al. **Year: 2009**		
METHOD OF ADVERSE EVENTS REPORTING:	Not reported	
ADVERSE EVENTS	**INF-treated**	**Non-INF-treated**
	1 conversion of PPD skin test; normal chest x-ray. 1 varicella infection and hospitalization for antiviral therapy because of rapid progression of rash. One malignancy; 3 years after diagnosis. 1 death 2 years after diagnosis: cardiac arrest secondary to cardiac arrhythmia, patient had previously suffered a near sudden death before diagnosis of CD.	No additional information.

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Kristensen et al.**[33] **Year: 2006** **Country:** Sweden	
FUNDING:	Supported by the Osterlund and Kock Foundations, Inc; the 80-year Fund of King Gustav V, and Reumatikerforbundet	
RESEARCH OBJECTIVE:	To describe the use of the LUNDEX index to compare long-term efficacy and tolerability of biologic therapies in RA patients treated in clinical practice.	
DESIGN:	**Study design:** Observational **Setting:** Multicenter **Sample size:** 949	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg SQ, twice weekly 3 years 309	**INF** 3 mg/kg at 0,2,6,& 12 weeks and then every 8 weeks 3 years 640
INCLUSION CRITERIA:	Patients diagnosed with RA according to clinical judgment of the treating physician; treated at 8 centers in Southern Sweden during the period March 1999 through January 2004; unsuccessful treatment with ≥ 2 DMARDs, including MTX;	
EXCLUSION CRITERIA:	Previous treatment with biologic therapy	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

Authors: Kristensen et al. **Year: 2006**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **Disease severity:** NR (mean disease duration 13.4 years)	
	ETA	**INF**
Mean age (years):	55.1	56.2
Sex (% female):	82	75
Ethnicity:	NR	NR
Other germane population qualities:		
• Mean disease duration (years)	14.7	12.7
• DMARD use (No.)	4.2	3.6
• MTX use (%)	31	73
• DAS28 score	5.9	5.6
• HAQ score	1.6	1.4
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** LUNDEX = (fraction of starters still in the study at time T) x (fraction responding at time T) **Secondary Outcome Measures:** HAQ; VAS for pain and general health; physician's global assessment of disease activity (Evalglobal); 28-joint TJC & SJCs; ESR; CRP; ACR20; ACR50; ACR70; EULAR. **Timing of assessments:** 0,3,6, & 12 months, then every 3-6 months	

RESULTS:	**Health Outcome Measures:**
	• ETA had the highest overall LUNDEX values; ~55% of these patients fulfilled ACR20 response criteria at 12 months (~40% after 3 years).
	• ~45% of patients started on INF fulfilled ACR20 response criteria at 12 months (~30% at 3 years)
	• ACR 20: % response at 36 months = 63 (ETA) vs. 61 (INF) (P = NS)
	  • % response at 24 months = 65 (ETA) vs. 56 (INF) (P = NS)
	  • % response at 12 months = 69 (ETA) vs. 53 (INF) (P = 0.001)
	  • % response at 6 months = 61 (ETA) vs. 47 (INF) (P = NS)
	  • % response at 36 months = 63 (ETA) vs. 45 (INF) (P < 0.001)
	• 36 months- ACR50: 39 (ETA) vs. 39 (INF) (P = NS),ACR 70: 16 (ETA) vs. 18 (INF) (P = NS)
	• EULAR (moderate): % response at 36 months = 46 (ETA) vs. 29 (INF) (P = NS)
	• EULAR (good): % response at 36 months = 36 (ETA) vs. 45 (INF) (P = NS)
	Intermediate Outcome Measures:
	• INF had significantly lower adherence compared to ETA (P < 0.001); study cites this as possible reason for lower response rates for INF	

Authors: Kristensen et al. **Year: 2006**		
ADVERSE EVENTS: **Overall adverse effects reported:**	**ETA** NR	**INF** NR
Significant differences in adverse events:	NR	
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A	
ARE GROUPS COMPARABLE AT BASELINE:	No	
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	NR	
STATISTICAL ANALYIS ADEQUATE:	Yes	
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR	
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ETA** NR	**INF** NR
QUALITY RATING:	**Fair**	

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Lebwohl et al**.[164] **Year: 2005** **Country:** US
FUNDING:	Amgen Inc., Thousand Oaks, CA and its subsidiaries. Most of the authors were employees of Amgen during the conduct of the study.
RESEARCH OBJECTIVE:	To determine the incidence of cutaneous squamous cell carcinoma (SCC) in patients with RA receiving etanercept for up to 5 years.
DESIGN:	**Study design:** Retrospective observational study with historical controls **Setting:** Clinical trial participants receiving ETA from private and institutional practices **Sample size:** 1442 (4257 patient-years)
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** NR Mean 3.7 years 1442 (4257 pt-yrs)
INCLUSION CRITERIA:	Participant in one of various studies* of ETA in patients with RA; patients had active RA; and, received 10 to 50 mg ETA subcutaneously twice weekly for the majority of the time they received the study drug. Specific inclusion criteria varied by the included study. *783 from study with suboptimal response to at least 1 DMARD (8 studies); 557 patients diagnosed with RA within past 3 years, but had never received MTX; 102 patients were in a pharmacokinetic study of phase 3 study evaluating 2 different dosages of ETA in adult patients with RA.
EXCLUSION CRITERIA:	None.
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Varied by individual study.

<table>
<tr><td colspan="2">Authors: Lebwohl et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:

Mean age (years):
Sex (% female):
Ethnicity (% white):
Other germane population qualities:
• Duration of disease, mean yrs
• Prior # DMARDs used
• Duration ETA exposure
o Mean
o Maximum</td><td>Groups similar at baseline: N/A
Disease severity: NR (probably at least moderate disease)

<u>ETA</u>
49.9
76.5
87.4

7.1
2.1

3.7
5.7</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td>Primary Outcome Measures:
Incidence of SCC for patients receiving ETA for up to 5 years</td></tr>
<tr><td>RESULTS:</td><td>Health Outcome Measures:
• Total # of cases of SCC reported from post-marketing database population: 4 cases
• Age and sex-matched expected incident cases based on
o From Arizona general population-based incidence study: 13.1 cases
o From Minnesota general population-based incidence study: 5.9 cases
• Number of cases of SCC per patient-year of exposure to ETA
o In the clinical trial population: 0.9/1000 patient-years
o From post-marketing surveillance data: .01/1000 patient-years

• Summary Statement: The incidence of SCC among patients taking ETA is likely no different from that of the general population.</td></tr>
</table>

Authors: Lebwohl et al. **Year: 2005**	
ADVERSE EVENTS: **Overall adverse effects reported:**	**N/A**
Significant differences in adverse events:	N/A
ANALYSIS:	**N/A**
ADEQUATE RANDOMIZATION:	N/A
ADEQUATE ALLOCATION CONCEALMENT:	N/A
BLINDING OF OUTCOME ASSESSORS:	N/A
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors:** Leonardi, et al.[114] **Year:** 2011 **Study name:** Randomized Controlled Evaluation of Adalimumab in Treatment of Chronic Plaque Psoriasis of the Hands and Feet (REACH) **Country:** US and Canada **Quality rating:** Fair	
FUNDING:	Abbott Laboratories (pharmaceutical industry)	
RESEARCH OBJECTIVE:		
DESIGN & SIZE:	**Study design:** placebo-controlled RCT **Setting:** multicenter **Number screened:** NR **Number eligible:** NR **Number enrolled:** 81 **Run-in/Wash-out period:** Washout periods of 30 days or 5 half-lives (whichever was longer) were required for biological, systemic, and investigational agents prior to baseline.	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Adalimumab (ADA)** 40mg every other week 16 weeks 49	**Placebo** NA 16 weeks 23
INCLUSION CRITERIA:	Adults 18 years and older diagnosed as having moderate to severe chronic plaque psoriasis of the hands and/or feet for at least 6 months with a Physician's Global Assessment of the hands and/or feet (hfPGA) score of 3 or higher at baseline and with evidence of psoriatic disease on at least 1 other area of skin outside the hands and/or feet.	
EXCLUSION CRITERIA:	Receipt of prior treatment with adalimumab, diagnosis of palmoplantar pustulosis	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Psoralen and UV-A phototherapy was not allowed within 4 weeks of baseline; topical therapies on the hands and/or feet (except low- to mid-potency corticosteroids [classes VI and VII]), UV-B phototherapy, and excessive sun exposure or tanning bed use were not allowed within 2 weeks of baseline.	

Authors: Leonardi, et al. **Year:** 2011		
POPULATION CHARACTERISTICS:	**ADA**	**Placebo**
Mean age (years):	49.0	54.8
Sex (% female):	57%	65%
Ethnicity:	92% white	87% white
Class naïve:	NR	NR
Other germane population qualities:		
• **Mean PASI**	8.8	5.7
• **Mean body surface area involvement**	8.9%	5.1%
• **Mean duration of psoriasis**	14.9 years	11.5 years
• **Received prior systemic therapy (%)**	NR	NR
RESULTS:	**Primary Outcome Measure:** 31% of ADA patients achieved hfPGA score of clear (0) or almost clear (1) compared with 4% of placebo (p=0.01). **Secondary Outcome Measures:** 51% of ADA patients achieved hfPGA score of clear (0), almost clear (1), or mild (2) compared with 26% of placebo (p=NR). 29% of ADA patients achieved >75% improvement in ESIF (ESIF 75) relative to baseline compared with 4% of placebo (p=0.03). 43% of ADA patients achieved >50% improvement in ESIF (ESIF 50) relative to baseline compared with 17% of placebo (p=0.04). Mean % improvement in total ESIF score relative to baseline was 41% for ADA patients, compared with 21% for placebo (p=NR). In patients with palmar involvement, mean % improvement in total ESIF score relative to baseline was 47% for ADA patients, compared with 20% for placebo (p=0.01). In patients with plantar involvement, mean % improvement in total ESIF score relative to baseline was 41% for ADA patients, compared with 35% for placebo (p=0.67). In patients with psoriatic nail disease, mean % improvement in total NAPSI relative to baselime was 50% for ADA patients, compared with 8% for placebo (p=0.02) Mean pain score was 26.6 for ADA patients, compared with 43.4 for placebo (p=0.048). In patients with pain score >0 at baseline, mean % improvement in pain score was 31% for ADA patients, compared with 9% for placebo (p=0.39).	

Authors: Leonardi, et al. **Year:** 2011		
METHOD OF ADVERSE EVENTS REPORTING:	Laboratory data, physical examinations, and vital signs (and, presumably, patient self-report).	
ADVERSE EVENTS (%):	**ADA**	**Placebo**
Overall adverse effects reported:	63% reported any AE 0% reported a serious AE 35% reported an infectious AE Opportunistic only: 2% (oral candidiasis)	70% reported any AE 4% reported a serious AE 44% reported an infectious AE Opportunistic only: 0%
• infections		
• URTI	NR	NR
• abnormal LFT	NR	NR
• herpes simplex	NR	NR
• pneumonia	NR	NR
• tb	NR	NR
• ISR	NR	NR
• malignant diseases	0%	4% (N=1, breast cancer)
• serious hepatic events	2%	0%
• psoriasis	4%	9%
ATTRITION (*overall*):	**Overall attrition:** 19.7% **Attrition differential high:** ? (10%)	
ATTRITION (*treatment specific*):	**ADA**	**Placebo**
Attrition overall:	16%	26%
Attrition due to adverse events:	6%	9%

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Lichtenstein et al.**[165] **Year: 2006** **Country:** Multinational	
FUNDING:	NR; at least one author affiliated with Centocor (makers of INF)	
RESEARCH OBJECTIVE:	To examine safety of CD therapies, including infliximab	
DESIGN:	**Study design:** Observational (prospective registry) **Setting:** Multicenter **Sample size:** 6,290 patients (212 centers)	
INTERVENTION: N/A **Dose:** **Duration:** **Sample size:**	**INF** NR Mean 1.9 years 3,179	**Other treatments** NR Mean 1.9 years 3,111
INCLUSION CRITERIA:	Diagnosis of CD; no participation in any clinical trials; Age ≥ 18 (although not a criterion when enrollment began).	
EXCLUSION CRITERIA:	NR	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

<table>
<tr><td colspan="3">Authors: Lichtenstein et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: Yes, but trends towards INF group being sicker
Disease severity: Mild-to-moderate</td></tr>
<tr><td></td><td><u>INF</u></td><td><u>Other</u></td></tr>
<tr><td>Mean age (years):</td><td>40.3</td><td>44.7</td></tr>
<tr><td>Sex (% female):</td><td>57.9</td><td>57.1</td></tr>
<tr><td>Ethnicity (% white):</td><td>88.8</td><td>89.3</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td></tr>
<tr><td>• Surgical admissions (No.)</td><td>17.5</td><td>13.8</td></tr>
<tr><td>• Medical admissions (No.)</td><td>14.4</td><td>9.1</td></tr>
<tr><td>• Disease severity mild-to-moderate (%)</td><td>50.1</td><td>47.9</td></tr>
<tr><td>• Prednisone use (%)</td><td>27.4</td><td>16.1</td></tr>
<tr><td>• Immunomodulator use (%)</td><td>49.4</td><td>32.2</td></tr>
<tr><td>• Narcotic analgesics use (%)</td><td>9.8</td><td>5.4</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: Rate of death; rate of serious infection

Secondary Outcome Measures: NR

Timing of assessments: Enrollment, then semiannually</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
• Mortality rates = 0.53 per 100 patient-years in INF group vs. 0.43 per 100 patient-years in other treatments group (RR 1.24; [95% CI, 0.729 – 2.102]; P = 0.43).
• In adjusted model, only age (OR, 1.07; P < 0.001), duration of CD (OR 1.03; P = 0.006), and use of prednisone (OR 2.10; P = 0.016) were independent predictors of death.
• Use of INF was not a significant predictor of mortality.
• Although significant in unadjusted model, INFs effect on risk for serious infection in adjusted model was not significant (OR, 0.99; P = 0.97).
• In adjusted model race (OR, 0.54 for white vs. non-white, P = 0.030), CD duration (OR, 1.02; P = 0.011), moderate-to-severe CD (OR 2.11 vs. remission; P = 0.02), and use of prednisone (OR 2.21; P < 0.001), and use of narcotic analgesia (OR, 2.38; P < 0.001) were independent predictors of serious infection.</td></tr>
</table>

Authors: Lichtenstein et al. **Year: 2006**	
ADVERSE EVENTS (%): **Overall adverse events reported:** • Death, N • Serious infection, N	**Total cohort** NR 55 106
Significant differences in adverse events:	See Health Outcomes
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ADEQUATE RANDOMIZATION:	N/A
ADEQUATE ALLOCATION CONCEALMENT:	N/A
BLINDING OF OUTCOME ASSESSORS:	N/A
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	NR
QUALITY RATING:	**Fair**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Listing et al.**[166] **Year: 2005** **Country:** Germany			
FUNDING:	Joint grant from Essex, Wyeth, Amgen, and Abbott			
RESEARCH OBJECTIVE:	To estimate the incidence rates of serious and non-serious infections in patients with RA who start treatment with a biologic agent, and to compare these rates with those in patients with RA who receive conventional treatment.			
DESIGN:	**Study design:** Prospective cohort study **Setting:** Population-based **Sample size:** 1,529			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 512	**INF** 346	**AKA** 70	**DMARDs (control)** 601
INCLUSION CRITERIA:	Age 18-75, enrolled up to 9/1/2003;Cases: patients who met the ACR criteria for RA diagnosis and had new treatment with ETA, INF, or AKA; Controls: patients started on DMARD therapy after failure of ≥ 1 other DMARD, or with additional DMARD added to existing DMARD.			
EXCLUSION CRITERIA:	NR			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR			

Authors: Listing et al. **Year: 2005**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **Disease severity:** NR			
	ETA	**INF**	**AKA**	**DMARDs (control)**
Mean age (years):	53.7	53.6	54.3	56.5
Sex (% female):	78.1	70.8	77.1	82.7
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• TJC	13.3	12.7	12.6	10.0
• SJC	10.5	10.8	10.2	7.7
• Median disease duration (yrs)	9	8	13	6
• DMARD use (%)	51.6	89.6	71.4	0
• MTX use (%)	33	64.5	61.4	20.1
• Glucocorticoids, any dose (%)	87.4	85.2	87.0	77.2
• DAS28 score	6.1	6.0	6.1	5.4
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Adverse events; DAS28; ESR; CRP; morning stiffness; and numerical rating scale for pain, general health, or fatigue. **Secondary Outcome Measures:** **Timing of assessments:** Baseline, 3,6, & 12 months			
RESULTS:	**Health Outcome Measures:** • See adverse events table			

Authors: Listing et al. **Year: 2005**			
ADVERSE EVENTS per 100 patient-years:	**ETA**	**INF**	**Control**
Overall adverse effects reported:	22.6	28.3	6.8
• Total serious adverse events	6.4	6.2	2.3
• Respiratory tract infections*	7.0	11.4	1.8
• Flu-like illness+	2.7	4.0	0.7
• Skin infections^	6.0	7.7	2.6
• Bone & joint infection	1.03	0.61	0.18
• Urogenital tract infection$	2.69	1.54	0.70
• Sepsis/urosepsis	0.62	0	0.35
Significant differences in adverse events:	Total # of adverse events per 100 patient-years was 22.6 (95% CI 18.7-27.2) for ETA patients, 28.3 (95% CI 23.1-34.7) for INF patients, 6.8 (95% CI 5.0-9.4) for controls ($P < 0.0001$). Higher risk of infections for AKA, ETA, INF compared with DMARDS. Also a significant difference in serious adverse events ($P = 0.0016$); *$P < 0.0001$; +$P = 0.0038$; ^$P = 0.0017$; $$P = 0.036$		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	Yes		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	NR		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 11.1% **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	NR		
QUALITY RATING:	**Fair**		

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Listing**[167] **Year: 2008** **Country:** Germany		
FUNDING:	Unconditional, joint grants from Essex and Wyeth since 2001, from Essex, Wyeth, and Amgen since January 2003, and from Essex, Wyeth, Amgen, and Abbott since September 2003.		
RESEARCH OBJECTIVE:	The hazard risk of developing or worsening heart failure in rheumatoid arthritis (RA) patients treated with tumor necrosis factor inhibitors.		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** German biologics register **Sample size:**		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Anti-TNF** NR 5 years 2757	**Control** NR 5 years 1491	**drug 3**
INCLUSION CRITERIA:	Treated with ADA, ETA, INF, or conventional DMARDs		
EXCLUSION CRITERIA:	Treated with AKA		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Listing **Year: 2008**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe	
	Anti-TNF	**Control**
Mean age (years):	53.7	56.1
Sex (% female):	78.1	78.9
Ethnicity:	NR	NR
Other germane population qualities:		
• Tender joint count	NR	NR
• Swollen joint count	9.3	6.8
• Mean disease duration	9 yrs	6yrs
• # DMARD use	3.6	1.9
• MTX use (%)	NR	NR
• Corticosteroids use	2302	1132
• DAS score	5.8	5.1
• HAQ score	NR	NR
• Comorbidity – Heart failure/CHD/CVD/DM/ Chronic lung disease	2.7/5.4/37.3/8.2/7.3	1.5/7.0/38.2/8.6/6.4
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** all adverse events reported as heart failure, acute heart failure, congestive heart failure, or ventricular failure between May 1, 2001 and December 1, 2006 **Timing of assessments:** Baseline and at 3-, 6-, 12-, 18-, 24-, 30-, 36-, 48-, and 60-month follow-up	
RESULTS:	**Health Outcome Measures:** • Risk related to treatment with anti-TNF adjusted HR 1.66 [95% confidence interval 0.67–4.1], *P* = 0.28). • Adjusted HR for heart failure Anti-TNF vs. conventionals 1.85 95% CI 0.88-3.90 *P* = 0.11 • Adjusted HR for heart failure de novo Anti-TNF vs. conventionals 2.19 95% CI 0.90-5.33 *P* = 0.083 • Adjusted HR for heart failure in 98 patients prevalent heart failure Anti-TNF vs. conventionals 1.18 95% CI 0.30-4.733.90 *P* = 0.81	

Authors: Listing **Year: 2008**	
ADVERSE EVENTS: **Overall adverse effects reported:**	**Anti-TNF** see results
Significant differences in adverse events:	No
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	No
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** Annual 5.1% **Attrition differential high:** NR
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**All** at 48 months 15.5% 2.4% died
QUALITY RATING:	**Good**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Lovell et al.**[60-62] **Year: 2000, 2003, and 2006** **Country:** US		
FUNDING:	Immunex Corporation, Children's Hospital Foundation of Cincinnati, NIH		
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of etanercept in children with PJRA		
DESIGN:	**Study design:** RCT and open label extension **Setting:** Academic medical centers (children's hospitals) **Sample size:** 51 and 58		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 4 months 26	**ETA** 0.4 mg/kg body weight/2x weekly 4 months 25	**Extension** 0.4 mg/kg body weight/2x weekly up to 2 years/4 years 58/34
INCLUSION CRITERIA:	Ages 4-17 with active PJRA; active disease despite treatments with NSAIDs and MTX at doses of at least 10 mg/sq meter of body surface area per week; normal or nearly normal platelet, white cell, and neutrophil counts, hepatic aminotransferase levels, and results of renal function tests		
EXCLUSION CRITERIA:	Pregnant and lactating patients were excluded along with patients with major concurrent medical conditions		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs, low doses of corticosteroids (≤.2 mg of prednisone /kg/day with a max of 10 mg/day) or bother were permitted		

Authors: Lovell et al.
Year: 2000, 2003, 2006

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease characteristic: Polyarticular (mean disease duration 5.8 years)

	Placebo	ETA	Extension 2 years	Extension 4 years
Mean age (years):	12.2	8.9	10	10.6
Sex (% female):	58	76	67	81
Ethnicity: white (%)	88	56	74	84
Other germane population qualities:				
• Disease duration mean (years)	6.4	5.3	5.9	5.9
• TJC	NR	NR	NR	NR
• SJC	NR	NR	NR	NR
• DMARD use (%)	73	64	74	100
• MTX use (%)	69	64	72	100
• Corticosteroids use (%)	50	24	38	41
• DAS score	NR	NR	NR	NR
• HAQ score	NR	NR	NR	NR

OUTCOME ASSESSMENT:

Primary Outcome Measures: Number of patients with disease flare (disease flare is based on worsening of 30% of more in 3 or 6 response variables and a minimum of 2 active joints)
Secondary Outcome Measures: Articular severity score, duration of morning stiffness, degree of pain, and CRP
Timing of assessments: day 1, day 15, and at the end of each month

RESULTS:

Health Outcome Measures:

- Significantly more in placebo group (81%) than patients in ETA group (28%) had disease flare ($P = 0.003$)
- Rates of flare were constant and significantly lower in ETA group ($P < 0.001$) after adjustment for baseline effects
- At study endpoint , 72% of ETA group and 23% of placebo group met definition of 50% improvement (P = NR)
- Over 4 years the rate of serious adverse events 0.13 per patient year; the rate of serious infections 0.04 per patient-year.

Authors: Lovell et al. **Year: 2000; 2003; 2006**				
ADVERSE EVENTS:	**Open label**	**Double-blind portion**	**Extension 2 years**	**Extension 4 years**
Overall adverse effects reported:	NR	NR	NR	NR
▪ **Serious adverse events requiring hospitalization**	3%	NR	16% NR	NR NR
• ISR	39%	4%	NR	NR
• URTI	35%	NR	NR	NR
• Headache	20%	NR	NR	NR
• Abdominal pain	16%	NR	NR	NR
• Vomiting	14%	NR	NR	NR
• Rash	10%	NR	NR	NR
• Varicella-Zoster virus	NR	NR	5% requiring hospitalization	NR

Significant differences in adverse events:	Unable to determine- NR				
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No				
ADEQUATE RANDOMIZATION:	Yes				
ADEQUATE ALLOCATION CONCEALMENT:	NR				
BLINDING OF OUTCOME ASSESSORS:	NR				
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** Yes				
ATTRITION (*treatment specific*):	**Open label**	**ETA**	**Placebo**	**Extension 2 years**	**Extension 4 years**
Loss to follow-up:	5	6 (24%)	19 (63%)	10 (17%)	24 (42%)
Withdrawals due to adverse events:	1	6- Disease flare	18-Disease flare	2-Adverse events 7-lack of efficacy	4-Adverse events 6-lack of efficacy
QUALITY RATING:	**Fair**				

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Lovell et al.**[63] **Year: 2008** **Country:** Multinational					
FUNDING:	Abbott Labs					
RESEARCH OBJECTIVE:	Efficacy and safety of ADA, in children with polyarticular-course juvenile rheumatoid arthritis					
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 171					
INTERVENTION:	**Open MTX**	**Open No**	**MTX Pla**	**MTX ADA**	**No Pla**	**No ADA**
Dose:	24 mg/m eow	24 mg/m eow	N/A	24 mg/m eow	N/A	24 mg/m eow
Duration:	16 wks	16 wks	32 wks	32 wks	32 wks	32 wks
Sample size:	85	86	37	38	28	30
INCLUSION CRITERIA:	4 to 17 years of age with polyarticular-course juvenile rheumatoid arthritis who had active disease (at least five swollen joints and at least three joints with limitation of motion) that had not responded adequately to treatment with NSAIDs					
EXCLUSION CRITERIA:	Clinically significant deviations in hematologic, hepatic, or renal indicators; ongoing infection or had recently had a major infection requiring hospitalization or intravenous antibiotics; recent live or attenuated vaccines; previously treated with other biologic agents at any time or recently treated with intravenous immune globulin, cytotoxic agents, investigational agents, DMARDs other than MTX, or corticosteroids administered by the intraarticular, intramuscular, or intravenous route.					
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable dosages of NSAIDs and low-dose corticosteroids, pain medications were also allowed except for the 12 hours preceding an assessment of the joints.					

Authors: Lovell et al.
Year: 2008

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: Moderate-severe

	Open MTX	Open No	MTX Pla	MTX ADA	No Pla	No ADA
Mean age (years):	11.4	11.1	10.8	11.7	11.3	11.1
Sex (% female):	80	78	81	79	71	77
Ethnicity (% Caucasian):	95	88	97	95	96	87
Other germane population qualities:						
• Mean disease duration	4.0	3.6	4.0	4.3	2.9	3.6
• DMARD use (%)	9	9	19	3	11	13
• MTX use (%)	100	21	100	100	14	27
• Corticosteroids use (%)	5	2	5	5	4	0

OUTCOME ASSESSMENT:

Primary Outcome Measures: percentage of patients not receiving MTX who had a disease flare during the double-blind phase of the study (weeks 16 to 48).

Secondary Outcome Measures: ACR Pedi 30, 50, 70, 90, 100

Timing of assessments: screening, at baseline (day 1), between days 2 and 10, at weeks 2 and 4, and every 4 weeks through week 48 or withdrawal from the study.

RESULTS:

Health Outcome Measures:

- Open label portion
- ACR Pedi at week 16 ADA ACR PEDI 30 74% ACR PEDI 50 64% ACR Pedi 70 46% ACR Pedi 90 26%
- ACR Pedi at week 16 ADA+MTX ACR PEDI 30 94% ACR PEDI 50 91%ACR Pedi 70 71% ACR Pedi 90 28%
- 48 weeks (Double blinded portion)
- No MTX disease flares ADA 13 of 30 [43%] vs. placebo 20 of 28 [71%], *P*=0.03
- MTX disease flares, ADA 14 of 38 (37%) vs. placebo 24 of 37 (65%) (*P*=0.02)

Authors: Lovell et al. **Year: 2008**						
ADVERSE EVENTS per pt yr of exposure:	**Open MTX**	**Open No**	**MTX Pla**	**MTX ADA**	**No Pla**	**No ADA**
Overall adverse effects reported:	15.5	15.3	10.3	12.8	14.4	11.9
• ISR	5.2	5.7	3.8	4.0	1.9	4.9
• Contusion	0.5	0.2	0.5	0.7	0.5	0.1
• Nasopharyngitis	0.2	0.1	0.4	0.3	0.5	0
• URTI	0.3	0.4	0.3	0.3	0.6	0.4
• Viral infection	0.3	0.3	0.2	0.4	0.4	0.6
• Vomiting	0.2	0.1	0.1	0.2	0.1	0
• Excoriation	0.2	0.2	0.1	0.6	0.2	0.4
Significant differences in adverse events:	NR					
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR					
ADEQUATE RANDOMIZATION:	NR					
ADEQUATE ALLOCATION CONCEALMENT:	NR					
BLINDING OF OUTCOME ASSESSORS:	Yes					
ATTRITION (*overall*):	**Overall attrition:** 25% overall 6% open label **Attrition differential high:**					
ATTRITION (*treatment specific*):	**Open MTX**	**Open No**	**MTX Pla**	**MTX ADA**	**No Pla**	**No ADA**
Attrition overall:	2%	10%	3%	8%	0	3%
Attrition due to adverse events:	1%	2%	0	0	0	0
QUALITY RATING:	**Fair**					

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Marchesoni et al.**[168] **Year: 2009** **Study name: LORHEN Registry** **Country: Italy** **Quality rating: Fair**		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To evaluate survival on the three commercially available anti-TNF-α agents (infliximab, etanercept, adalimumab) in a cohort of patients recorded in the Lombardy Rheumatology Network (LORHEN) registry.		
DESIGN & SIZE:	**Study design:** Cohort **Setting:** Multicenter (4 tertiary Rheumatologic Centres in Lombardy) **Sample size:** 1064		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Etanercept** NR Mean 21.48 months 242	**Adalimumab** NR Mean 20.84 months 303	**Infliximab** NR Mean 25.62 months 519
INCLUSION CRITERIA:	All patients with RA diagnosed on the basis of the 1987 ACR criteria, DAS28 >3.5, and treated with at least one dose of an anti-TNF agent at one of four Rheumatology Centres in Italy (and therefore entered into the LORHEN registry), with at least 6 months of follow-up (including discontinuations within first 6 months).		
EXCLUSION CRITERIA:	Active infection, a history of malignancy, pre-malignant conditions, class III/IV congestive heart failure, and demyelinating disorders.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Methotrexate and corticosteroids; otherwise NR.		

Authors: Marchesoni et al. **Year: 2009**	
POPULATION CHARACTERISTICS:	**Population**
Mean age (years): **Sex (% female):** **Ethnicity:** **Class naïve:** Other germane population qualities: • **Tender joint count** • **Swollen joint count** • **Mean disease duration** • **DMARD use (%)** • **MTX use (%)** • **Corticosteroids use (%)** • **DAS score** • **HAQ score**	55.84 83.2% NR NR NR NR 9.44 NR 84.5% 84.2% 5.90 1.46
RESULTS:	**Primary Outcome Measures:** <u>Etanercept vs Adalimumab vs Infliximab</u> Risk of Anti-TNF Discontinuation Due to Adverse Events, Adjusted HR (95% CI): Ref vs 2.09 (1.29-3.38), P=0.003 vs 1.49 (0.93-2.40), P=0.101

Authors: Marchesoni et al. **Year: 2010**			
METHOD OF ADVERSE EVENTS REPORTING:	NR		
ADVERSE EVENTS (%):	**Etanercept**	**Adalimumab**	**Infliximab**
Overall adverse effects reported: • infections • URTI • abnormal LFT • herpes simplex • pneumonia • tb • ISR	NR (only listed AEs that led to discontinuation)	NR (only listed AEs that led to discontinuation)	NR (only listed AEs that led to discontinuation)
ATTRITION (*overall*):	**Overall attrition:** 405 (38.1%) **Attrition differential high:**		
ATTRITION (*treatment specific*):	**Etanercept**	**Adalimumab**	**Infliximab**
Attrition overall:	68 (28.1%)	111 (36.6%)	226 (43.5%)
Attrition due to adverse events:	28 (11.6%)	60 (19.8%)	106 (20.4%)

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: McDonald et al.**[169] **Year: 2010** **Study name: NR** **Country:** USA **Quality rating: Fair**		
FUNDING:	Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service project number IAF 06–026, and NIH K12RR023249 and KL2RR024994.		
RESEARCH OBJECTIVE:	HZ risk, risk factors, treatments and outcomes in a large national cohort of veterans with rheumatoid arthritis (RA), with a particular focus on the contribution of different classes of immunosuppressive medications to the risk of HZ. Group 1 (treatment of mild disease) included hydroxycholoroquine, sulfasalazine, auranofin, injectable gold, and penicillamine. Group 2 (treatment of moderate disease) included methotrexate, leflunomide, azathioprine, cyclophosphamide, cyclosporine, and anakinra. Group 3 (treatment of severe disease) included the tumor necrosis factor-alpha (TNF) antagonists (etanercept, infliximab, and adalimumab),		
DESIGN & SIZE:	**Study design:** Retrospective cohort study **Setting:** Veterans Affairs Healthcare System **Number screened: 20816** **Number eligible: 20357** **Number enrolled:** 20,357 **Run-in/Wash-out period: NA**		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Group 1** NR NR 9673	**Group 2** NR NR 12888	**Group 3** NR NR 3661
INCLUSION CRITERIA:	All veterans who had an ICD-9-CM code diagnosis of RA during the study period and who, after at least a 4-month history of receiving medications from the VA during the study period, subsequently received a first prescription for a disease-modifying anti-rheumatic drug (DMARD).		
EXCLUSION CRITERIA:	Diagnosis of HZ at any time prior to receiving a DMARD, or did not have at least two separate outpatient or inpatient clinical encounters during the study period.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

Authors: McDonald et al. **Year: 2010**		
POPULATION CHARACTERISTICS: ***of patients receiving TNF-a Antagonists***	**HZ** N = 96	**No HZ** N=3565
Mean age (years):	58.5	57.8
Sex (% female):	10.4	8.9
Ethnicity:	NR	NR
Class naïve:		
Other germane population qualities:		
• **DMARD use (%)**		
• **MTX use (%)**	54.2	51.0
• **Corticosteroids use (%)**	62.5	54.7
RESULTS:	**Primary Outcome Measures:** Incidence of HZ was significantly higher in medication group 2 compared to medication group 1 (11.18 per 1000 patient-years vs. 8.00 per 1000 patient-years, P < 0.0001), and in medication group 3 compared to medication group 1 (10.60 per 1000 patientyears vs. 8.00 per 1000 patient-years; *P* < 0.0001 **Secondary Outcome Measures:** Risk Factors for Herpes Zoster (HZ) Among Patients Receiving Tumor Necrosis Factor-Alpha Antagonists (Medication Group 3) Etanercept HZ 64.6 (11, 5–29) No HZ 69.0 (16, 6–33) HR (95% CI) **0.62 (0.40–0.95)** Infliximab HZ 33.3 (8, 3–27) No HZ 21.7 (14, 5–30) HR (95% CI) 1.32 (0.85–2.03) Adalimumab HZ 16.7 (5, 4–10) No HZ 32.8 (9, 4–18) HR (95% CI) **0.53 (0.31–0.91)**	

Authors: McDonald et al. **Year: 2010**	
METHOD OF ADVERSE EVENTS REPORTING:	See Primary and secondary results above
ADVERSE EVENTS (%):	NA
Overall adverse effects reported:	NA
ATTRITION (*overall*):	**Overall attrition:** NA **Attrition differential high:** NA
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	NA

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors:** Mease, et al.[81] **Year:** 2011 **Study name:** N/A **Country:** Multinational **Quality rating:** Fair			
FUNDING:	Bristol-Myers Squibb (pharmaceutical)			
RESEARCH OBJECTIVE:	To assess the safety and efficacy of abatacept, a selective T cell costimulation modulator, in patients with psoriatic arthritis (PsA)			
DESIGN & SIZE:	**Study design:** RCT, double-blind, placebo-controlled **Setting:** Multicenter **Number screened:** NR **Number eligible:** NR **Number enrolled:** 170 **Run-in/Wash-out period:** Patients with intolerance of, or an inadequate response to, infliximab, adalimumab, or etanercept discontinued these anti-TNF therapies at screening, and following a washout period of ≥28 days, these patients were assessed for arthritis and psoriasis before randomization.			
INTERVENTION:	**Drug 1**	**Drug 2**	**Drug 3**	**Drug 4**
Dose:	Abatacept 30/10 mg/kg	Abatacept 10 mg/kg	Abatacept 3 mg/kg	Placebo
Duration:	30 mg/kg given on Days 1, 15, followed by 10 mg/kg on day 29, and every 28 days there after	Days 1, 15, 29, and every 28 days there after	Days 1, 15, 29, and every 28 days there after	Days 1, 15, 29, and every 28 days there after
Sample size:	45	40	43	42
INCLUSION CRITERIA:	Adult patients who met the criteria of the Classification of Psoriatic Arthritis (CASPAR) Study Group and had active arthritis (defined as the presence of ≥3 swollen joints and ≥3 tender joints), active plaque psoriasis (with at least 1 qualifying target lesion [TL] ≥2 cm in diameter), and a disease duration of ≥3 months were eligible for enrollment in the study. Patients were required to have had an inadequate response to DMARDs, including, but not limited to, MTX or anti-TNF agents. Response to MTX was considered inadequate if it had been taken at a dosage of ≥15 mg/week for ≥2 months prior to randomization. Patients with intolerance of, or an inadequate response to, infliximab, adalimumab, or			

	etanercept discontinued these anti-TNF therapies at screening, and following a washout period of ≥28 days, these patients were assessed for arthritis and psoriasis before randomization.
EXCLUSION CRITERIA:	Key exclusion criteria: use of any investigational drug within 28 days before randomization, any prior treatment with abatacept, evidence of latent or active tuberculosis, or evidence of chronic or clinically significant infection or malignancy. Women who were pregnant or lactating were excluded.
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Aside from MTX, no DMARD was continued during the 6-month double-blind treatment period. MTX was continued at a stable dosage only if it had been taken at a stable dosage for ≥3 months prior to screening. A decrease in the MTX dosage was allowed in cases of toxicity. The dosage of nonsteroidal antiinflammatory drug (NSAID) remained unchanged throughout the study unless a decrease in dosage was required because of toxicity. Concomitant corticosteroid treatment was allowed if the dosage (no more than 10 mg of prednisone or its equivalent) had been stable for ≥28 days.

Authors: Mease, et al. **Year: 2011**				
POPULATION CHARACTERISTICS:	**Drug 1**	**Drug 2**	**Drug 3**	**Drug 4**
Mean age (years):	51.5	50.8	50.3	52.6
Sex (% female):	54	35	51	45
Ethnicity (% Caucasian):	100	95	98	98
Class naïve:	NR	NR	NR	NR
Other germane population qualities:				
• **Mean # of tender joints**	19.6	25.2	22.7	21.3
• **Mean # of swollen joints**	10.3	12.5	10.3	10.5
• **Mean # w/ psoriasis covering ≥3% of BSA**	20	21	21	21
• **Previous NSAID use (%)**	58	68	73	55
• **Concomitant MTX use (%)**	58	60	60	55
• **Concomitant Corticosteroids use (%)**	21	28	27	19
• **HAQ DI score (range 0-3)**	1.2	1.3	1.1	1.2
RESULTS:	**Primary Outcome Measures:** **ACR20 at day 169** Drug 1: 42% (P = 0.022); Drug 2: 48% (P = 0.006); Drug 3: 33% (P = 0.121); Drug 4: 19% **Secondary Outcome Measures:** **Investigator's Global Assessment of Psoriasis (% clear or almost clear)** Drug 1: 21%; Drug 2: 25%; Drug 3: 38%; Drug 4: 26% **Target lesion 50 response (TL50)** Drug 1:36%; Drug 2:33%; Drug 3:30%; Drug 4: 17% **HAQ DI (% patients achieving a minimum clinically meaningful improvement defined as ≥0.3 point decrease from baseline to day 169)** Drug 1: 35; Drug 2: 45; Drug 3: 36; Drug 4: 19			

	SF-36 (change from baseline) PCS score (mean) – Drug 1: 7.3; Drug 2: 9.3; Drug 3: 6.3; Drug 4: 0.2 MCS score (mean) – Drug 1: 4.5; Drug 2 (4.4; Drug 3: 3.2; Drug 4: 2.4 **ACR50 at day 169** Drug 2: 25% (results for other doses reported in graph) **ACR70 at day 169** Drug 2: 13% (results for other doses reported in graph) **PASI50 at day 169 (% (95% CI))** Drug 1: 35 (14 to 56); Drug 2: 29 (9 to 48); Drug 3: 43 (22 to 64); Drug 4: 14 (-1 to 29) **PASI70 at day 169 (% (95% CI))** Drug 1: 10 (-3 to 23); Drug 2: 14 (-1 to 29); Drug 3: 38 (17 to 59); Drug 4: 5 (-4 to 14)

Authors: Mease, et al. **Year: 2011**				
METHOD OF ADVERSE EVENTS REPORTING:	Laboratory tests, monitoring (not described)			
ADVERSE EVENTS (%):	**Drug 1**	**Drug 2**	**Drug 3**	**Drug 4**
Overall adverse effects reported:	29 (67%)	31 (78%)	31 (69%)	30 (70)
• Serious Adverse Events	4 (9%)	2 (5%)	0	1 (2%)
• Cholecystitis	1 (2%)	0	0	0
• Osteomyelitis	1 (2%)	0	0	0
• Gastroenteritis	0	1 (3%)	0	0
• Basal cell carcinoma	1 (2%)	0	0	0
• Dizziness	0	1 (3%)	0	0
• Personality disorder	0	0	0	1 (2%)
• Psychiatric decompensation	0	0	0	1 (2%)
• Overdose	1 (2%)	0	0	0
• Infusion reaction	2 (5%)	2 (5%)	0	0
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall attrition:** 147 (86%) completed the study **Attrition differential high:** No (highest differential was 17% between group 3 (96%) and group 4 (79%))			
	Drug 1	**Drug 2**	**Drug 3**	**Drug 4**
Attrition overall:	6 (14%)	6 (15%)	2 (4%)	9 (21%)
Attrition due to adverse events:	1 (2%)	2 (5%)	1 (2%)	3 (7%)

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Mohan et al.**[170] **Year: 2004** **Country:** Multinational		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To summarize all cases of TB following the use of etanercept, that were reported to the Adverse Event Reporting System (AERS) from November 1998 through March 2002.		
DESIGN:	**Study design:** Case series, Database analysis **Setting:** population-based **Sample size:** N/A		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** NR N/A 25 cases		
INCLUSION CRITERIA:	All patients receiving ETA and reported to have active TB		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A		

Authors: Mohan et al. **Year: 2004**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** N/A
	Patients with TB (n=25)
Mean age at diagnosis (years):	59
Sex (% female):	72
Ethnicity:	NR
Other germane population qualities:	NR
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** NR **Secondary Outcome Measures:** NR **Timing of assessments:** NR
RESULTS:	**Health Outcome Measures:** • As of April 2002, a total of 25 reports of TB associated with ETA therapy had been reported to the FDA from 11/1998 through 3/2002. • 17 cases (68%) were reported from the US, 7 (28%) from Europe, and 1 (4%) from India. • 46% of the 24 patients with a reported clinical manifestation had pulmonary TB . • 2 deaths occurred among the 25 patients. • 17 US cases of TB have been reported to the FDA. • According to ETA manufacturer, 113,238 patients have been treated with ETA in the US between 11/1998 and 5/2002, with an estimated 172,212 patient-years of exposure; thus the reporting rate of TB among patients in the US receiving ETA is ~10 cases / 100,000 patient-years of exposure. • The median interval between first dose and diagnosis of TB was 11.5 months

Authors: Mohan et al. **Year: 2004**	
ADVERSE EVENTS: **Overall adverse effects reported:**	N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	N/A
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	N/A
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	NR
QUALITY RATING:	**N/A**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Nuki et al**.[171] **Year: 2002** **Country:** Multinational (Europe)		
FUNDING:	Amgen, INC		
RESEARCH OBJECTIVE:	Long-term safety and maintenance in the treatment of RA with anakinra. Safety was evaluated for all 472 patients, long term efficacy for 309 that continued into extension.		
DESIGN:	**Study design:** RCT 24 weeks, then double-blind parallel extension of 52 weeks for a total of 76 weeks **Setting:** Multicenter **Sample size:** 472 in 24 week study (309 in 52 week extension)		
INTERVENTION: Extension phase **Dose:** **Duration:** **Sample size:**	**AKA** 30 mg 52 weeks 111	**AKA** 75 mg 52 weeks 103	**AKA** 150 mg 52 weeks 95
INCLUSION CRITERIA:	Patients that had completed the initial 24 week study		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Nuki et al. **Year: 2002**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline: Yes** **Disease severity:** Mild-moderate-severe	
	Placebo to AKA (76)	**AKA to AKA (233)**
Mean age (years):	53.1	52.7
Sex (% female):	69.7	76.8
Ethnicity:	NR	NR
Other germane population qualities:		
• TJC	32.7	33.7
• SJC	24.5	26.4
• Mean disease duration	3.7	4.1
• DMARD use (%)	73.7	71.7
• MTX use (%)	NR	NR
• Corticosteroids use (%)	40.8	47.6
• DAS score	N/A	N/A
• HAQ score	1.5	1.5
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20; radiographs; safety **Timing of assessments:** 24th week of extension for efficacy and 52nd week for safety analysis	
RESULTS:	**Health Outcome Measures:** • Overall AKA was well tolerated at all dose levels up to 76 weeks **Intermediate Outcome Measures:** • ACR 20 Placebo to AKA All doses Week 24 - 26 (34%) Week 48 - 39 (51%) ($P = 0.007$) AKA to AKA All doses Week 24 - 84 (36.1%) Week 48 - 97 (41.6%) ($P = 0.118$)	

Authors: Nuki et al. **Year: 2002**	**Extension phase – Weeks 24 to 76**		**Placebo phase – Weeks 0 to 24**	
ADVERSE EVENTS:	**Placebo to AKA (76)**	**AKA to AKA (233)**	**Placebo**	**AKA**
Overall adverse effects reported:	NR	NR	NR	NR
• Leukopenia	1 (1.3%)	4 (1.7%)	0	1 (0.3%)
• Infection	1 (1.3%)	4 (1.3%)	1 (0.8%)	4 (1.1%)
• Malignancy	1 (1.3%)	1 (0.4%)	0	2 (0.6%)
• Arthritis flare	4 (5.2%)	14 (6.0%)	17 (14%)	31 (8.8%)
• Granulocytopenia			0	17 (4.8%)
• Eosinophilia			0	17 (4.8%0
Significant differences in adverse events:	Hematologic changes under AKA therapy was the second most common reason for discontinuation in the extension phase (7.7%)			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No			
ADEQUATE RANDOMIZATION:	**Yes**			
ADEQUATE ALLOCATION CONCEALMENT:	N/A			
BLINDING OF OUTCOME ASSESSORS:	N/A			
ATTRITION (*overall*):	**Overall loss to follow-up:** 91 (29%) **Loss to follow-up differential high:** No			
ATTRITION (*treatment specific*):	**Placebo to AKA (76)**	**AKA to AKA (233)**		
Loss to follow-up:	21 (28%)	70(30%)		
Withdrawals due to adverse events:	14 (18%)	32 (14%)		
QUALITY RATING:	**N/A**			

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Pallavicini et al.**[172] **Year: 2010** **Study name: None** **Country: Italy** **Quality rating: Poor**		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To compare cancer risk in a RA cohort population treated with TNF antagonists, and identify the characteristics of the patients at higher risk.		
DESIGN & SIZE:	**Study design:** Observational **Setting:** Multicenter (4 tertiary Rheumatologic Centres) **Sample size:** 1064		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Etanercept** NR Mean 23.32 months 242	**Adalimumab** NR Mean 23.32 months 303	**Infliximab** NR Mean 23.32 months 519
INCLUSION CRITERIA:	All patients with RA diagnosed on the basis of the 1987 ACR criteria and treated with at least one dose of an anti-TNF agent at one of four Rheumatology Centres in Italy, and therefore entered into the Lombardy Rheumatology Network (LORHEN) registry.		
EXCLUSION CRITERIA:	NR.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Methotrexate, other DMARDs, and corticosteroids; otherwise NR.		

Authors: Pallavicini et al. **Year: 2010**	
POPULATION CHARACTERISTICS:	**Total population**
Mean age (years):	55.84
Sex (% female):	83.2%
Ethnicity:	NR
Class naïve:	NR
Other germane population qualities:	
• **Tender joint count**	11.35
• **Swollen joint count**	10.06
• **Mean disease duration**	NR (30.5% <5 years, 31.8% 5-10 years, and 37.8% <10 years)
• **DMARD use (%)**	NR
• **MTX use (%)**	84.5%
• **Corticosteroids use (%)**	84.2%
• **DAS score**	5.90
• **HAQ score**	1.46
RESULTS:	**Primary Outcome Measures:** **Cancer incidence rate:** Etanercept: 4 cases; 433.31 patient-years; IR 9.23; 95% CI, 0.18 to 18.28 Adalimumab: 8 cases; 527.22 patient-years; IR 15.17; 95% CI, 4.66 to 25.69 Infliximab: 6 cases; 1108.12 patient-years; IR 5.41; 95% CI, 1.08 to 9.75 **Secondary Outcome Measures:** **Risk of cancer – univariate and multivariate hazard ratios by baseline characteristics:** Age – Unit increase: P=0.016; HR 1.06 (95% CI, 1.01–1.10); P=0.009; Adjusted HR 1.07 (95% CI, 1.02–1.12) Gender – Male: P=0.001; HR 4.95 (95% CI, 1.97–12.48); P=0.000; Adjusted HR 5.95 (95% CI, 2.33–15.18) *Biological drugs:*

	Etanercept: HR 1 Adalimumab: P=0.407; HR 1.66 (95% CI, 0.50–5.52) Infliximab: P=0.412; HR 0.59 (95% CI, 0.17–2.09) *Disease duration:* <5 years: HR 1 5-10 years: P=0.196; HR 0.45 (95% CI, 0.14–1.51) >10 years: P=0.269; HR 0.55 (95% CI, 0.19–1.59) *Corticosteroids:* None: HR 1; Adjusted HR 1 0-5 mg: P=0.433; HR 2.28 (95% CI, 0.29–17.78); P=0.402; Adjusted HR 2.42 (95% CI, 0.31–18.99) >5 mg: P=0.078; HR 6.58 (95% CI, 0.81–53.46); P=0.078; Adjusted HR 6.68 (95% CI, 0.81–55.18) *Previous DMARDs:* 2: HR 1 3: P=0.898; HR 0.93 (95% CI, 0.29–2.92) ≥4: P=0.947; HR 1.04 (95% CI, 0.35–3.09) *Associated DMARDS:* None: HR 1; Adjusted HR 1 Methotrexate: P=0.026; HR 0.31 (95% CI, 0.11–0.87); P=0.043; Adjusted HR 0.34 (95% CI, 0.12–0.97) Tender joints – Unit increase: P=0.277; HR 0.96 (95% CI, 0.88–1.04) Swollen joints – Unit increase P=0.472; HR 1.03 (95% CI, 0.95–1.12) HAQ – Unit increase: P=0.716; HR 0.87 (95% CI, 0.40–1.88) ESR – Unit increase: P=0.318; HR 0.99 (95% CI, 0.96–1.01) DAS 28 – Unit increase: P=0.216; HR 0.74 (95% CI, 0.46–1.19) Average follow-up from the start of anti-TNF therapy to evidence of cancer was 13.04±8.52 months, and the average age at diagnosis was 64.29±9.38 years.

Authors: Pallavicini et al. **Year: 2010**			
METHOD OF ADVERSE EVENTS REPORTING:	NR; recorded every 6 months.		
ADVERSE EVENTS (%):	**Etanercept**	**Adalimumab**	**Infliximab**
Overall adverse effects reported:	NR	NR	NR
• infections	NR	NR	NR
• URTI	NR	NR	NR
• abnormal LFT	NR	NR	NR
• herpes simplex	NR	NR	NR
• pneumonia	NR	NR	NR
• tb	NR	NR	NR
• ISR	NR	NR	NR
ATTRITION (*overall*):	**Overall attrition:** NA **Attrition differential high:** NA		
ATTRITION (*treatment specific*):	**Etanercept**	**Adalimumab**	**Infliximab**
Attrition overall:	NA	NA	NA
Attrition due to adverse events:	NA	NA	NA

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Paller et al.[118] and Siegfried et al.[119] and Langley et al.[120]** **Year: 2008, 2010, 2011** **Country:** US and Canada **Quality rating:** Fair	
FUNDING:	Immunex, a wholly owned subsidiary of Amgen, and by Wyeth Pharmaceuticals.	
RESEARCH OBJECTIVE:	Assess the efficacy and safety of etanercept in children and adolescents with moderate-to-severe plaque psoriasis.	
DESIGN & SIZE:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 211; 138 in withdrawal-retreatment phase	
INTERVENTION: **Dose:** **Duration:** **Sample size:** *Withdrawal-retreatment period:* **Dose:** **Duration:** **Sample size:**	**Etanercept** 0.8 mg per kg 12 weeks 106 **Etanercept** Max 50 mg for weights ≥62 kg 12 weeks 69	**Placebo** NA 12 weeks 105 **Placebo** NA 12 weeks 69
INCLUSION CRITERIA:	4 to 17 years; stable, moderate-to-severe plaque psoriasis at screening, defined as a psoriasis area-and-severity index (PASI) score of at least 12), a static physician's global assessment of at least 3 (where 0 indicates clear and 5 severe psoriasis), and psoriasis involvement of at least 10% of the BSA; a history of psoriasis for at least 6 months; and previous or current treatment with phototherapy or systemic psoriasis therapy (e.g., methotrexate, cyclosporine, or retinoids) or psoriasis considered by the investigator as poorly controlled with topical therapy.	
EXCLUSION CRITERIA:	Pregnancy or lactation (sexually active patients were required to use contraception); guttate, erythrodermic, or pustular psoriasis; other skin conditions that would interfere with study evaluations; previous treatment with anti-TNF agents; major concurrent medical conditions; treatment with psoralen and ultraviolet A (PUVA), ultraviolet A, ultraviolet B, systemic psoriasis medications, oral or parenteral corticosteroids, topical corticosteroids, topical vitamin A or D analogue preparations, anthralin, or calcineurin inhibitor within a 14-day washout period before the study; and treatment with biologic agents within a 30-day washout period	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Low-to-moderate-potency topical steroids on the scalp, axillae, or groin.	

Authors: Paller et al. and Siegfried et al. and Langley et al. **Year: 2008, 2010, 2011**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline**		
	Etanercept	**Placebo**	**Withdrawal-Retreatment Period**
Mean age (years):	14	13	13 (median)
Sex (% female):	48	50	51
Ethnicity:	78% white	71% white	78% white
Other germane population qualities:			
• **Mean PASI**	16.7	16.4	16.7 (median)
• **Mean body surface area involvement**	21.0	20.0	20.5 (median)
• **Mean duration of psoriasis**	6.8 years	5.8 years	5.8 years (median)
• **Received prior systemic therapy (%)**	55	59	57
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PASI 75 at week 12 **Secondary Outcome Measures:** PASI 50 and 90, physicians global assessment of clear or almost clear, Children's Dermatology Life Quality Index **Timing of assessments:** Baseline weeks 2 ,4, 6, 8, 12, 16 and every 4 weeks Following the 12 week double-blind period, all patients received open-label etanercept for 24 weeks. At the end of this period, patients who received 75% improvement in PASI response from baseline (PASI 75) were re-randomized to a 12-week, double-blind withdrawal-treatment period. During this phase, patients received either placebo or etanercept as long as they maintained a clinical response, defined as PASI 75. Patients whose response fell below PASI 75 were retreated with etanercept in an open-label fashion until study completion. PASI 75 was assessed every 4 weeks during the 12-week, double-blind withdrawal-retreatment period.		
RESULTS:	**Health Outcome Measures at 12 weeks:** • PASI 75: etanercept 57% vs. placebo 11%, p<0.001 • PASI 50: etanercept 75% vs. placebo 23%, p<0.001 • PASI 90: etanercept 27% vs. placebo 7%, p<0.001		

	• Physicians global assessment of clear or almost clear: etanercept 53% vs. placebo 13%, p<0.001 • CDLQI mean improvement: etanercept 52% vs. placebo 18% **Withdrawal-Retreatment period:** Etanercept (received etanercept throughout withdrawal-retreatment) vs. Placebo (received placebo in withdrawal phase) vs. Placebo (received etanercept in retreatment phase) • Percentage of patients who achieved PASI 75 at: Week 40: 81% vs. 75% vs. N/A Week 44: 82% vs. 76% vs. 27% Week 48: 80% vs. 85% vs. 36% • Percentage of patients who achieved PGA clear/almost clear at: Week 40: 69% vs. 60% vs N/A Week 44: 65% vs. 57% vs 33% Week 48: 58% vs. 68% vs 29% • In the group treated with blinded or open-label etanercept, 80% patients maintained or regained PASI 75 at the end of the 12-week period. In all, 70% patients on blinded etanercept maintained PASI 75 at every study visit during the 12-week period, compared with 54% patients who did so on blinded placebo. • At the time the 29 patients on placebo began receiving etanercept retreatment, their mean improvement from baseline in the PASI response had decreased to 47.4%. After 4 to 8 weeks of retreatment, their mean improvement from baseline in the PASI response was 64.4%. • Of the 137 patients who completed the 12-week period, 95 (69%) remained on blinded placebo or blinded etanercept for the 12-week period. In the placebo group, 40/69 (58%) patients remained on blinded placebo throughout the period, and 29/69 (42%) received etanercept retreatment. In the etanercept group, 55/68 (81%) patients remained on blinded etanercept. The remaining 13 (19%) patients on etanercept entered the open-label retreatment phase, although one patient entered without losing PASI 75.

Authors: Paller et al. and Siegfried et al. and Langley et al. **Year: 2008, 2010, 2011**			
ADVERSE EVENTS:	**Etanercept**	**Placebo**	
Overall adverse effects reported (event rates per 100 pt/yrs:	554.5	765.4	
• URTI	54.6	69.1	
• Headache	32.8	95.7	
• Nasophyrantgitis	31.5	53.2	
• Influenza	14.0	15.9	
• Streprococcal pharygitis	13.3	5.3	
• Cough	12.1	10.6	
• Pharyngolaryneal pain	12.1	31.9	
• Vomiting	12.1	10.6	
• Nasal congestion	10.3	15.9	
• Skin papilloma	9.7	0	
Overall adverse effects reported:	Double-blind withdrawal phase:	Double-blind withdrawal phase:	Open-label retreatment phase: **Etanercept**
• Overall adverse effects	52.9%	46.4%	42.9%
• At least 1 serious AE	0%	0%	0%
• Headache	8.8%	2.9%	NR
• Nasophyrantgitis	10.3%	2.9%	NR
• URTI	NR	NR	14.3%
• Sinitius	NR	NR	7.1%
• Injection site reaction	1.5%	1.4%	2.4%
ATTRITION (*overall*):	**Overall attrition:** 3 (plus 1 in withdrawal-retreatment phase) **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**Etanercept**	**Placebo**	
Attrition overall:	2%	1%	
Attrition due to adverse events:	0%	1%	

URTI: upper respiratory tract infection.

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Rodgers et al. (Health Technology Assessment)[83]** **Year: 2011** **Country: UK** **Quality rating:**
FUNDING:	Health Technology Assessment programme of the National Institute for Health Research.
DESIGN & SIZE:	**Study design:** Systematic review **Number of patients:** 982 (effectiveness; safety NR) **Trials:** Effectiveness =6 (in 43 publications), Safety=32
OBJECTIVE OF REVIEW:	To determine the clinical effectiveness, safety and cost-effectiveness of etanercept, infliximab and adalimumab for the treatment of active and progressive psoriatic arthritis in patients who have an inadequate response to standard treatment (including DMARD therapy).
ELIGIBILITY CRITERIA:	Randomized controlled trials (including any open-label extensions of these RCTs) were included in the evaluation of efficacy. Information on the rate of serious adverse events was sought from regulatory sources [the US Food and Drug Administration (FDA), European Medicines Agency (EMEA)]. If these failed to report the necessary data to calculate event rates then nonrandomized studies that provided these data for etanercept, infliximab and adalimumab were included in the review. If multiple nonrandomized studies were identified, inclusion was limited to those studies reporting outcomes for a minimum of 500 patients receiving biologic therapy. For the evaluation of the effectiveness of etanercept, infliximab and adalimumab, included studies were of adults with active and progressive psoriatic arthritis with an inadequate response to previous standard therapy (including at least one DMARD). Trials of effectiveness had to specify that the patients had psoriatic arthritis, with the definition and/or the inclusion criteria for Psoriatic arthritis stated. For the assessment of adverse effects, studies of patients with other conditions were eligible for inclusion in the review.
STUDIES INCLUDED IN REVIEW:	**Effectiveness** (not including companions): ADEPT 2005, Genovese 2007, IMPACT 2005, IMPACT 2 2005, Mease 2000, Mease 2004. **Adverse events**: Antoni 2008, Brassard 2006, Breedveld 2006, Burmester 2007, Carmona 2005, Caspersen 2008, Colombel 2004, Colombel 2007, Curtis 2007, Dixon 2006, Dixon 2007, Dreyer 2009, Favalli 2009, Feltelius 2005, Fidder 2009, Fleischmann 2006, Gomez-Reino 2003, Gomez-Reino 2007, Horneff 2009, Klareskog 2006, Listing 2005, Mease 2006, Moreland 2006, Oka 2006, Rudwaleit 2009, Schiff 2006, Schnitzler 2009, St. Clair 2004, Takeuchi 2008, Westhovens 2006, Wolfe 2004.

LITERATURE SEARCH DATES:	June 9-17, 2009
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	For effectiveness, six RCTs (total of 43 publications), consisting of two placebo-controlled RCTs for each of the three agents: etanercept (Mease 2000 and Mease 2004), infliximab (IMPACT 2005 and IMPACT 2 2005), and adalimumab (ADEPT 2005 and Genovese 2007). For adverse events, 32 publications were included, which reported treatment with etanercept, infliximab or adalimumab in 500 or more patients, and reported either adverse event rates directly or provided sufficient information to calculate these rates.

Authors: Rodgers et al. **Year: 2011**	
DATA SYNTHESIS METHODS:	Where sufficient clinically and statistically homogeneous data were available, data were pooled using standard meta-analytic method. Given the small number of trials available, a fixed-effects model was used to pool outcomes where pooling was appropriate. Sensitivity analyses were undertaken when permitted by sufficient data (e.g. exclusion of concomitant MTX treatment). The rates of serious adverse effects of these biologic agents were synthesized narratively. As trials conducting head-to-head comparisons of etanercept, infliximab and adalimumab were not available the possibility of conducting some form of indirect comparison was investigated. Meta-analysis using indirect comparisons enables data from several sources to be combined, while taking into account differences between the different sources, in a similar way to, but distinct from, how a random-effects model takes into account between-trial heterogeneity. As with a mixed-treatment comparison (MTC), Bayesian indirect comparisons need a 'network of evidence' to be established between all of the interventions of interest.
MAIN RESULTS: (RESULTS IN SUBGROUPS)	**Psoriatic Arthritis Response Criteria (PsARC):** Etanercept (at 12 weeks): RR 2.60; 95% CI, 1.96 to 3.45; P<0.00001; I^2=34% Infliximab (at 14 weeks): RR 3.44; 95% CI, 2.53 to 4.69; P<0.0001; I^2=68% Adalimumab (at 12 weeks): RR 2.24; 95% CI, 1.74 to 2.88; P<0.0001; I^2=0% Mean probability of a PsARC response: 71% for etanercept, 79% for infliximab, and 59% for adalimumab, compared with 25% for placebo. **American College of Rheumatology (ACR) 20:** Etanercept (at 12 weeks): RR 4.19; 95% CI, 2.74 to 6.42; P<0.00001; I^2=0% Infliximab (at 14 weeks): RR 5.47; 95% CI, 3.43 to 8.71; I^2=0% Adalimumab (at 12 weeks): RR 3.65; 95% CI, 2.57 to 5.17; P<0.0001; I^2=38% Mean probability of an ACR 20 response: 61% for etanercept, 68% for infliximab and 56% for adalimumab, compared with 14% for placebo. **ACR 50:** Etanercept (at 12 weeks): RR 10.84; 95% CI, 4.47 to 26.28; P<0.00001; I^2=0% Infliximab (at 14 weeks): RR 13.75; 95% CI, 5.11 to 37.00; P<0.0001; I^2=0% Adalimumab (at 12 weeks): RR 10.08; 95% CI, 4.74 to 21.44; P<0.0001; I^2=0% Mean probability of an ACR 20 response: 36% for etanercept, 43% for infliximab and 32% for adalimumab, compared with 5% for placebo.

	ACR 70: Etanercept (at 12 weeks): RR 16.28; 95% CI, 2.20 to 120.54; P=0.006; I^2=0% Infliximab (at 14 weeks): RR 17.67; 95% CI, 3.46 to 90.14; P=0.001; I^2=0% Adalimumab (at 12 weeks): RR 26.05; 95% CI, 5.18 to 130.88; P<0.0001; I^2=0% Mean probability of an ACR 20 response: 16% for etanercept, 20% for infliximab and 13% for adalimumab, compared with 2% for placebo. **Health Assessment Questionnaire (HAQ):** Etanercept (at 12 weeks), percent change from baseline: RR -48.99; 95% CI, 38.53 to 59.44; P<0.0001; I^2=0% Infliximab (at 14 weeks), percent change from baseline: WMD -60.37; 95% CI, -75.28 to -45.46); I^2=3% Adalimumab (at 12 weeks), change from baseline: WMD -0.27; 95% CI, -0.36 to -0.18; P<0.0001; I^2=0.6% Mean change in HAQ in patients achieving a PsARC response: -0.630 for etanercept, -0.657 for infliximab, and -0.477 for adalimumab, compared with -0.244 for placebo. Mean change in HAQ in patients not achieving a PsARC response: -0.190 for etanercept, -0.194 for infliximab, and -0.130 for adalimumab, compared with 0 for placebo. **Psoriasis Area and Severity Index (PASI) 50:** Mean probability of a PASI 50 response: 40% for etanercept, 91% for infliximab and 74% for adalimumab, compared with 13% for placebo. **PASI 75:** Mean probability of a PASI 75 response: 18% for etanercept, 77% for infliximab and 48% for adalimumab, compared with 4% for placebo. **PASI 90:** Mean probability of a PASI 90 response: 7% for etanercept, 56% for infliximab and 26% for adalimumab, compared with 2% for placebo. The results of evidence synthesis found that infliximab appears to be the most effective of the three biologics. Across all outcomes of joint and skin disease at 12 weeks, infliximab is associated with the highest probabilities of response.
ADVERSE EVENTS:	Rates of serious infection: etanercept 0.6%–13.2%, infliximab 0.8%–13.8%, adalimumab 0.4%–5.1% Rates of malignancy: etanercept 1%–5.7%, infliximab 0.16%–5.1%, adalimumab 0.1%–1.1% Rates of activation of TB for the treatment: etanercept 0%–1.4%, infliximab 0.06%–4.6%, adalimumab 0%–0.4%

	Rates of mortality: etanercept 0%–3.1%, infliximab 0.06%–2.0%, adalimumab 0.5%–0.9% Rates of withdrawal due to AE: etanercept 0%–13.6%, infliximab 6.4%–12.8%, adalimumab 5.8%–10.7%
LIMITATIONS OF PRIMARY STUDIES	NR

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Ruiz Garcia et al.**[41] **Year: 2011** **Country: Spain** **Quality rating: Good**
FUNDING:	
DESIGN & SIZE:	**Study design:** Systematic Review **Number of patients: 2394 for effectiveness, 2094 for safety** **Trials: 5**
OBJECTIVE OF REVIEW:	**To assess the effectiveness and safety of certolizumab pegol in patients with RA who have not responded well to conventional disease modifying anti-rheumatic drugs (DMARDs).**
ELIGIBILITY CRITERIA:	Randomised controlled trials that compared certolizumab pegol with any other agent including placebo or methotrexate (MTX) in adult RA patients with active rheumatoid arthritis despite current or prior treatment with conventional DMARDs, such as methotrexate (MTX).
STUDIES INCLUDED IN REVIEW:	Anonymous (CDP870-004 2001) - published and unpublished data, 2001 UCB (CDP870-014 2009) - unpublished data only, 2008 Choy et al., 2002 Fleischmann, 2007 (FAST4WARD 2005 – published data only) RAPID 1, 2005 (published data only) RAPID 2, 2007 (published data only)
LITERATURE SEARCH DATES:	1966 – November 2009
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	5. RCTs that compared certolizumab pegol with any other agent including placebo in adult RA patients with active RA despite current or psior treatment with DMARDs 6. Trials that were fully published as a paper or available as a complete trial report. Where published only abstracts the trial reports were requested from the manufacturers 7. Studies having at least three months of follow-up to assess effectiveness 8. To assess safety: studies having a suboptimal length of follow-up, from eight weeks. Types of participants: adults (18 years and older) with RA who have persistent disease activity despite current or previous use of conventional DMARDs. Types of intervention: Certolizumab (CDP870) at any dose. The comperators were placebo or any disease modifying anti-rheumatic drug including other biologic agents used to treat RA.

Authors: Ruiz Garcia et al. **Year: 2011**	
DATA SYNTHESIS METHODS:	Authors used fixed-effect models throughout, except where heterogeneity exists in which case a random-effects model was used as it introduces less bias than excluding trials altogether. When studies were homogeneous they pooled them. Forest plots (mean differences and risk ratios) were done. They chose the fixed-effect model to pool the data because statistical heterogeneity was not high and it was reasonable from a clinical point of view. They used the GRADE software to provide an overall grading of the quality of the evidence by outcome.
MAIN RESULTS: (RESULTS IN SUBGROUPS)	ACR 50 (Follow-up: mean 24 weeks): Assumed Risk: 58 per 1000, corresponding risk: 349 per 1000 (223 to 545), RR 6.01 (3.84 to 9.4) [2 studies, N=965] HAQ change from baseline (Follow-Up: mean 24 weeks): control group: mean change: 1.6, intervention group: 0.39 lower (0.45 to 0.32 lower) [2 studies, N=965] Proportion of patients achieving DAS <2.6 (Remission): Assumed Risk: 12 per 1000, corresponding Risk: 45 per 1000 (28 to 73), OR 3.88 (2.33 to 6.45) [2 studies, N=957] All Withdrawals: Assumed Risk: 715 per 1000, corresponding risk: 279 per 1000 (257 to 307), RR 0.39 (0.36 to 0.43) [5 studies, N=2107] ---------- Assumed risk: Control Corresponding risk: Summary of findings Certolizumab pegol 200mg sc (with or without MTX) versus Placebo (with or without MTX)
ADVERSE EVENTS:	Serious adverse events (Follow-Up: mean 24 weeks): assumed risk: 46 per 1000, corresponding risk: 89 per 1000 (56 to 137), OR 2.02 (1.24 to 3.3) [2 studies, N=964] Withdrawals due to adverse events (Follow-up: 24-52 weeks): Assumed Risk: 23 per 1000, corresponding risk: 43 per 1000 (26 to 71), OR 1.93 (1.15 to 3.23) [4 studies, N=2071]
LIMITATIONS OF PRIMARY STUDIES	Absence of publication of some of the trials carried out with certolizumab pegol in RA

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Ruperto et al.**[64] **Year: 2007** **Country:**	
FUNDING:	Centocor	
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of INF in the treatment of juvenile rheumatoid arthritis (JRA).	
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 122	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF + MTX** 3 mg/kg 14 weeks 62	**Placebo + MTX** N/A 14 weeks 60
INCLUSION CRITERIA:	At least 4 years but no more than 18 years old, a diagnosis of JRA, suboptimal response to MTX after 3 months, at least 5 active joints, and no active systemic symptoms.	
EXCLUSION CRITERIA:	Active uveitis, serious infection including tuberculosis, malignancy, or prior treatment with any TNF inhibitor.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX and intraarticular corticosteroid injections, low-dose corticosteroids , 1 NSAID, 1 analgesic that was not an NSAID, folic acid prophylaxis (required for all patients taking MTX), and narcotic or opioid analgesics	

Authors: Ruperto et al. **Year: 2007**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe	
	INF + MTX	**Placebo + MTX**
Mean age (years):	11.3	11.1
Sex (% female):	88.3	79.0
Ethnicity:	86.2	88.3
Other germane population qualities:		
• Tender joint count	NR	NR
• Swollen joint count	NR	NR
• Mean disease duration	4.2	3.6
• DMARD use (other than MTX) (%)	40	31.1
• MTX use (%)	100	100
• Corticosteroids use (%)	43.3	34.4
• DAS score	NR	NR
• C-HAQ score	1.2	1.2
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR Pedi 30 **Secondary Outcome Measures:** ACR Pedi 50 and ACR Pedi 70 and # patients with 0 joints with active arthritis **Timing of assessments:** "… recorded throughout the study"	
RESULTS:	**Health Outcome Measures:** ACR Pedi 30 - INF 37 of 58 [63.8%] versus placebo 29 of 59 [49.2%] $P = 0.12$ ACR Pedi 50 - INF 29 of 58 [50%] versus placebo 20 of 59 [33.9%]; $P = 0.078$ ACR Pedi 70 - INF 13 of 58 [22.4%] versus placebo 7 of 59 [11.9%]; $P = 0.130$ Number of joints with active arthritis INF vs. placebo $P = 0.016$	

Authors: Ruperto et al. **Year: 2007**		
ADVERSE EVENTS: **Overall adverse effects reported:** • **Serious adverse events** • Infections • Serious infections • Infusion reactions	**INF + MTX (0-52 weeks)** 96.7% 31.7% 68.3% 8.3% 9.1%	**Placebo + MTX (0-14 weeks)** 81.7% 5.0% 46.7% 3.3% 3.4%
Significant differences in adverse events:	N/A- denominators are different	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 5	
ADEQUATE RANDOMIZATION:	Yes	
ADEQUATE ALLOCATION CONCEALMENT:	Method NR	
BLINDING OF OUTCOME ASSESSORS:	Method NR	
ATTRITION (*overall*):	**Overall attrition:** 4% at 14 weeks, 19% at 52 weeks **Attrition differential high:** No	
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**INF + MTX** 3% at 14 weeks 0 at 14 weeks	**Placebo + MTX** 5% at 14 weeks 0 at 14 weeks
QUALITY RATING:	**Fair**	

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Ruperto et al.**[65,66] **Year: 2008, 2010** **Country:** Europe, Latin America and USA		
FUNDING:	Bristol-Myers Squibb		
RESEARCH OBJECTIVE:	To assess the safety and efficacy of ABA, in children with juvenile idiopathic arthritis who had failed previous treatments.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 190 run- in phase; and 122 RCT		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Open label run-in** 10 mg/kg days 1,15,29,57,85 4 months 190	**ABA** 10 mg/kg every 28 days 6 months 60	**Placebo** NA 6 months 62
INCLUSION CRITERIA:	Age 6 – 17 years; $\geq$ 5 active joints (those with swelling or, in the absence of swelling, limited range of motion, accompanied by either pain or tenderness) and active disease (at least two active joints and two joints with a limited range of motion)patients with inadequate response or intolerance to at least one DMARD, including biological agents		
EXCLUSION CRITERIA:	Active uveitis, major concurrent medical conditions; pregnant or lactating.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable MTX and folinic acid or folic acid.		

Authors: Ruperto et al. **Year: 2008, 2010**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Mild-moderate-severe		
	Open label	**ABA**	**Placebo**
Mean age (years):	12.4	12.6	12.0
Sex (% female):	72	72	73
Ethnicity:	77% white, 8% black, 15% other	77% white, 8% black, 15% other	79% white, 7% black, 15% other
Other germane population qualities:			
• Active joint count	12.7	12.6	12.0
• Swollen joint count	NR	NR	NR
• Mean disease duration	4.4	3.8	3.9
• DMARD use (%)	NR	NR	NR
• MTX use (%)	74	80	74
• Corticosteroids use (%)	NR	NR	NR
• DAS score	NR	NR	NR
• HAQ score	CHAQ 1.3	1.3	1.2
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Time to flare of juvenile idiopathic arthritis **Secondary Outcome Measures:** Proportion of patients who had disease flare; the changes from baseline in each of the six ACR core variables; and assessment of safety and tolerability, HRQOL via CHQ, pain, sleep quality, and participation in daily activity assessments **Timing of assessments:** screening, baseline, and at each dosing visit in the 4-month open-label lead-in period (days 1, 15, 29, 57, 85, 113) and the 6-month double-blind period (days 29, 57, 85, 113, 141, 169).		
RESULTS:	**Health Outcome Measures: ABA versus placebo at end of 6 month double blind period** • **Time to flare** - insufficient events to analyze * • Proportion of patients having flare - 12 (20%) vs. 33 (53%) *P* = NR • 30% or greater improvement at end, 49 (82%) vs. 43 (69%) *P* = 0.1712 • 50% or greater improvement at end, 46 (77%) vs. 32 (52%) *P* = 0.0071		

	• 70% or greater improvement at end, 32 (52%) vs. 19 (31%) *P* = 0.0185 • 90% or greater improvement at end, 24 (40%) vs. 10 (16%) *P* = 0.0062 • Inactive disease status 18 (30%) vs. 7 (11%) *P* = 0.0195 • Children's missed less school days per month 0.55 vs. 1.61 *P* = 0.033 • Parents' missed usual activity days per month 0.50 vs. 1.93 *P* = 0.109 • C-HAQ 0.5 (0.7) vs. 0.7 (0.7) *P* = NR • CSHQ total 42.8 (5.8) vs. 45.0 (6.0) *P* = 0.076 • No differences in sleep quality (*P* = 0.076) • No differences in pain reduction (*P* = 0.105)

Authors: Ruperto et al. **Year: 2008, 2010**			
ADVERSE EVENTS:	**Open label**	**ABA**	**Placebo**
Overall adverse effects reported:	70%	62%	55%
• Infections	36%	45%	44%
• Nausea	10%	3%	7%
• Headache	13%	5%	2%
• Cough	9%	0	3%
• Diarrhea	9%	2%	2%
Significant differences in adverse events:	None		
ANALYSIS:	**ITT:** Yes (no ITT-analysis for quality of life data) **Post randomization exclusions:** none		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 11% in open label run-in phase, 34% in RCT **Attrition differential high:** Yes		
ATTRITION (*treatment specific*):	**Open label**	**ABA**	**Placebo**
Overall attrition:	11%	18.3%	50%
Attrition due to adverse events:	0.5%	0	0
QUALITY RATING:	**Fair**		

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Saad et al.**[173] **Year: 2009** **Study name: BSRBR** **Country: UK** **Quality rating: Fair**		
FUNDING:	British Society for Rheumatology (who receives some funding from UK pharmaceutical companies, including Abbott, Amgen, Schering Plough, and Wyeth Pharmaceuticals).		
RESEARCH OBJECTIVE:	To assess persistence with first-course and second-course treatment with anti-TNF agents in a prospective cohort of psoriatic arthritis patients and to identify factors associated with and reasons for drug discontinuation.		
DESIGN & SIZE:	**Study design:** Prospective cohort. **Setting:** Multicenter (UK) **Sample size:** 566		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Etanercept** 25 mg twice weekly or 50 mg once weekly NR 316	**Adalimuab** 40 mg every 2 weeks NR 88	**Infliximab** NR (says the recommended dose is 5 mg/kg administered at weeks 0, 2, 6 and 8, and then every 8 weeks thereafter) NR 162
INCLUSION CRITERIA:	Subjects with a physician diagnosis of psoriatic arthritis who had started treatment with etanercept, infliximab or adalimumab (and were therefore included in the registry).		
EXCLUSION CRITERIA:	Patients not registered within 6 months of starting therapy.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Methotrexate, Sulfasalazine, and steroid; otherwise, NR.		

Authors: Saad et al. **Year: 2009**	
POPULATION CHARACTERISTICS:	**Population**
Mean age (years): **Sex (% female):** **Ethnicity:** **Class naïve:** Other germane population qualities: • **Tender joint count** • **Swollen joint count** • **Mean disease duration** • **DMARD use (%)** • **MTX use (%)** • **Corticosteroids use (%)** • **DAS score** • **HAQ score**	45.7 53 NR 100 13.4 8.9 12.4 NR NR NR 6.4 1.9
RESULTS:	**Primary Outcome Measures:** All anti-TNF first course vs Etanercept vs Infliximab vs Adalimumab Survivor function for patients stopping their initial anti-TNF therapy because of adverse events by year of follow-up, mean (95% CI): Year 1: 0.96 (0.94 to 0.97) vs 0.97 (0.94 to 0.98) vs 0.93 (0.87 to 0.96) vs 0.99 (0.92 to 0.99) Year 2: 0.92 (0.89 to 0.95) vs 0.95 (0.92 to 0.97) vs 0.86 (0.78 to 0.91) vs 0.92 (0.75 to 0.98) Year 3: 0.87 (0.84 to 0.92) vs 0.91 (0.84 to 0.95) vs 0.72 (0.72 to 0.89) vs 0.92 (0.75 to 0.98) **Secondary Outcome Measures:** Etanercept vs Infliximab vs Adalimumab: Univariate and multivariate Cox proportional hazard analysis for drug discontinuation due to adverse events, HR (95% CI): Univariate analysis: Ref vs 2.42 (1.26 to 4.68), P<0.05 vs 1.11 (0.37 to 3.33) Multivariate analysis: Ref vs 3.12 (1.41 to 6.89), P<0.05 vs 0.74 (0.21 to 2.66)

Authors: Saad et al. **Year: 2009**			
METHOD OF ADVERSE EVENTS REPORTING:	The rheumatology consultants/nurse specialists were sent a 6-monthly postal follow-up questionnaire for 3 years and then annual follow-ups thereafter. This consultant follow-up questionnaire recorded details of all anti-TNF therapies received, including start and stop dates and reasons for discontinuation. In addition, data were recorded for calculation of the DAS-28.		
ADVERSE EVENTS (%):	**Etanercept**	**Adalimumab**	**Infliximab**
Overall adverse effects reported:	NR (only reported adverse events leading to withdrawal)	NR (only reported adverse events leading to withdrawal)	NR (only reported adverse events leading to withdrawal)
• infections	NR	NR	NR
• URTI	NR	NR	NR
• abnormal LFT	NR	NR	NR
• herpes simplex	NR	NR	NR
• pneumonia	NR	NR	NR
• tb	NR	NR	NR
• ISR	NR	NR	NR
ATTRITION (*overall*):	**Overall attrition:** NR (only reported survivor function by year of follow-up) **Attrition differential high:** NA		
ATTRITION (*treatment specific*):	**Etanercept**	**Adalimumab**	**Infliximab**
Attrition overall:	NR	NR	NR
Attrition due to adverse events:	See Results	See Results	See Results

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Salmon-Ceron et al.**[174] **Year: 2011** **Study name: NA** **Country: France** **Quality rating: Fair**		
FUNDING:	Government and Abbott, Schering Plough, and Wyeth		
RESEARCH OBJECTIVE:	To describe the spectrum of non-tuberculosis opportunistic infections associated with anti-TNF therapy and identify their risk factors.		
DESIGN & SIZE:	**Study design:** Case-control **Setting:** Specialty clinics and pharmacy registry data **Sample size:** 43 cases		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** NR NR 29	**ADA** NR NR 10	**ETA** NR NR 4
INCLUSION CRITERIA:	Cases: all validated cases of opportunistic infections in the registry with a labeling indication for use of anti-TNF treatment; patients were included in the analysis if they were being treated with an anti-TNF agent at the time of first symptoms of OI or if the anti-TNF treatment had been stopped <24 months before the first symptoms. Controls: patients treated with anti-TNF agents for a labeled indication, in whom no OI had evere developed.		
EXCLUSION CRITERIA:	No additional criteria.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Not reported		

Authors: Salmon-Ceron et al. **Year: 2011**	
POPULATION CHARACTERISTICS:	
Mean age (years): **Sex (% female):** **Ethnicity:** **Class naïve:** Other germane population qualities: • **Tender joint count** • **Swollen joint count** • **Mean disease duration** • **DMARD use (%)** • **MTX use (%)** • **Corticosteroids use (%)** • **DAS score** • **HAQ score**	Cases: Mean age 50.7 (SD 16.6 years) 58.8% female Ethnicity not reported 60.5% rheumatoid arthritis; 7% spondyloarthritis; 18.6% Crohn's disease or ulcerative colitis; 2.3% each psoriasis, polyarteritis nodosa, idiopathic juvenile arthritis, sarcoidosis, mesenteric fibrosis, pyoderma gangrenosum
RESULTS:	**Primary Outcome Measures:** Incidence of opportunistic infection

Authors: Salmon-Ceron et al. **Year: 2011**			
METHOD OF ADVERSE EVENTS REPORTING:	Collected 3-year French registry data.		
ADVERSE EVENTS	**INF**	**ADA**	**ETA**
Annual adjusted incidence rate of opportunistic	290.9 (0.0 to 835.8) per 100,000 patient-years	61.8 (0.0 to 162.5) per 100,000 patient-years	7.1 (0.0 to 24.2) per 100,000 patient-years
Risk factors of opportunistic infection for patients receiving anti-TNF therapy (multivariate analysis)	OR 17.6 (4.3 to 72.9)	10.0 (2.3 to 44.4)	1 (reference)

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Salliot et al.**[175] **Year: 2009** **Country:** Multinational
FUNDING:	Two authors have received grants from pharmaceutical companies
DESIGN:	**Study design:** Systematic review & meta-analysis **Number of patients:** 6461 (745 RIT, 2945 ABA, 2771 AKA)
AIMS OF REVIEW:	To assess if RIT, ABA or AKA increases the risk of serious infections in patients with RA in published RCTs.
STUDIES INCLUDED IN META-ANALYSIS:	12 trials: ABA 5 trials (Moreland 2002, Kremer 2003 and 2005, Genovese 2005, Kremer 2006, Weinblatt 2006); AKA 4 trials (Bresnihan 1998, Cohen 2002, Cohen 2004, Schiff 2004); RIT 3 trials (Edwards 2004, Emery 2006, Cohen 2006)
TIME PERIOD COVERED:	Up to October, 2007
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized double-blind placebo controlled trials with a follow-up of 12-48 weeks
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adult patients with RA according to ACR criteria with active disease despite DMARDs; 81% female with a mean age at inclusion of between 46 and 57 yrs

Authors: Salliot et al. **Year: 2009**	
CHARACTERISTICS OF INTERVENTIONS:	RIT (500mg or 1000mg), AKA (30-50 mg) or ABA (0.5 – 10 mg/kg) vs. placebo
MAIN RESULTS:	Number (%) of patients with at least 1 serious infection; OR (95% CI) RIT vs. placebo: 17 (2.3%) vs. 6 (1.5%); 1.45 (0.56-3.73) ABA vs. placebo: 49 (2.5%) vs. 18 (1.8%); 1.35 (0.78-2.32) AKA vs. placebo: 30 (1.4%) vs. 4 (0.5%); 2.75 (0.90-8.35) Risk of serious infections stratified by high-and low-dose: OR (95% CI) High dose RIT (1000 mg) vs. placebo: 1.68 (0.64-4.35) High dose ABA (10 mg/kg) vs. placebo: 1.35 (0.70-2.29) High dose AKA (≥ 100 mg) vs. placebo: 3.40 (1.11-10.46) Low dose RIT (500 mg) vs. placebo: 0.24 (0.01-4.33) Low dose ABA (≤ 2 mg/kg) vs. placebo: 0.84 (0.13-5.30) Low dose AKA (< 100 mg) vs. placebo: 0.51 (0.03-8.27) Analyses of subgroups according to age (< or > to median 52.7 yrs), concomitant intake of steroids (median 65% of patients) and RF positivity (median positivity 78% of patients) confirmed these results (data NR)
ADVERSE EVENTS:	See main results
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	A systematic review of the literature using PUBMED, EMBASE, Cochrane library and abstracts databases (American College of Rheumatology and European League Against Rheumatism annual meetings) was performed up to October 2007. This search was completed with data from the FDA, the European Agency for the Evaluation of Medicinal Products, and manufacturers.
STANDARD METHOD OF APPRAISAL OF STUDIES:	NR
QUALITY RATING:	**Fair**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Schiff et al.**[176] **Year: 2006** **Country:** Multinational
FUNDING:	Abbott Labs
RESEARCH OBJECTIVE:	To assess the safety of adalimumab in global clinical trials and postmarketing surveillance among patients with RA
DESIGN:	**Study design:** Retrospective data analysis of clinical trials; postmarketing surveillance **Setting:** Multi-clinical **Sample size:** 10,050 (12, 506 patient years)
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA** Various Various 10050
INCLUSION CRITERIA:	Patients from randomized controlled trials, open label extensions, and two phase IIIb open label trials were and post-marketing spontaneous reports of adverse events in the United States
EXCLUSION CRITERIA:	N/A
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR

<table>
<tr><td colspan="2">Authors: Schiff et al.
Year: 2006</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:

Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• TJC
• SJC
• Mean disease duration
• DMARD use (%)
• MTX use (%)
• Corticosteroids use (%)
• DAS score
• HAQ score</td><td>Groups similar at baseline: N/A
Disease severity: Mild-moderate-severe</td></tr>
<tr><td>NR</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td>Primary Outcome Measures: Serious adverse events including TB, and malignancies</td></tr>
<tr><td>RESULTS:</td><td>Health Outcome Measures:
Rates per 100 patient years-
TB 0.27
Histoplasmosis 0.03
Demyelinating diseases 0.08
Lymphoma 0.12
SLE/lupus-like syndrome 0.10
CHF 0.28
• Incidence of Adverse events do not increase over time
• Long-term ADA treatment was generally safe</td></tr>
</table>

Authors: Schiff et al. **Year: 2006**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	NR
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	**N/A**
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	N/A
STATISTICAL ANALYIS ADEQUATE:	N/A
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A
QUALITY RATING:	**N/A**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Schiff**[43] **Year: 2008** **Country:** International		
FUNDING:	Bristol-Myers Squibb, Princeton, New Jersey, USA		
RESEARCH OBJECTIVE:	To evaluate the mean change from baseline in Disease Activity Score (based on erythrocyte sedimentation rates; DAS28 (ESR)) for the ABA vs. placebo groups at day 197		
DESIGN:	**Study design:** RCT **Setting:** International, Multi-center **Sample size:** 431		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ABA** 500-1000mg, days 1, 15, 29, and every 28 days thereafter 365 days (12 months) 156	**Placebo** N/A 197 days (6 months) 110	**INF** 3mg/kg, days 1, 15, 43, 85, and every 56 days thereafter 365 days (12 months) 165
INCLUSION CRITERIA:	(ACR) criteria for RA, age ≥ 18, RA ≥ 1 year, inadequate response to MTX, as demonstrated by ongoing active disease (at randomization SJC >10, TJC >12, and CRP >1 mg/dl. All patients had received MTX >15 mg/week for >3 months prior to randomization (stable for at least 28 days) and washed out all DMARDs (>28 days prior) except for MTX. Anti-TNF-therapy naïve.		
EXCLUSION CRITERIA:	All patients were screened for TB by purified protein derivative (PPD) testing and chest x ray.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids ((10 mg of prednisone or equivalent daily (stable for >25 out of 28 days prior to randomization)), and/or stable NSAIDs (including acetyl salicylic acid, and analgesics not containing aspirin or NSAIDs). No MTX dose adjustments were permitted except in the occurrence of adverse events (AEs). Between days 198–365, dose modification was permitted for MTX ((25 mg weekly) and oral corticosteroids ((10 mg prednisone or equivalent daily); hydroxychloroquine, sulfasalazine, gold, or azathioprine were also permitted. Premedication prior to infusions of study drug was left at the discretion of the investigator (not required by protocol).		

Authors: Schiff **Year: 2008**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Mild-moderate-severe		
	ABA	**Placebo**	**INF**
Mean age (years):	49.0 (12.5)	49.4 (11.5)	49.1 (12.0)
Sex (% female):	83.3%	87.3%	82.4%
Ethnicity:	80.8% caucasian	76.4% caucasian	80.6% caucasian
Other germane population qualities:			
• Tender joint count (SD)	31.3 (13.9)	30.3 (11.7)	31.7 (14.5)
• Swollen joint count (SD)	21.3 (8.6)	20.1 (7.0)	20.3 (8.0)
• Mean disease duration (SD)	7.9 (8.5)	8.4 (8.6)	7.3 (6.2)
• DMARD use (%)	100%	100%	100%
• MTX use (%)	100%	100%	100%
• Corticosteroids use (%)	75.6%	70.0%	71.5%
• DAS28 (ESR) score	6.9	6.8	6.8
• HAQ-DI score	1.8 (0.6)	1.8 (0.7)	1.7 (0.7)
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** reduction in disease activity, measured by DAS28 (ESR), with ABA vs. placebo at 6 months **Secondary Outcome Measures:** Mean reduction in DAS28 (ESR) with INF vs. placebo at 6 months. 6 months & 1 year: ABA vs. INF mean reduction in DAS28 (ESR); DAS28 (ESR) EULAR responses; low disease activity score (LDAS; DAS28 (ESR) ≤ 3.2); DAS28 (ESR)-defined remission (DAS28 (ESR), < 2.6); ACR 20, 50, 70 responses; HAQ-DI response rates (>0.3 improvement from baseline); SF-36: mean changes in PCS, MCS, & 8 subscales. Tertiary endpoints: comparative safety at 1 year ABA vs. INF. **Timing of assessments:** Baseline, 6 months, 1 year		
RESULTS:	**Primary Health Outcome Measures (6 months):** • reduction in DAS28 (ESR), ABA vs. placebo (–2.53 vs. –1.48, $P < 0.001$)		

	• ABA vs. placebo ACR20: 66.7 vs. 41.8%, *P* < 0.001, ACR50: 40.4 vs. 20.0%, P < 0.001; and ACR70: 20.5 vs. 9.1%, *P* = 0.019. • INF vs. placebo ACR20: 59.4 vs. 41.8%, *P* = 0.006; ACR 50: 37.0 vs. 20.0%, P = 0.004; and ACR70: 24.2 vs. 9.1%, *P* = 0.002. **Health Outcome Measures (head-to-head, day 365):** • a greater reduction in DAS28 (ESR) was observed with ABA than with INF –2.88 vs. –2.25; estimate of difference (95% CI) = –0.62 (–0.96, –0.29). **Intermediate (Secondary) Outcome Measures (head-to-head, day 365):** • proportion of patients achieving a good EULAR response (ABA 32.0 vs. INF 18.5%, estimate of difference (95% CI) = 13.5% (3.6, 23.3)), • LDAS (ABA 35.3 vs. INF 22.4%, estimate of difference (95% CI) = 12.9 (2.1, 23.7)), • DAS28 (ESR)-defined remission (ABA 18.7 vs. INF 12.2%, estimate of difference (95% CI) = 18.7 (–2.2, 15.2)) • ACR20 responses were higher with ABA than with INF (ACR20: 72.4 vs. 55.8%, difference of 16.7, 95% CI = 5.5, 27.8). • percentages of ACR50 and 70 responders were numerically higher with ABA vs. INF treatment (with overlapping 95% CIs for the estimate of difference for ACR50: 45.5 vs. 36.4%, estimate of difference (95% CI) = 9.1 (–2.2, 20.5); ACR70: 26.3 vs. 20.6%, estimate of difference (95% CI) = 5.7 (–4.2, 15.6), respectively) • HAQDI responses were maintained in the ABA and INF groups (57.7 and 52.7%, respectively, estimate of difference (95% CI) = 5.0 (–6.5, 16.5)) • greater improvements from baseline in the PCS were observed with ABA vs. INF (difference of 1.93, 95% CI = 0.02, 3.84). Improvements in the MCS (difference of 1.92, 95% CI = –0.30, 4.15) and in all eight subscales were also numerically higher with ABA vs. INF

Authors: Schiff **Year: 2008**			
ADVERSE EVENTS:	**ABA (365 days)**	**Placebo (6 months)**	**INF (365 days)**
Overall adverse effects reported:	89.1%	83.6%	93.3%
• Serious infections	1.9%	4.2%	8.5%
• Serious AEs	9.6%	11.5%	18.2%
• Acute infusional AEs	7.1%	10.0%	24.8%
• Infections and infestations	1.9%	2.7%	8.5%
Significant differences in adverse events:	a higher proportion of patients in the INF group compared with the placebo group reported related SAEs (4.8 vs. 2.7%), discontinued due to AEs (4.8 vs. 0.9%), and discontinued due to SAEs (2.4 vs. 0%). The higher frequency of SAEs in the INF vs. placebo groups was largely due to an increase in serious infections (4.2 vs. 2.7%, respectively)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** None		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 11% **Attrition differential high:** No		
ATTRITION (*treatment specific*):	**ABA**	**Placebo**	**INF**
Attrition overall:	10.9%	5.4%	14.5%
Attrition due to adverse events:	2.6%	0.9%	7.3%
QUALITY RATING:	**Fair**		

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Schneeweiss**[177] **Year: 2007** **Country:** USA				
FUNDING:	Engalitcheff Arthritis Outcomes Initiatives, Baltimore, Maryland				
RESEARCH OBJECTIVE:	To assess the association between the initiation of anti–tumor necrosis factor (anti-TNF) therapy and the risk of serious bacterial infections in routine care.				
DESIGN:	**Study design:** Retrospective – cohort study **Setting:** Pennsylvania Medicare beneficiaries **Sample size:** 15,597				
INTERVENTION:	**MTX**	**TNF antagonists**	**Cytotoxic DMARDs**	**Nontoxic DMARDs**	**Glucocorticoids**
Dose:	NR	NR	NR	NR	NR
Duration:	.58 yrs	1.29 yrs	0.64 yrs	0.73 yrs	0.20 yrs
Sample size:	1900	469	654	1957	10617
INCLUSION CRITERIA:	Medicare beneficiaries ages 65 years and older with RA who initiated use of a DMARD, including anti-TNF_ and glucocorticoids, between 1995 and 2003, patients had to demonstrate use of the health care system by filling at least 1 prescription for any drug and having at least 1 physician service in each of 2 consecutive 6-month periods in addition to being enrolled in the PACE program. Patients were identified as having RA if, at 3 physician visits, they had a diagnosis of RA				
EXCLUSION CRITERIA:	Any cancer (except nonmelanoma skin cancer) or human immunodeficiency virus/acquired immunodeficiency syndrome				
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes – 84% of patients starting anti-TNF took at least one other DMARD.				

Authors: Schneeweiss **Year: 2007**					
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe				
	MTX	**TNF antagonists**	**Cytotoxic DMARDs**	**Nontoxic DMARDs**	**Glucocorticoids**
# treatments	1900	469	654	1957	10617
Follow-up (yrs)	0.58	1.29	0.64	0.73	0.20
Mean age (years):	76	75	76	76	79
Sex (% female):	88	91	91	89	88
Ethnicity: % white/black/other	92/7/1	92/7/1	92/7/1	92/7/1	93/6/1
Other germane population qualities:					
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Hospitalization for serious bacterial infection **Secondary Outcome Measures:** Hospitalization due to opportunistic infection **Timing of assessments:** N/A				
RESULTS:	**Health Outcome Measures:** • **See AEs** **Intermediate Outcome Measures:** • **See AEs**				

Authors: Schneeweiss **Year: 2007**					
ADVERSE EVENTS: event rate per 100 pt/yrs **Overall adverse effects reported:**	**MTX**	**TNF antagonists**	**Cytotoxic DMARDs**	**Nontoxic DMARDs**	**Glucocorticoids**
• Pneumonia	1.47 (0.75–2.18)	2.33(1.12-3.54)	1.43 (0.29-2.57)	0.91 (0.42-1.40)	3.16 (2.41-3.91)
• Septicemia or bacteremia	2.20(1.33-3.07)	2.16 (1.00-3.32)	3.66 (1.84-5.48)	2.31 (1.53-3.09)	6.34 (5.3-7.38)
• Osteomyelitis	0.27 (0.07-0.48)	0.49 (000-1.05)	0.48 (000-1.14)	0.63 (0.22-1.04)	0.80 (0.42-1.18)
• Any bacterial infection	3.77 (2.64-4.9)	4.89 (3.15-6.62)	5.36 (3.18-7.54)	3.75 (2.70-4.74)	9.39 (8.14-10.6)
Significant differences in adverse events:	Glucocorticoid users' incidence of serious bacterial infections was significantly higher than average incidence in this population (RR 2.1; 1.5 – 3.1); the risk of septicemia or bacteremia was particularly pronounced (RR 2.5) no increased rate of serious bacterial infections for those who initiated anti-TNF therapy (RR 1.0) or any other DMARDs compared with MTX				
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A				
ARE GROUPS COMPARABLE AT BASELINE:	No – there were differences in amount of followup, Anti –TNF 1.29 yr, glucocorticoids 0.2 yrs.				
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes				
STATISTICAL ANALYIS ADEQUATE:	Yes				
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A				
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A				
QUALITY RATING:	**Good**				

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Setoguchi et al.**[178] **Year: 2008** **Country:** US			
FUNDING:	NR			
RESEARCH OBJECTIVE:	Whether TNF α antagonists pose an increased risk of HF in older patients with RA.			
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Medicare and drug benefit programs in 2 states (health care utilization databases) **Sample size:** 6595			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**TNFA with heart failure** 225	**MTX with heart failure** 808	**TNFA without heart failure** 777	**MTX without heart failure** 3783
INCLUSION CRITERIA:	Subjects aged ≥65, at least one recorded diagnosis of RA and filled at least one prescription of any TNFA ETA, INF, and ADA or MTX after the first RA diagnosis, at least one clinical service during each of 4 consecutive 6-month periods before the use of disease-modifying antirheumatic drugs (DMARDs)			
EXCLUSION CRITERIA:	Patients who had a diagnosis of HF in an outpatient file but no HF noted in a hospital discharge summary (n = 339)			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Corticosteroids, DMARDs, nonsteroidal anti-inflammatory drug			

<table>
<tr><td colspan="5">Authors: Setoguchi et al.
Year: 2008</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="4">Groups similar at baseline:
Disease severity: NR</td></tr>
<tr><td></td><td><u>TNFA with heart failure</u></td><td><u>MTX with heart failure</u></td><td><u>TNFA without heart failure</u></td><td><u>MTX without heart failure</u></td></tr>
<tr><td>Mean age (years):</td><td>73</td><td>77
84</td><td>72</td><td>74</td></tr>
<tr><td>Sex (% female):</td><td>89</td><td>92</td><td>90</td><td>89</td></tr>
<tr><td>Ethnicity: White</td><td>88</td><td></td><td>89</td><td>91</td></tr>
<tr><td>Other germane population qualities:
• Tender joint count
• Swollen joint count
• mean follow-up
• DMARD use (%)
• Noncytotoxic DMARDs (%)
• Corticosteroids use (%)
• DAS score
• HAQ score</td><td>

1,6
24
35
67</td><td>

1,7
4
22
56</td><td>

1,8
24
32
59</td><td>

2,5
5
26
48</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="4">Primary Outcome Measures: Effects of TNFAs compared to MTX on HF and/or death
Secondary Outcome Measures: deaths
Risk of death among patients with previous HF
Timing of assessments: study endpoints :the last use of TNFA or MTX, death, end of the study period, occurrence of HF</td></tr>
<tr><td>RESULTS:</td><td colspan="4">Health Outcome Measures:
Incidence rates of HF hospitalization: in TNFA users : without history of HF crude rate ratio 1.43, with previous HF 1.39
Risk of TNFAs on HF hospitalization of combined group of patients with and without previous HF: HR 1.70, 95% CI 1.07-2.69)

Risk of death among patients with previous HF: adjusted hazard ratio 4.19 of death compared with MTX users (95% CI 1.48-11.89)
Intermediate Outcome Measures:</td></tr>
</table>

Authors: Setoguchi et al. **Year: 2008**		
ADVERSE EVENTS: **Overall adverse effects reported:** • HF admission Incidence Rate	TNFA with previous HF 108 with no HF 19 2 groups combined 35	MTX with previous HF 76 with no HF 14 2 groups combined 21
Significant differences in adverse events:	70% increase in the risk of HF hospitalization among users of TNFA compared with users of MTX, regardless of history of previous HF	
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A	
ARE GROUPS COMPARABLE AT BASELINE:	NR	
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes	
STATISTICAL ANALYIS ADEQUATE:	Yes	
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A	
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**drug 1** N/A	**drug 2** N/A **drug 3**
QUALITY RATING:	**Fair**	

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Setoguchi et al.**[179] **Year: 2006** **Country:** US and Canada	
FUNDING:	Engalitchheff Arthritis Outcomes Initiative, Arthritis Foundation, and by a research grant from Novartis.	
RESEARCH OBJECTIVE:	To estimate the association between treatment with biologic disease-modifying antirheumatic drugs (DMARDs) and development of cancer in patients with RA.	
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Population based **Sample size:** 8458	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Biologic DMARD** Various various 1152	**MTX** Various various 7306
INCLUSION CRITERIA:	≥ 65 years in the US and Canada who had at least 1 claim with a diagnosis of RA and who were dispensed at least 1 prescription of any DMARD or corticosteroid after the first RA diagnosis during the study period	
EXCLUSION CRITERIA:	a diagnosis of any cancer (except non-melanoma skin cancer) or human immunodeficiency virus infection	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A	

Authors: Setoguchi et al. **Year: 2006**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe	
	Biologic DMARD	**MTX**
Mean age (years):	71.4	73.4
Sex (% female):	73.1	73.1
Ethnicity:	NR	NR
Other germane population qualities: • ETA • INF • AKA • MTX use (%) • Corticosteroids use (%)	743 [64%], 381 [33%], 28 [2%] 39%	NA NA NA 100%
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** diagnosis of cancer **Timing of assessments:** when occurred	
RESULTS:	**Health Outcome Measures:** No increase in haematologic (HR: 1.37, 95% CI 0.71-2.65) or solid tumors (HR 0.91, 95% CI 0.65-1.26) with anti-TNF drugs compared with MTX	

Authors: Setoguchi et al. **Year: 2006**		
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	**Biologic DMARD** see results	**MTX**
Significant differences in adverse events:	N/A	
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:**	
ARE GROUPS COMPARABLE AT BASELINE:	Yes	
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes	
STATISTICAL ANALYIS ADEQUATE:	Yes	
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:**	
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**Biologic DMARD**	**MTX**
QUALITY RATING:	**Fair**	

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Simon et al.**[180] **Year: 2008** **Country:** Multinational (Europe & North America)
FUNDING:	Bristol-Myers Squibb
DESIGN:	**Study design:** Pooled data with meta-analysis **Number of patients:** 4134 in ABA trials, 41529 in DMARD cohorts
AIMS OF REVIEW:	To provide context for the malignancy experience in the RA ABA clinical development program (CDP) by performing comparisons with similar RA patients and the general population.
STUDIES INCLUDED IN META-ANALYSIS	7 ABA trials compared with 5 RA DMARD cohorts and with the general population (from the SEER cancer registry)
TIME PERIOD COVERED:	Up to 2007
CHARACTERISTICS OF INCLUDED STUDIES:	5 ABA trials were randomized, double-blind, placebo-controlled trials; all were 6-12 months in duration
CHARACTERISTICS OF INCLUDED POPULATIONS:	Adults with RA; most patients were 45-74 yrs of age

Authors: Simon et al. **Year: 2008**	
CHARACTERISTICS OF INTERVENTIONS:	Trials: ABA vs. placebo RA cohorts: non-biologic DMARDs only
MAIN RESULTS:	Summary SIR comparing the rate of total malignancies (excluding NMSC) in the ABA CDP with the pooled IR from the RA cohorts was 0.68 (95% CI: 0.37–1.26), indicating that the overall risk of cancer was not significantly increased in ABA treated patients compared to RA patients treated with DMARDs. For the comparison of the ABA clinical trial malignancy experience with the general population, the calculated SIR comparing cancer IRs in RA patients treated with ABA with IRs in the general population (SEER cancer registry) was 0.82 (95% CI: 0.61-1.08) for total malignancy excluding NMSC.
ADVERSE EVENTS:	See main results
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	NR
QUALITY RATING:	**Fair**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Singh et al.**[47] **Year: 2011** **Country:** Various **Quality rating: Good**
FUNDING:	Canadian Institute of Health Research, Knowledge Synthesis Grant, Canada-funding for logistics, organization and administrative support
DESIGN & SIZE:	**Study design:** Systematic Review **Number of patients:** 50,010 patients in RCTs, 11,954 patients in open label extension studies. **Trials:** 163 and 46 open label extension studies
OBJECTIVE OF REVIEW:	To compare the adverse effects of etanercept, adalimumab, infliximab, golimumab, certolizumab, anakinra, tocilizumab, abatacept, rituximab therapy in patients with any disease condition except human immuno deficiency disease.
ELIGIBILITY CRITERIA:	RCTs, controlled clinical trials and open label extension studies that studies one of the biologics for use in any indication with the exception of HIV/AIDS and that reported any adverse outcomes were considered for inclusion
STUDIES INCLUDED IN REVIEW:	163 RCTS and 46 open label extension studies included in this review
LITERATURE SEARCH DATES:	Up until January 2010
INCLUDED STUDIES:	No. of trials, extension studies Studies by drugs Abatacept: 6, 2 Adalimumab: 22 ,10 Anakinra: 5, 2 Certolizumab pegol: 6,1 Etanercept: 42, 10 Golimumab: 8,1 Infliximab: 40,18 Rituximab: 30, 1

	Tocilizumab: 5, 1 <u>Types of condition (of interest)</u> Rheumatoid arthritis: 63, 18 Psoriasis: 15, 8 IBD: 12, 1 Ankylosing spondylitis: 10, 10 Psoriatic arthritis: 7, 7 Crohn's disease: 6, 0 Ulcerative colitis: 6,0 Duration of studies: mean (SD; median): 49.9 (8.7; 50.5), 79.9 (24.2; 87.0) Age: mean (SD; median): 49.9(8.7; 50.5), 79.9(24.2; 87.0) % female: mean (SD; median): 56.3(20.6; 56.8), 57.3 (24.5; 61.7) % Caucasian: mean (SD; median): 85.5 (16.8; 89.7), 79.9 (24.2; 87.0) Doses Etanercept: 50mg qweek, Infliximab: 3mg/kg q8weeks, Adalimumab: 40mg q2weeks, Golimumab: 50mg q4weeks, Certolizumab Pegol 400mg monthly, Anakinra 100mg qday, Rituximab 500 or 1000mg-2 weeks apart, Abatacept: 500-1000mg Q4 weeks, Tocilizumab 4mg/kg q4weeks

Authors: Singh et al. **Year: 2009**	
DATA SYNTHESIS METHODS:	Mixed –effects logistic regression using an arm-based, random-effects model within an empirical Bayes framework and applied a Poisson distribution as the default option.
MAIN RESULTS: (RESULTS IN SUBGROUPS)	NA (safety study)
ADVERSE EVENTS:	Indirect comparison network meta analysis results OR, 95% CI, reporting only pairwise comparisons that are statistically significant. <u>Serious adverse events</u> abatacept-certolizumab 0.45 (0.24 to 0.82), abatacept-etanercept 0.53 (0.32 to 0.88), abatacept-infliximab 0.50(0.31 to 0.82), abatacept-rituximab 0.59 (0.36 to 0.98), abatacept-tocilizumab 0.52 (0.27 to 0.99), anakinra*-certolizumab 0.38 (0.18 to 0.82), anakinra-etanercept 0.45 (0.22 to 0.91), anakinra-infliximab 0.43 (0.21 to 0.86), anakinra-tocilizumab 0.44 (0.20 to 0.99) <u>Serious infections</u> Abatacept-certolizumab 0.16 (0.06 to 0.43), abatacept-infliximab 0.39 (0.20 to 0.77), abatacept-tocilizumab 0.36 (0.15 to 0.83), adalimumab-certolizumab 0.32 (0.13 to 0.76), anakinra-certolizumab 0.31 (0.10 to 0.95), certolizumab-etanercept 3.32 (1.43 to 7.75), certolizumab-golimumab 2.73 (1.04 to 7.13), certolizumab-infliximab 2.42 (1.05 to 5.60), certolizumab-placebo 3.51 (1.59 to 7.79), certolizumab-rituximab 3.61 (1.53 to 8.48) <u>Total adverse events</u> Adalimumab-placebo 1.22 (1.03 to 1.45) Infliximab - placebo 1.33 (1.13 to 1.57) <u>Withdrawals due to adverse events</u> Abatacept-infliximab 0.53 (0.29 to 0.95) Adalimumab-infliximab 0.50 (0.32 to 0.78) Etanercept-infliximab 0.63 (0.41 to 0.95) Golimumab-infliximab 0.55 (0.30 to 0.99) Infliximab-placebo 2.04 (1.43 to 2.91)
LIMITATIONS OF PRIMARY STUDIES	Trials were of short duration with median length being 6 months.

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors:** Singh et al.[48] **Year:** 2010 **Country:** Multinational **Quality rating:** Good
FUNDING:	
DESIGN & SIZE:	**Study design:** Systematic Review **Number of patients:** 1714 **Trials:** 4
OBJECTIVE OF REVIEW:	To compare the efficacy and safety of golimumab in adults with rheumatoid arthritis
ELIGIBILITY CRITERIA:	(RCTs) or Controlled Clinical Trials (CCTs) (methods of allocating participants to a treatment which are not strictly random, e.g., date of birth, hospital record number or alternation)
STUDIES INCLUDED IN REVIEW:	Smolen, 1999 Keystone, 2009 Kay, 2008 Emery, 2009
LITERATURE SEARCH DATES:	June 30, 2009 (original search), August 16, 2009 (update search)
INCLUDED STUDIES: (Study design, characteristics of included population, characteristics of included interventions)	**Characteristics of Included Studies:** RCTs or Controlled Clinical Trials (CCTs) (methods of allocating participants to a treatment which are not strictly random, e.g., date of birth, hospital record number or alternation) **Characteristics of Included Populations:** Adults 18 years or older, with RA meeting the 1987 American College of Rheumatology Classification criteria for RA. 1 study was prior methotrexate failure and biologic failure (Smolen 99), 3 studies were naïve populations **Characteristics of Interventions:** Interventions compared are golimumab alone or in combination with DMARDs or biologics vs. placebo plus methotrexate or golimumab alone or in combination with DMARDs or biologics compared to other DMARDs or biologics. There were no restrictions with regard to dosage or duration of intervention.

Authors: Singh et al. **Year: 2010**	
DATA SYNTHESIS METHODS:	Meta-analysis
MAIN RESULTS: (RESULTS IN SUBGROUPS)	Results reported as Risk Ratio and 95% CI [RR (95% CI)] for golimumab 50 mg every 4 weeks + methotrexate vs. placebo + methotrexate ACR20 (14-24 wk): 1.53 (1.3-4.9) [4 studies] ACR 50 (14-24 wk): 2.57 (1.3-4.9) [4 studies] ACR70 (14-24 wk): 2.8 (1.3-5.98) [4 studies] Good EULAR response (14-24 wk): 1.47 (1.15-1.89) [4 studies] DAS Low Disease Activity (14-16 wk): 1.64 (1.15-2.34) [2 studies] DAS remission (risk difference): 0.10 (0.06 -0.14) [4 studies] HAQ change≥.22 (14 wk): 1.79 (1.38-2.31) [1 study] Change in HAQ score (14 wk): -0.25 (-0.29 to - 0.21) [1 study] HAQ scores (14 wk): -0.20 (-0.25 to -0.15) [1 study] Change in DAS scores (16 wk): -1.1 (-1.69 to -0.51) [1 study]
ADVERSE EVENTS:	Results reported as Risk Ratio and 95% CI [RR (95% CI)] for golimumab 50 mg every 4 weeks + methotrexate vs. placebo + methotrexate Adverse Events (16-24 wk) 1.05 (0.93, 1.18) [4 studies] Serious Adverse Events (16-24 wk) 1.05 (0.62, 1.78) [4 studies] Infections (16-24 wk) 1.03 (0.84, 1.25) [4 studies] Serious Infections (16-24 wk) 1.06 (0.40, 2.86) [4 studies] Tuberculosis (16-24 wk) 3.04 (0.12, 74.01) [4 studies] Lung Infections (16-24 wk) 0.97 (0.55, 1.70) [2 studies] Cancer (16-24 wk) 0.81 (0.16, 4.18) [4 studies] All Withdrawals (14-24 wk) 0.50 (0.31, 0.81) [4 studies] Withdrawals due to Adverse Events (14-16 wk) 0.56 (0.24, 1.29) [3 studies] Withdrawals due to Inefficacy (14-16 wk) 0.43 (0.15, 1.21) [3 studies] Death (24-52 wk) 1.02 (0.11, 9.71) [4 studies]
LIMITATIONS OF PRIMARY STUDIES	For the primary outcome of ACR50, there was statistically significant heterogeneity in the golimumab 50 mg and 100 mg every four weeks plus methotrexate versus placebo plus methotrexate groups with I2 values of 76%and 77% (P values of 0.005 for each). None of the studies were designed with safety as primary outcome.

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Solomon et al.**[181] **Year: 2006** **Country:** US	
FUNDING:	Engalitcheff Arthritis Outcomes Initiative; other relevant grant support was provided by the Arthritis Foundation, the NIH (grants K23-AR-48616, K24-02123, and P60-AR-47782), and research grants from Merck, Pfizer, and Savient.	
RESEARCH OBJECTIVE:	To investigate the effects of various immunosuppressive medications on the risk of cardiovascular events among a group of older patients with RA.	
DESIGN:	**Study design:** Nested case-control **Setting:** **Sample size:** 946 cases (266 on biologics monotherapy or biologics + MTX)	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Biologics monotherapy** NR N/A 149	**Biologics + MTX** NR N/A 117
INCLUSION CRITERIA:	The source cohort was derived from Medicare beneficiaries receiving a drug benefit from the state of Pennsylvania. These individuals were required to have been diagnosed as having RA on at least 2 visits and to have filled a prescription for an immunosuppressive agent. Cases were defined as those patients who were hospitalized for a cardiovascular event such as myocardial infarction or stroke.	
EXCLUSION CRITERIA:	NR	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs, coxib, clopidogrels, beta-blockers, statins	

Authors: Solomon et al. **Year: 2006**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** NR	
	Cases	
Mean age (years):	81	
Sex (% female):	89	
Ethnicity (% white):	93	
Other germane population qualities:		
• Tender joint count	NR	
• Swollen joint count	NR	
• Mean disease duration	NR	
• DMARD use (%)	NR	
• MTX use (%)	NR	
• Corticosteroids use (%)	NR	
• DAS score	NR	
• HAQ score	NR	
• Prior MI	99	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** cardiovascular events **Timing of assessments:** N/A	
RESULTS:	**Health Outcome Measures:** • **Adjusted risk for cardiovascular events**	
	Biologics monotherapy	**Biologics + MTX**
Total No.	149	117
No (%) of cases	12 (8.1)	8 (6.8)
Composite primary outcome	1.0 (0.5, 1.9)	0.8 (0.3, 2.0)
MI (OR compared with MTX)	1.7 (0.5, 5.7)	1.8 (0.5, 6.8)
Stroke (OR compared with MTX)	1.5 (0.6, 4.1)	1.3 (0.4, 4.0)

Authors: Solomon et al. **Year: 2006**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	N/A
Significant differences in adverse events:	
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	**Cannot determine**
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Strangfeld et al.[182]** **Year: 2010** **Study name:** **Country: Germany** **Quality rating: Fair**	
FUNDING:	Essex Pharma, Wyeth Pharma, Amgen/Biovitrum, Abbott, Bristol-Myers Squibb, Roche, UCB.	
RESEARCH OBJECTIVE:	To investigate the risk of new or recurrent malignancy in patients with RA receiving biologics compared to conventional DMARDs, and to study the risk of patients with a history of malignancy receiving anti-TNF therapy.	
DESIGN & SIZE:	**Study design:** Prospective cohort **Setting:** Germany (multicenter) **Sample size:** 5120	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Biologics** NR NR 1774	**Conventional DMARDs** NR NR 3346
INCLUSION CRITERIA:	Patients aged 18 to 75 years meeting the ACR criteria for RA, enrolled in German biologics register RABBIT between May 1, 2001 and December 31, 2006 (enrolled at the start of treatment with a biologic agent or a conventional DMARD after failure of at least one other DMARD). Patients had to have at least one follow-up visit and the baseline status regarding comorbid conditions had to be available in order to be included in analyses.	
EXCLUSION CRITERIA:	Missing follow-up information or missing co-morbid condition status.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

Authors: Strangfeld et al. **Year: 2010**	
POPULATION CHARACTERISTICS:	**Population**
Mean age (years):	Patients with prior malignancy: 63.7 (SD 8.4); Patients without prior malignancy: 54.4 (SD 12.1)
Sex (% female):	78.2%
Ethnicity:	NR
Class naïve:	NR
Other germane population qualities:	
• **Tender joint count**	NR
• **Swollen joint count**	NR
• **Mean disease duration**	Patients with prior malignancy: 9 (median); Patients without prior malignancy: 8 (median)
• **DMARD use (%)**	NR
• **MTX use (%)**	NR
• **Corticosteroids use (%)**	NR
• **DAS score**	Patients with prior malignancy: 5.6 (SD 1.2); Patients without prior malignancy: 5.5 (SD 1.3)
• **HAQ score**	NR
RESULTS:	**Primary Outcome Measures:** HRs of developing a malignancy, multivariate analysis: Ever exposed to: Conventional DMARDs only: Referent Anti-TNF agents: 0.70 (95% CI, 0.44 to 1.12), P=0.133 Anakinra: 1.39 (95% CI, 0.56 to 3.48), P=0.480

Authors: Strangfeld et al. **Year: 2010**			
METHOD OF ADVERSE EVENTS REPORTING:	At baseline and at predefined time points of follow-up (3, 6, 12, 18, 24, 30, 36, 48, 60 months) rheumatologists assessed the clinical status including serious and non-serious adverse events according to the International Conference on Harmonization E2A guidelines. All adverse events were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) by one of the authors. Reported malignancies were considered as *events of interest*, and an additional query asking for diagnostic and treatment details and cancer history was sent to the reporting rheumatologist.		
ADVERSE EVENTS (%):	**Anti-TNF (ever exposed to)**	**Anakinra (ever exposed to)**	**Conventional DMARD only**
Overall adverse effects reported:			
• infections	NR	NR	NR
• URTI	NR	NR	NR
• abnormal LFT	NR	NR	NR
• herpes simplex	NR	NR	NR
• pneumonia	NR	NR	NR
• tb	NR	NR	NR
• ISR	NR	NR	NR
• recurrence of prior malignancy, crude incidence rates	45.5 (95% CI, 20.8 to 86.3)/1,000 patient years	32.3 (95% CI, 0.8 to 179.7)/1,000 patient years	31.4 (95% CI, 10.2 to 73.4)/1,000 patient years
ATTRITION (*overall*):	**Overall attrition:** NA **Attrition differential high:** NA		
ATTRITION (*treatment specific*):	**Drug 1**	**Drug 2**	**Drug 3**
Attrition overall:	NA	NA	NA
Attrition due to adverse events:	NA	NA	NA

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Strangfeld et al.**[183] **Year: 2009** **Country:** Germany				
FUNDING:	RABBIT has been supported by an unconditional joint grant from Essex pharma (since 2001), Wyeth pharma (since 2001), Amgen (since January 2003), Abbott (since September 2003), Hoffmann-La Roche (since January 2007), and Bristol- Myers Squibb (since July 2007).				
RESEARCH OBJECTIVE:	To investigate whether TNFα inhibitors together as a class, or separately as either monoclonal anti– TNFα antibodies (ADA, INF) or a fusion protein (ETA), are related to higher rates of herpes zoster in patients with rheumatoid arthritis.				
DESIGN:	**Study design:** retrospective cohort **Setting:** Data from the German biologics register RABBIT, a prospective cohort **Sample size:** 5040				
INTERVENTION:	**ETA**	**INF**	**ADA**	**Total TNFα inhibitors**	**Controls**
Dose: **Duration:** **Sample size:**	N/A N/A 1252	N/A N/A 591	N/A N/A 1423	N/A N/A 3266	N/A N/A 1774
INCLUSION CRITERIA:	From May 1, 2001, to December 31, 2006, all patients with rheumatoid arthritis starting new treatment with either INF, ETA, ADA, or AKA and patients who were changing their DMARD treatment after at least 1 DMARD failure (control group) were asked by their rheumatologist to participate in the register. Once enrolled, data collection from the patients would continue until the end of 2011.				
EXCLUSION CRITERIA:					
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:					

Authors: Strangfeld et al. **Year: 2009**						
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe					
	ETA **N = 1252**	**INF** **N = 591**	**ADA** **N = 1423**	**Total** **N = 3266**	**Controls** **N = 1774**	***P* Value**
Age, mean (SD), y	53.8 (12.5)	52.9 (12.7)	54.2 (12.0)	53.8 (12.3)	56.2 (11.4)	.001
Women, No. (%)	975 (77.8)	433 (73.3)	1141 (80.2)	2549 (78.0)	1394 (78.6)	.66
Rheumatoid factor–positive, No. (%)	1008 (80.5)	469 (79.4)	1143 (80.4)	2620 (80.3)	1271 (71.7)	.001
FFbH score, mean (SD) b	56.0 (22.9)	55.3 (21.6)	58.6 (23.4)	57.0 (22.9)	66.6 (21.5)	.001
Disease duration, median (IQR), y	9 (4-16)	8.5 (4-14)	10 (5-17)	9 (5-16)	6 (3 -12)	.001
DAS28, mean (SD)	5.8 (1.3)	5.9 (1.2)	5.7 (1.3)	5.8 (1.3)	5.0 (1.3)	.001
CRP, median (IQR), mg/L	16 (5-37)	17 (7-41)	13 (5-30)	17 (8-38)	8 (3-22)	.001
Previous DMARD therapies, No. (%)	3.6 (1.4)	3.7 (1.5)	3.5 (1.4)	3.5 (1.4)	1.8 (1.1)	.001
Glucocorticoids, No. (%)	1073 (86.1)	498 (84.4)	1154 (81.6)	2725 (83.8)	1354 (76.5)	.001
Prednisolone 10 mg/d, No. (%)	440 (35.1)	217 (36.7)	416 (29.2)	1073 (32.9)	343 (19.3)	.001
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Hazard ratio (HR) of herpes zoster episodes following anti– TNFα treatment. **Secondary Outcome Measures:** **Timing of assessments:**					
RESULTS:	**Health Outcome Measures:**					

	• Incidence rates for episodes of herpes zoster during anti–TNFα treatment and DMARD treatment were 9.8 (95% CI, 7.5-12.6) per 1000 patient-years and 5.1 (95% CI, 3.2-7.8) per 1000 patient-years. • For the monoclonal antibodies and ETA, the rates were 11.1 (95% CI, 7.9-15.1) per 1000 patient-years and 8.1 (95% CI, 5.0-12.4) per 1000 patient-years, respectively. • In subgroup analysis, no significantly increased risk of herpes zoster for patients treated with ETA were found, whereas patients treated with either INF or ADA had a significantly increased risk (HR, 1.82 [95% CI, 1.05-3.15]) (Table 3), although this risk was lower than the study's predefined HR threshold of 2.5 for clinical significance. • Univariate Cox regression analysis showed risk of herpes zoster with DMARDs: (HR, 1 [Reference]; Anti–TNFα agents: (HR, 1.84 [95% CI, 1.13-3.00], ETA: (HR, 1.55 [95% CI, 0.85-2.82]; ADA/INF: (HR, 2.05 (95% CI, 1.22-3.45)

Authors: Strangfeld et al. **Year: 2009**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	**drug 1**	**drug 2**	**drug 3**
Significant differences in adverse events:			
ANALYSIS:	**ITT:** **Post randomization exclusions:**		
ARE GROUPS COMPARABLE AT BASELINE:	Yes		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall attrition:** **Attrition differential high:**		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**drug 1**	**drug 2**	**drug 3**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Suissaet al.**[184] **Year: 2006** **Country:** Canada		
FUNDING:	Sanofi-Aventis, the Canadian Institutes of Health Research, the Fonds de la recherché en sante´ du Que´bec, and Bristol-Myers Squibb		
RESEARCH OBJECTIVE:	To assess the risk of acute myocardial infarction (AMI) associated with the use of disease-modifying antirheumatic drugs (DMARDs) and other medications commonly used in rheumatoid arthritis (RA).		
DESIGN:	**Study design:** nested case-control **Setting:** Canada **Sample size:** 6138 (from a cohort of 107,908)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**drug 1**	**drug 2**	**drug 3**
INCLUSION CRITERIA:	≥18 years old, diagnosis of RA (ICD-9 code 714) between January 1999 and December 2003. Cohort entry was the date of the first prescription for an anti-RA medication after January 1, 1999		
EXCLUSION CRITERIA:	AMI, old AMI		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	No restrictions		

Authors: Suissa et al. **Year: 2006**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **Disease severity:** Mild-moderate-severe	
	AMI	**controls**
Mean age (years):	65 (12)	65 (12)
Sex (% female):	55	55
Ethnicity:	NR	NR
Other germane population qualities:		
• Tender joint count	NR	NR
• Swollen joint count	NR	NR
• Mean disease duration	NR	NR
• DMARD use (%)	37	39
• MTX use (%)	NR	NR
• Corticosteroids use (%)	NR	NR
• DAS score	NR	NR
• HAQ score	NR	NR
• Ischaemic heart disease	19	8
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** the rate ratio (RR) of AMI for each of the anti-RA medication classes, including biologic agents (with or without other DMARDs but not leflunomide) **Secondary Outcome Measures:** N/A **Timing of assessments:** NR	
RESULTS:	**Health Outcome Measures:** • The adjusted RR of an AMI for the current use of biologic agents (RR 1.30, 95% CI 0.92–1.83) • adjusted RR ETA 0.63 (95% CI 0.34–1.17) & INF 1.58 (95% CI 0.82–3.05) **Intermediate Outcome Measures:**	

Authors: Suissa et al. **Year: 2006**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	NA
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	NA
QUALITY RATING:	**Fair**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Suissa et al.**[185] **Year: 2004** **Country:** USA/Canada	
FUNDING:	Aventis	
RESEARCH OBJECTIVE:	Risk of hepatic events associated with the use of leflunomide and other DMARDs in patients with Rheumatoid Arthritis	
DESIGN:	**Study design:** retrospective nested case-control **Setting:** inpatient or outpatient encounter between January 1, 1998, and December 31, 2001 (Protocare longitudinal health benefit claims database, PharMetrics Integrated Outcomes Database) **Sample size:** 1402	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** NR NR NR	**INF** NR NR NR
INCLUSION CRITERIA:	use of leflunomide, methotrexate, gold compounds, anti–tumor necrosis factor α agents, antimalarials, minocycline, chelating agents, sulfasalazine, or cytotoxics, 18 years or older	
EXCLUSION CRITERIA:	less than 3 months of eligibility in the health insurance plan before cohort entry with the outcome of interest during the 3-month period before cohort entry	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:		

Authors: Suissa et al. **Year: 2004**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** N/A	
	PharMetrics	Protocare
	33,009	8876
Mean age (years):	49	59
Sex (% female):	75	76
Ethnicity:		
Other germane population qualities:		
• DMARD use (%)	100	99.5
• MTX use (%)	45	57
• Leflunomide(%)	14	6
• Biologic DMARD	4	0.5
• Other DMARD	37	36
• Leflunomide use at any time during follow-up (%)	16	14
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Hepatic events, subacute liver necrosis (ICD 9 code 570), cirrhosis without use of alcohol (ICD 9 code 571.5), hepatic coma (ICD 9 code 572.2), and toxic, noninfectious hepatitis (ICD 9 code 573.3)	
RESULTS:	**Health Outcome Measures:** • 25 cases of serious hepatic events, for an overall rate of 4.9 per 10,000 per year. • 411 nonserious hepatic events, for a rate of 80.0 per 10,000 per year **serious hepatic events** • biologic DMARDs (RR = 5.5; 95% CI: 1.2 to 24.6) **nonserious hepatic events** • biologic DMARDs (RR = 1.5; 95% CI: 1.0 to 2.3)	

Authors: Suissa et al. **Year: 2004**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	See Results
Significant differences in adverse events:	Fivefold increase in the risk of serious hepatic events associated with the use of biologic DMARDs significant for nonserious hepatic events not requiring hospitalization.
ANALYSIS:	**ITT:** **Post randomization exclusions:**
ARE GROUPS COMPARABLE AT BASELINE:	Subjects from the Protocare cohort were about 10 years older than those from the PharMetrics cohort
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** NA **Attrition differential high: NA**
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	NA
QUALITY RATING:	**NA**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Takeuchi et al.**[186] **Year: 2008** **Country:** Japan
FUNDING:	Tanabe Seiyaku Co., Ltd
RESEARCH OBJECTIVE:	Safety of INF in patients with RA
DESIGN:	**Study design:** Observational – postmarketing surveillance study **Setting:** Multicenter **Sample size:** 5000
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 3 mg/kg at weeks 0,2,6 and then every 8 weeks 6 months 5000
INCLUSION CRITERIA:	All patients treated with INF between July /2003 and Dec 2004 with active disease despite treatment with MTX of greater than 6 mg /week for at least 3 months
EXCLUSION CRITERIA:	N/A – but in order for institutions to prescribe INF they had to agree to participate fully in this study.
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes

Authors: Takeuchi et al. **Year: 2008**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe
	INF
Mean age (years):	55.1 years
Sex (% female):	79
Ethnicity:	NR – assume Asian 100%
Other germane population qualities:	3.1
• Hepatic disorder	2.5
• Cardiac disorder	9.4
• Diabetes Mellitus	4.7
• Respiratory disease	1.2
• Haematological disease	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Adverse events and adverse drug reactions were compared to a clinical trial that was conducted in Japan
RESULTS:	**Health Outcome Measures:** **See adverse events and risk factors for bacterial pneumonia** OR 95% CI Comorbid Respiratory disease Yes vs. none 3.90 (2.35–6.47) $P < 0.001$ Male vs. female 1.94 (1.29–2.93) $P = 0.001$ 40s and under vs. 50s 0.25 (0.10–0.66) 50s 1.00 (reference) , $P < 0.001$ 60s vs. 50s 1.90 (1.18–3.07) 70s and over vs. 50s 2.57 (1.48–4.45)

Authors: Takeuchi et al. **Year: 2008**		
ADVERSE EVENTS: **Overall adverse effects reported:** • Serious ADRs • ADRs Per 100 pt/yrs • infections • Serious infections	**PMS n = 5000** 28% 6.2 59.38 (59.07 to 59.69) 18.35 (18.18 to 18.52) 8.56 (8.44-8.68)	**Japanese clinical trial n = 141** 67.4 10.6 72.16 (70.1 to 73.61) 39.50 (38.4 to 40.57) 8.36 (7.87-8.85)
Significant differences in adverse events:	N/A	
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A	
ARE GROUPS COMPARABLE AT BASELINE:	Yes	
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	NR	
STATISTICAL ANALYIS ADEQUATE:	Yes	
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A	
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A	
QUALITY RATING:	N/A	

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Tsai et al.**[187] **Year: 2011** **Study name: PEARL** **Country: Taiwan and Korea** **Quality rating: Fair**	
FUNDING:	Centocor, Inc.	
RESEARCH OBJECTIVE:	To assess the efficacy and safety of ustekinumab in Taiwanese and Korean patients with moderate-to-severe psoriasis.	
DESIGN & SIZE:	**Study design:** Placebo-controlled trial **Setting:** Multicenter **Number screened:** NR **Number enrolled:** 159 **Number randomized:** 121 **Run-in/Wash-out period:** NR	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Ustekinumab** 45 mg at weeks 0, 4, 16 36 weeks (*only week 12 results, before placebo cross-over, are reported here*) 61	**Placebo** Placebo at weeks 0, 4 (*cross-over to ustekinumab 45 mg at weeks 12 and 16 are not reported here*) 36 weeks (*only week 12 results, before cross-over to ustekinumab, are reported here*) 60
INCLUSION CRITERIA:	Adults (age 20 years or older) of Korean or Taiwanese ancestry with a diagnosis of moderate-to-severe plaque psoriasis. At baseline, patients were required to have a Psoriasis Area and Severity Index (PASI) of at least 12, to have at least 10% of their body surface area affected by their psoriasis, and be candidates for systemic or phototherapy.	
EXCLUSION CRITERIA:	Patients who received biologic psoriasis therapy within 3 months, systemic psoriasis medications or phototherapy within 4 weeks, or topical psoriasis medications within 2 weeks of randomization. Patients with a previous history of chronic or recurrent infectious disease or a history of malignancy. Patients with newly identified latent TB were only eligible if active TB was ruled out and appropriate treatment was initiated either prior to, or simultaneously with, the first administration of study agent.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

Authors: Tsai et al. **Year: 2011**	
POPULATION CHARACTERISTICS:	**Population**
Mean age (years): **Sex (% female):** **Ethnicity (%):** **Class naïve:** Other germane population qualities: • **Mean PASI** • **Mean body surface area involvement (%)** • **Mean duration of psoriasis** • **Received prior systemic therapy (%)**	40.6 14.9 Taiwanese/Chinese: 49.6 Korean: 50.4 NR 24.1 38.8 12.9 71.1
RESULTS:	**Primary Outcome Measures:** Placebo vs Ustekinumab 45mg Clinical responses at week 12: PASI 50: 8 (13.3%) vs 51 (83.6%); P<0.001 PASI 75: 3 (5.0%) vs 41 (67.2%); P<0.001 PASI 90: 1 (1.7%) vs 30 (49.2%); P<0.001 PASI 100: 0 (0.0%) vs 5 (8.2%); P=0.024 **Secondary Outcome Measures:** Physician's Global Assessment at week 12: Cleared or minimal: 5 (8.3%) vs 43 (70.5%); P<0.001 Cleared: 0 (0.0%) vs 17 (27.9%); P<0.001 Change in Dermatology Life Quality Index from baseline to week 12: Mean (SD): -0.5 (6.5) vs -11.2 (7.1) Median: 0.0 vs -11.0; P<0.001

Authors: Tsai et al. **Year: 2011**		
METHOD OF ADVERSE EVENTS REPORTING:	Adverse events, including TB, were routinely monitored, and standard laboratory parameters were assessed at each study visit through week 36.	
ADVERSE EVENTS (%):	**Placebo**	**Ustekinumab**
Overall adverse effects reported (week 12):	70%	65.6%
• infections	23.3%	32.8%
• URTI	11.7%	11.5%
• abnormal LFT	3.3%	0.0%
• herpes simplex	NR	NR
• pneumonia	NR	NR
• tb	NR	NR
• ISR	5.0%	1.6%
• pruritus	26.7%	8.2%
• psoriasis	10.0%	3.3%
• serious adverse events	3.3%	0.0%
ATTRITION (*overall*):	**Overall attrition:** 7.4% **Attrition differential high:** No	
ATTRITION (*treatment specific*):	**Placebo**	**Ustekinumab**
Attrition overall:	8.3% (week 12)	6.6% (week 12)
Attrition due to adverse events:	5% (week 12)	0% (week 12)

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Virkki et al.**[188] **Year: 2010** **Study name: ROB-FIN** **Country:** Finland **Quality rating: Fair**	
FUNDING:	Victoria Foundation, the Wilhelm and Else Stockmann Foundation, the Waldemar von Frenckell Foundation, Finska Läkaresällskapet, the Perklen Foundation, the Sigrid Jusélius Foundation, the Center of Excellence of the Academy of Finland, ORTON Foundation, EVO grants and the TBGS National Graduate School of Musculoskeletal Disorders and Biomaterials. The ROB-FIN register was financially supported by grants from Abbott, Roche, Schering-Plough, UCB, and Wyeth.	
RESEARCH OBJECTIVE:	Performance of biological drugs in psoriatic arthritis (PsA) in a routine care setting, using the Finnish national register of biological treatment (ROB-FIN).	
DESIGN & SIZE:	**Study design:** Prospective cohort study **Setting:** Outpatient rheumatology clinics of central or regional hospitals **Number screened: 154** **Number eligible: 127** **Number enrolled: 115 analyzed** **Run-in/Wash-out period: None**	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Infliximab** 5mg/kg at 0, 2, and 6 weeks and then every 8 weeks. Up to 2 years 39	**Etanercept** 25 MG 2 times a week Up to 2 years 76
INCLUSION CRITERIA:	Patients starting biological therapy between June 2000 and February 2006 were included if the patient had been diagnosed with psoriatic arthritis; and if a baseline report, i.e., patient demographic data and disease profile at commencement of biological therapy	
EXCLUSION CRITERIA:	None	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes	

Authors: Virkki et al. **Year: 2010**	
POPULATION CHARACTERISTICS:	Overall
Mean age (years): **Sex (% female):** **Ethnicity:** **Class naïve:** Other germane population qualities: • **DMARD use (%)** • **MTX use (%)** • **Corticosteroids use (%)**	Median 50 40.9 NR NR 84 51 40
RESULTS:	**Primary Outcome Measures:** Article reports at 3 months ACR 20 Inliximab 79% (22/28) Etanercept 76% (34/45) ACR 50 Infliximab 64% (18/28) etanercept 49% (22/45)

Authors: Virkki et al. **Year: 2010**			
METHOD OF ADVERSE EVENTS REPORTING:	AEs are reported in Konttinen L, Honkanen V, Uotila T, Pöllänen J, Waahtera M, Romu M, et al. Biological treatment in rheumatic diseases: results from a longitudinal surveillance: adverse events. Rheumatol Int 2006; 26:916-22.		
ADVERSE EVENTS (%):			
Overall adverse effects reported:	Overall adverse events and withdrawals due to adverse events similar: Injection-site reactions more frequent with etanercept than ustekinumab		
ATTRITION (*overall*):	**Overall attrition:** 3 months 118/127 **Attrition differential high:** No		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**Infliximab** 28/39	**Etanercept** 45/76	**Infliximab and etanercept**

URTI: upper respiratory tract infection; LFT: liver function test; ISR: injection site reaction; tb: tuberculosis

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Weinblatt et al.**[54] **Year: 2007** **Country:** Multicenter US		
FUNDING:	Bristol-Myers Squibb		
RESEARCH OBJECTIVE:	Efficacy and safety of ABA in combination with ETA in active RA		
DESIGN:	**Study design:** RCT with an open-label long-term extension (LTE) phase **Setting:** Multicenter (40 centers in the US) **Sample size:** 121(2:1 ratio), LTE 80		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ABA + ETN 25 mg twice wkly** 2 mg/kg intravenously on days 1, 15, 30, every 4 weeks 6 months 85	**Placebo + ETN 25 mg twice wkly** 6 months 36	LTE **ETN 25 mg twice wkly+abatacept 10 mg/kg** 80
INCLUSION CRITERIA:	>18 years of age and met the criteria of the American College of Rheumatology (ACR) for RA, functional class I, II or III. Patients must have received ETA 25 mg twice weekly for >3 months, >8 swollen joints (66-joint count) and >10 tender joints (68-joint count).		
EXCLUSION CRITERIA:	Active or latent infection, recent opportunist infection, TB requiring treatment within the previous 3 years, history of cancer within the previous 5 years or history of drug or alcohol misuse. Pregnant and nursing women		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Low-dose corticosteroids (≤10 mg/day) or NSAIDs stable during the study (6mo). hydroxychloroquine, sulfasalazine, leflunomide or MTX was allowed after 6 months (LTE)		

<table>
<tr><td colspan="3">Authors: Weinblatt et al.
Year: 2007</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: Yes
Disease severity: active RA</td></tr>
<tr><td></td><td><u>ABA</u></td><td><u>Placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>49.8 (23–73) 1</td><td>54.3 (28–71)</td></tr>
<tr><td>Sex (% female):</td><td>78</td><td>72</td></tr>
<tr><td>Ethnicity/Caucasian%:</td><td>94</td><td>100</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td></tr>
<tr><td>• Tender joint count</td><td>28.7 (14)</td><td>29.2 (13.2)</td></tr>
<tr><td>• Swollen joint count</td><td>19.6 (9.4)</td><td>20.1 (10.5)</td></tr>
<tr><td>Mean disease duration years</td><td>13 (10.1)</td><td>12.8 (8.6)</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: of the double-blind phase: modified ACR20 response rate at 6 months. of the of the LTE: safety and tolerability of abatacept in combination with ETA during long-term administration
Secondary Outcome Measures: double-blind phase: modified ACR 50 response at 6 months
Timing of assessments: RCT at 6 mo, LTE at 1 year</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures: ABA 2 mg/ kg and ETA vs. placebo and ETA at 6 mo
ACR 20 48.2% vs. 30.6%; P = 0.072
ACR 50 25.9% vs. 19.4% P = 0.448
ACR 70 10.6% vs. 0% P = 0.042
ABA 2 mg/ kg and ETA vs. placebo and ETA at 1 year
ACR 20 48.2% vs. 30.6%
ACR 50 28.2% vs. 16.7%
ACR 70 9.4% vs. 5.6% P = 0.481

Modified HAQ response Change (from baseline to 1 year) abatacept 2 mg/ kg and ETA vs. placebo and ETA
- 0.3 (0.5) vs - 0.2 (0.4)</td></tr>
</table>

Authors: Weinblatt et al. **Year: 2007**			
ADVERSE EVENTS:	**ABA**	**Placebo**	**LTE**
Overall adverse effects reported:	79 (92.9)	32 (88.9)	78 (97.5)
• URTI	20 (23.5)	5 (13.9)	23 (28.8)
• Serious infections	3 (3.5)	0	1 (1.3)
• Discontinuations due to AEs	10 (11.8)	1 (2.8)	8 (10)
• Deaths	0	0	1 (1.3)
Significant differences in adverse events:	Yes		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 1 pt.		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 34 **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*):	**ABA**	**Placebo**	
Loss to follow-up:	20	14	
Withdrawals due to adverse events:	6	1	
QUALITY RATING:	**Fair**		

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Wolfe and Michaud** [189] **Year: 2007** **Country:** USA
FUNDING:	Grant support from Abbott, Amgen, Wyeth-Australia, Merck, and Pfizer.
RESEARCH OBJECTIVE:	To ascertain the relationship between anti–tumor necrosis factor (anti-TNF) therapy, MTX (MTX), and the risk of lymphoma in patients with rheumatoid arthritis
DESIGN:	**Study design:** Retrospective cohort **Setting:** Rheumatology practices **Sample size:** 190591
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Participants** Various on-going 19591
INCLUSION CRITERIA:	Patients in the study were participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of the outcomes of RA, who completed semiannual questionnaires in the period from 1998 through 2005. Patients were recruited on an ongoing basis from the practices of US rheumatologists
EXCLUSION CRITERIA:	N/A
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A

Authors: Wolfe and Michaud **Year: 2007**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe
	Participants
Mean age (years):	59
Sex (% female):	77.2
Ethnicity:	NR
Other germane population qualities:	
• Mean disease duration	14.1 yrs
• Biologic agent use	55.3%
• INF use	40.3%
• ETA use	7.6%
• ADA use	68.0%
• MTX use	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Odds and rate of lymphoma
RESULTS:	**Health Outcome Measures:** Overall- lymphoma IR 105.9 (95% CI 86.6–129.5) per 100,000 person-years of exposure vs. SEER IR 1.8 (95% CI 1.5–2.2). OR anti-TNF therapy vs. not anti-TNF therapy was 1.0 (95% CI 0.6–1.8 [*P* _ 0.875]). OR for lymphoma anti-TNF plus MTX vs. MTX treatment alone was 1.1 (95% CI 0.6–2.0 [*P* = 0.710]).

Authors: Wolfe and Michaud **Year: 2007**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	See Results
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** No **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	N/A
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N//A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Good**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Wolfe et al.**[190] **Year: 2004** **Country:** Multinational	
FUNDING:	Centocor	
RESEARCH OBJECTIVE:	To determine the baseline rate of TB in RA prior to the introduction of infliximab and to determine the rate of TB among those currently receiving inf.	
DESIGN:	**Study design:** Observational- prospective cohort study **Setting:** Multicenter **Sample size:** 17,242	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	Pre-INF Various N/A 10,782	INF Various 2.5 years 6,640
INCLUSION CRITERIA:	RA and use of inf	
EXCLUSION CRITERIA:	N/A	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

Authors: Wolfe et al. **Year: 2004**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes with slight exceptions in age and sex **Disease severity:** N/A	
	Pre-INF	INF
Mean age (years):	59.8	61.4
Sex (% female):	76.9	73.5
Ethnicity (% white):	NR	NR
	90.9	94.4
Other germane population qualities:		
• Corticosteroid use (%)	54.6	50.4
• MTX use (%)	47.9	74.6
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** TB **Timing of assessments:** N/A	
RESULTS:	**Health Outcome Measures:** ▪ In the pre-inf group, 1 case of TB developed during 16,173 patient-years of follow-up, yielding a rate of 6.2 cases (95% CI 1.6-34.4) per 100,000 patient years. ▪ In the inf group, the TB incidence rate among patients was 61.9 cases per 100,000 patient years. ▪ None of the TB patients had undergone a TB skin test and no cases of TB occurred in the 44-59% that had received the test.	

Authors: Wolfe et al. **Year: 2004**	
ADVERSE EVENTS: **Overall adverse effects reported:**	Pre-INF or INF N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ADEQUATE RANDOMIZATION:	N/A
ADEQUATE ALLOCATION CONCEALMENT:	N/A
BLINDING OF OUTCOME ASSESSORS:	N/A
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	INF N/A N/A
QUALITY RATING:	**Fair**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Wolfe et al.**[191] **Year: 2007** **Country:** US
FUNDING:	
RESEARCH OBJECTIVE:	**Biologic Treatment of Rheumatoid Arthritis and the Risk of Malignancy**
DESIGN:	**Study design:** Observational study **Setting:** Registry, members of the US National Data Bank for Rheumatic Diseases (NDB) from the practices of US rheumatologists **Sample size:** 13,001 (6,282 received biologics)
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Biologics** various 3 years 6282
INCLUSION CRITERIA:	1 cancer-free phase before study participation and at least 2 observations
EXCLUSION CRITERIA:	For each specific cancer, patients with that preexisting cancer were excluded from the specific analysis of that cancer
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Prednisone , MTX , Leflunomide , Sulfasalazine , HCQ

Authors: Wolfe et al. **Year: 2007**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** NR
Mean age (years): **Sex (% female):** **Ethnicity:** White, not Hispanic origin **Other germane population qualities:** • Mean disease duration • MTX use (%) • Corticosteroids use (%) • Leflunomide • Sulfasalazine • HCQ • INF • ETA • ADA • AKA	58.5+/-13.1 78 92.5 16.7 +/- 12.7 56.9 45.6 18.7 9.4 25.2 19.9 7.6 0.4 0.3
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** 1) rate of malignancy in RA 2) all biologic therapies considered as a group Duration of fu 3.0 years
RESULTS:	**Health Outcome Measures:** 1) no increase in the overall rate of cancer in participating RA patients compared with SEER (Surveillance, Epidemiology, and End Results) data (SIR 1.0, 95% CI 1.0–1.1) lymphoma SIR 1.7, 95% CI 1.3–2.2 melanoma SIR 1.7, 95% CI 1.3–2.3 lung cancer SIR 1.2 95% CI 1.0–1.4 breast cancer SIR 0.8, 95% CI 0.6–0.9 colon cancer SIR 0.5, 95% CI 0.4–0.6 2) risk of nonmelanotic skin cancer (OR 1.5 [95% CI 1.2–1.8]) and possibly of melanoma (OR 2.3 [95% CI 0.9–5.4], *P* = 0.070) OR for all cancers overall 1.0 (95% CI 0.8–1.2) **Melanoma**: INF (OR 2.6 [95% CI 1.0–6.7], *P* = 0.056), ETA (OR 2.4 [95% CI 1.0–5.8], *P* = 0.054) **non-melanotic skin cancer**: INF (OR 1.7 [95% CI 1.3–2.2], *P* < 0.001), ETA (OR 1.2 [95% CI 1.0–1.5], *P* = 0.081)

Authors: Wolfe **Year: 2007**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	**See Results**
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	**NA**
QUALITY RATING:	**Good**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Wolfe et al.**[192] **Year: 2004** **Country:** U.S.
FUNDING:	Centocor, Inc.
RESEARCH OBJECTIVE:	To determine the frequency of heart failure in patients with RA, and to determine its predictors, particularly the use of anti-TNF therapy.
DESIGN:	**Study design:** retrospective cohort study **Setting:** Multicenter (National Data Bank for Rheumatic Diseases) **Sample size:** 13,171
INTERVENTION: **Dose:** **Duration:** **Sample size:**	Multiple
INCLUSION CRITERIA:	Participation in the National Data Bank for Rheumatic Diseases study of the outcomes of arthritis; patient at participating rheumatology clinic;
EXCLUSION CRITERIA:	NR
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A

Authors: Wolfe et al.
Year: 2004

POPULATION CHARACTERISTICS:

Groups similar at baseline: N/A
Disease severity: NR

	Total population	Anti-TNF	INF	ETA	No anti-TNF
Mean age (years):	61	60	61.5	56.7	61.5
Sex (% female):	77	78	77	80	76
Ethnicity: % white	94	95	96	92	92
Other germane population qualities:					
• Mean disease duration	14.9	14.2	13.8	15.2	15.5
• DMARD or anti-TNF use (%)	86	NR	NR	NR	NR
• MTX use (%)	56	67	76	44	47
• Prednisone use (%)	39	47	49	39	33
• DAS score	3.6	3.7	3.7	3.6	3.5
• HAQ score	1.1	1.2	1.2	1.1	1.0

OUTCOME ASSESSMENT:

Primary Outcome Measures: NR
Secondary Outcome Measures: NR
Timing of assessments: Every 6 months for a total of 2 years.

RESULTS:

Health Outcome Measures:

- There were 461 cases of heart failure in the 13,171 patients with RA (overall risk of 3.5%); after adjusting for demographic characteristics the risk was 3.9% (95% CI = 3.4% to 4.3%).
- Among all cases of heart failure, patients receiving anti-TNF therapy were less likely to have heart failure than those not receiving anti-TNF therapy (-1.2%; 95% CI -1.9 - -0.5%)
- Overall, the adjusted frequency of heart failure was 2.8% in those treated with anti-TNF vs. 3.9% in the remaining patients ($P = 0.03$).
- Frequency of heart failure was 5.2% in men and 3.0% in women.
- In examining incident cases of heart failure in patients under age 50, no increase was found (0/1569 patients using anti-TNF vs. 3/1401 most using anti-TNF therapy).

Authors: Wolfe et al. **Year: 2004**				
ADVERSE EVENTS: **Overall adverse effects reported:**	**All Anti-TNF**	**INF**	**ETA**	**No Anti-TNF**
• All Heart Failure: adjusted rate	2.8	2.6	2.9	3.4 to 3.9
• Incident Heart Failure: adjusted rate	0.2	0.2	0.3	0.2 to 0.3
Significant differences in adverse events:	No			
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A			
ARE GROUPS COMPARABLE AT BASELINE:	Yes			
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes			
STATISTICAL ANALYIS ADEQUATE:	Yes			
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR			
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	NR			
QUALITY RATING:	**Fair**			

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Wolfe et al.**[193] **Year: 2006** **Country:** US
FUNDING:	Bristol-Meyers-Squibb
RESEARCH OBJECTIVE:	To evaluate the treatment of RA and the risk of hospitalization for pneumonia
DESIGN:	**Study design:** Prospective cohort study **Setting:** Rheumatology clinics **Sample size:** 16,788
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Various RA treatments** NR NR NR
INCLUSION CRITERIA:	Participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of RA outcomes including 5,317 enrolled as part of an INF safety registry and 1,852 as part of a leflunomide safety registry.
EXCLUSION CRITERIA:	N/A
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes

Authors: Wolfe et al. **Year: 2006**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe
	Cohort
Mean age (years):	62.0
Sex (% female):	77.2
Ethnicity:	89.7% white, 4.8% black, 3.0% Hispanic, 1.0 Asian/Pacific Islander, 1.1% American Indian or Alaskan native, 0.5% Other
Other germane population qualities:	
• Mean disease duration	16.3 years
• DMARD use (lifetime #)	3.3
• MTX use (%)	54.5
• Prednisone use (%)	38.1
• HAQ score	1.1
• MTX (%)	54.5
• Hydroxychloroquine (%)	17.7
• Leflunomide (%)	14.4
• Sulfasalazine (%)	5.7
• INF (%)	36.9
• ETA (%)	12.8
• ADA (%)	4.3
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Hospitalization for pneumonia and the variables that effect this
RESULTS:	**Health Outcome Measures:** Effect of treatment variables on the risk of pneumonia (adjusted for demographic variables-age, sex, smoking, education, and enrollment) • Prednisone HR 1.7 [95% CI 1.5-2.1]) • Leflunomide HR 1.3 [95% CI 1.0-1.5], *P* = 0.036), • Sulfasalazine HR 0.7 [95% CI 0.4-1.0], *P* = 0.053). • ETA HR 0.8 [95% CI 0.6-1.0], *P* = 0.051).

Authors: Wolfe et al. **Year: 2006**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	**N/A**
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	N/A
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:**
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	N/A
QUALITY RATING:	**Fair**

Evidence Table 8. Targeted Immune Modulators – Adverse Events

STUDY:	**Authors: Zink et al.**[194] **Year: 2005** **Country:** Germany	
FUNDING:	Essex Pharma, Wyeth Pharma, Amgen, and Abbott	
RESEARCH OBJECTIVE:	To compare drug continuation rates in patients with RA who start on a biological agent or on a DMARD after previous DMARD failure.	
DESIGN:	**Study design:** retrospective cohort study **Setting:** Clinical **Sample size:** 1523	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Biologics** Varied 1 year 924	**DMARDs** Varied 1 year 599
INCLUSION CRITERIA:	18 - 75 years old; meeting ACR criteria for RA; "cases" if a new treatment with INF, ETA, or AKA; "controls" if a conventional DMARD treatment was begun after failure of at least one previous therapy	
EXCLUSION CRITERIA:	N/A	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

Authors: Zink et al.
Year: 2005

POPULATION CHARACTERISTICS:

Groups similar at baseline: No
Disease severity: Mild-moderate-severe

	ETA n=511	INF n=343	AKA n=70	Total Control Group n=599	Leflunomide n=120	Leflunomide+ MTX n=141
Mean age (years):	53.7	53.6	54.3	56.5	58.0	57.4
Sex (% female):	77.9	71.1	77.1	82.8	85.8	78.0
Ethnicity:	NR	NR	NR	NR	NR	NR
Other germane population qualities:						
• TJC	13.3	12.6	12.6	10.0	10.6	10.9
• SJC	10.4	10.7	10.2	7.7	7.4	8.5
• Mean disease duration	9.0	8.5	13.0	6.0	9.0	7.0
• Previous DMARD use (#)	3.9	3.7	4.2	2.1	2.4	2.2
• MTX use (%)	91.2	92.1	78.6	68.7	94.2	90.7
• Corticosteroids use (%)	NR	NR	NR	NR	NR	NR
• DAS score	6.1	6.0	6.1	5.4	5.5	5.6

OUTCOME ASSESSMENT:

Primary Outcome Measures: Treatment continuation at one year

Secondary Outcome Measures: Treatment continuation at 6 months

Timing of assessments: At each visit and every 6 months

RESULTS:

Health Outcome Measures:

- Treatment continuation at one year- ETA 68.6% (95% CI 62-75)) INF 65.4% (95% CI 58-73) AKA 59% (95% CI 41-77). AKA vs. ETA $P = 0.004$; $P = 0.03$ AKA vs. INF $P = 0.03$
- After 12 months, treatment discontinuation because of adverse events: INF: 18.7%; ETA: 12.6%; AKA: 16.3%

Authors: Zink et al. **Year: 2005**			
ADVERSE EVENTS: **Overall adverse effects reported:**	NR		
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	Yes		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*):	**ETA**	**INF**	**AKA**
Loss to follow-up:	31.4	34.6	41
Withdrawals due to adverse events:	12.6	18.7	16.3
QUALITY RATING:	**Fair**		

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Chung et al**.[144] **Year: 2003** **Country:** US		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To assess the effectiveness and safety of infliximab in patients with CHF		
DESIGN:	**Study design:** RCT **Study name: ATTACH (Anti-TNF Therapy Against Congestive Heart Failure)-Trial** **Setting:** University clinics (32 centers) **Sample size:** 150		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 28 weeks 49	**INF** 5 mg/kg 28 weeks 50	**INF** 10 mg/kg 28 weeks 51
INCLUSION CRITERIA:	Men and women at least 18 years old with stable New York Heart Association (NYHA) class III or IV heart failure associated with a radionuclide left ventricular ejection fraction ≤ 35% within 14 days before randomization		
EXCLUSION CRITERIA:	Hemodynamically significant obstructive valvular disease, cor pulmonale, restrictive or hypertrophic cardiomyopathy, constrictive pericarditis, or congenital heart disease; had experienced an acute myocardial infarction or coronary revascularization procedure within 2 months; or were likely to undergo coronary revascularization or heart transplant during the anticipated duration of the study; resuscitation from sudden death or a therapeutic discharge of an implanted implantable cardioverter defibrillator within 3 months or had received within 2 weeks or were likely to receive within the following 28 weeks any of the following: A class IC or III antiarrhythmic other than amiodarone; a calcium channel blocker other than amlodipine for hypertension or angina; a positive inotrope other than digoxin; or a NSAID other than aspirin; experienced a serious infection within 2 months; had latent TB or had had TB within 3 years; had a documented HIV infection; or had any other opportunistic infection within 6 months; treatment within 3 months of INF or other therapeutic agents that could interfere with the actions of TNFα (eg, ETA, pentoxifylline, thalidomide, or D2E7)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Vasodilators or nitrates		

<table>
<tr><td colspan="4">Authors: Chung et al.
Year: 2003</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: Moderate-severe</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>INF5</u></td><td><u>INF10</u></td></tr>
<tr><td>Mean age (years):</td><td>60 ± 12</td><td>62 ± 15</td><td>62 ± 13</td></tr>
<tr><td>Sex (% female):</td><td>24</td><td>14</td><td>16</td></tr>
<tr><td>Ethnicity (% white):</td><td>88</td><td>88</td><td>84</td></tr>
<tr><td>Current or prior angina (%):</td><td>29</td><td>18</td><td>24</td></tr>
<tr><td>Myocardial infarction (%):</td><td>63</td><td>50</td><td>67</td></tr>
<tr><td>Diabetes mellitus (%):</td><td>41</td><td>28</td><td>37</td></tr>
<tr><td>NYHA Class III/IV (%):</td><td>96/4</td><td>96/4</td><td>92/8</td></tr>
<tr><td>LVEF (%):</td><td>0.25 ± 0.07</td><td>0.23 ± 0.07</td><td>0.24 ± 0.06</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Change in clinical status, assessed by the clinical composite score, which categorized each patient as improved, worse, or unchanged using pre-specified criteria

Timing of assessments: 1,2,6,10,14,20,28 weeks</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• 10 mg/kg INF group were more likely to die or be hospitalized for heart failure than placebo (hazard ratio 2.84, 95% CI 1.01 to 7.97; nominal P = 0.043 using log-rank test)
• Patients in the 10 mg/kg INF group were more likely to be hospitalized for heart failure or for any reason than patients in the placebo or 5 mg/kg INF groups</td></tr>
</table>

Authors: Chung et al. **Year:2003**			
ADVERSE EVENTS: **Overall adverse effects reported (# of patients with 1 or more) n (%):** • Dizziness • Dyspnea • Hypotension • Angina • Serious AEs • Serious infections	**Placebo** 40 (83.3) 2 (4.2) 6 (12.5) 0 (0.0) 1 (2.1) (29.2) (2.1)	**INF5** 47 (92.2) 16 (31.4) 10 (19.6) 3 (5.9) 3 (5.9) (23.5) (5.9)	**INF10** 42 (84.0) 10 (20.0) 12 (24.0) 4 (8.0) 4 (8.0) (44.0) (8.0)
Significant differences in adverse events:	Yes		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** 6 in all, NR separately	**Overall loss to follow-up:** NR **Loss to follow-up differential high**: NR **Placebo** 1	**INF5** 2	**INF10** 5
QUALITY RATING:	**Fair**		

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Dixon et al.**[149] **Year: 2007** **Country:** UK		
FUNDING:	The British Society for Rheumatology is indirectly funded by Schering-Plough, Whety Laboratories, Abbot Laboratories, and Amgen		
RESEARCH OBJECTIVE:	To test the hypothesis that the anti-inflammatory effect of anti–tumor necrosis-α (anti-TNFα) therapy might lead to a reduction in the incidence of myocardial infarction (MI) in RA patients		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Data from BSRBR, a national prospective observational study **Sample size:** 10,829 (74 patients switched from comparison cohort and were included in analysis for both so actual number of patients=10,755); anti-TNF subgroup analysis: 7515		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Anti-TNFα nonresponders** N/A N/A 1638	**Anti-TNFα responders** N/A N/A 5877	
INCLUSION CRITERIA:	Registered with BSRBR; diagnosed with RA; followed up for ≥ 6 months by July 31, 2006; Anti-TNFα cohort: treated with an anti-TNF drug, registered with BSRBR within 6 months of starting biologic therapy		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Lipid-lowering drugs, NSAIDS		

Authors: Dixon et al. **Year: 2007**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR		
	Anti-TNFα nonresponders	**Anti-TNFα responders**	
Mean age (years):	57	56	
Sex (% female):	79	76	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Tender joint count	NR	NR	
• Swollen joint count	NR	NR	
• Median disease duration	11	7	
• DMARD use (%)	NR	100	
• MTX use (%)	NR	NR	
• Corticosteroids use (%)	45.3	42.9	
• DAS score	6.4	6.6	
• HAQ score	2.2	2.0	
• Prior MI (%)	2.9	2.6	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** MI rates **Timing of assessments:** N/A		
RESULTS:		**Nonresponders**	**Responders**
	Person-years	1815	9886
	No. of reported MIs	17	35
	Rate of MIs per 1000 person-yrs (95% CI)	9.4 (5.5-15.0)	3.5 (2.5-4.9)
	Incidence rate ratio	Referent	0.38 (0.21-0.67)
	Incidence rate ratio, adjusted for age and sex	Referent	0.38 (0.22-0.68)
	Incidence rate ratio, multivariate analysis	Referent	0.36 (0.19-0.69)
	Incidence rate ratio by sex, multivariate analysis		
	Male	Referent	0.31 (0.12-0.81)
	Female	Referent	0.46 (0.20-1.06)

Authors: Dixon et al. **Year: 2007**	
ADVERSE EVENTS: **Overall adverse effects reported:** •	See above
Significant differences in adverse events:	see results
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ARE GROUPS COMPARABLE AT BASELINE:	Yes
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes
STATISTICAL ANALYIS ADEQUATE:	Yes
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A
QUALITY RATING:	**Good**

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Fleischmann et al.**[195] **Year: 2005** **Country:** US
FUNDING:	Immunex Corporation
RESEARCH OBJECTIVE:	Long term safety of etanercept in elderly patients being treated for RA, AS, PsA
DESIGN:	**Study design:** Retrospective analysis **Setting:** 22 trials **Sample size:** 4322 (3893 unique subjects)
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**All** NR Various 4322 (3893 unique subjects)
INCLUSION CRITERIA:	Participants of 18 RA, 2 PsA, 2 AS trials.
EXCLUSION CRITERIA:	NR
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR

Authors: Fleischmann et al.
Year: 2005

POPULATION CHARACTERISTICS:

Groups similar at baseline:
Disease severity: Mild-moderate-severe

	RA		PsA		AS	
	Less than 65 years	**65 years and more**	**Less than 65 years**	**65 years and more**	**Less than 65 years**	**65 years and more**
Sample size:	2772	579	251	14	273	4
Median age (years):	47	70	46	70	42	65
Sex (% female):	77	73	46	71.4	24.5	0
Ethnicity (%white):	78.6	89.5	89.2	100	92.7	100
Other germane population qualities:	NR	NR	NR	NR	NR	NR

OUTCOME ASSESSMENT:

Primary Outcome Measures: Safety including all adverse events, serious adverse events, infectious events, medically important infections and deaths

Secondary Outcome Measures: Additional conditions of interest were also examined, demyelinating diseases, TB, lymphomas, and cardiovascular diseases.

Timing of assessments: N/A

RESULTS:

Health Outcome Measures:

- The incidence of all adverse events, serious adverse events, infectious events, medically important infections and malignancies were not significantly elevated in elderly subjects when compared with subjects less than 65 years of age
- Demyelinating diseases were seen only in subjects under the age of 65.

Authors: Fleischmann et al. **Year: 2005**				
	Age less than 65 years		**Age 65 years or more**	
ADVERSE EVENTS (%):	**Control (n= 1020)**	**ETA (n=2652)**	**Control (n= 170)**	**ETA (n=480)**
Overall adverse effects reported:	63.4	77.1	74.1	83.3
• Serious adverse event	4	14.3	17.6	29
• Infectious event	39.8	55.4	51.2	48.8
• Medically important event	1.3	4	7.1	10.4
Significant differences in adverse events:	Once the data is normalized with the control group data (patients from same studies that received placebo or MTX) there were no differences in adverse events or serious adverse events.			
ANALYSIS:	**ITT:** N/A **Post randomization exclusions: NR**			
ADEQUATE RANDOMIZATION:	**N/A**			
ADEQUATE ALLOCATION CONCEALMENT:	N/A			
BLINDING OF OUTCOME ASSESSORS:	No			
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR			
	Age less than 65 years		**Age 65 years or more**	
ATTRITION (*treatment specific*):	**Control (n= 1020)**	**ETA (n=2652)**	**Control (n= 1020)**	**ETA (n=2652)**
Loss to follow-up:	NR	NR	NR	NR
Withdrawals due to adverse events (%):	3.5	5.4	12.4	12.5
QUALITY RATING:	**Fair**			

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Fleischmann et al.,[154] Schiff et al.,[156] and Tesser et al.[157]** **Year: 2003 and 2004** **Country:** Multinational	
FUNDING:	Amgen Inc., Thousand Oaks, CA	
RESEARCH OBJECTIVE:	To evaluate the safety of anakinra in a large population of patients with RA, typical of those seen in clinical practice. Additionally to determine the safety in a sub-population of patients with comorbid conditions; and to examine concomitant medication's effect on adverse events.	
DESIGN:	**Study design:** RCT **Setting:** Multicenter (169 sites) **Sample size:** 1414 (1399 enrolled)	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**AKA** 100 mg/d 6 months 1116	**Placebo** N/A 6 months 283
INCLUSION CRITERIA:	18 years of age or older; RA diagnosed according to ACR criteria for at least 3 months; active disease defined by a minimum of 3 swollen joints and 3 tender joints or 45 minutes of morning stiffness; stable doses of NSAIDs and corticosteroids for one month; and stable doses of DMARDs for 2 months.	
EXCLUSION CRITERIA:	Pregnant or lactating; uncontrolled medical condition (e.g., diabetes with HgbA1c > 8%); malignancy other than basal cell carcinoma of the skin or in situ carcinoma of the cervix; Felty's syndrome; leukopenia; neutropenia; thrombocytopenia; abnormal liver function test result; hepatitis B or C positive; HIV positive.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDS, corticosteroids, and DMARDs (except TNF inhibitors) either alone or in combination	

Authors: Fleischmann et al. and Schiff et al. **Year: 2003 and 2004**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Mild to severe	
	AKA	**Placebo**
Mean age (years):	54.6	55.7
Sex (% female):	74.7	74.6
Ethnicity (%):		
• White	87.8	90.1
• Black	6.1	5.3
• Hispanic	4.4	3.5
• Other	1.7	1.1
Other germane population qualities:		
• TJC	22.6	22.6
• SJC	18.8	18.3
• DMARD use (excluding MTX) (%)	47.7	47.7
• MTX use (%)	51.9	59.4
• Corticosteroids use (%)	57.0	60.8
• DAS score	NR	NR
• HAQ score	NR	NR
Comorbidities (Schiff 2004), %:		
• Asthma	9.8	8.1
• COPD	12.9	11.0
• Pneumonia	9.1	6.7
• DM	7.4	7.4
• CAD	5.7	5.7
• CHF	3.2	3.2

Authors: Fleischmann et al. and Schiff et al. **Year: 2003 and 2004**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Safety (measured by adverse events, serious adverse events, infections, study discontinuation, and death; WHO adverse reaction term dictionary) **Secondary Outcome Measures:** NR **Timing of assessments:** Day 1, week 1, and months 1,3, and 6.
RESULTS:	**Health Outcome Measures:** • After 6 months, the rate of spontaneous adverse events was not different between AKA and placebo, except for ISRs, which occurred much more frequently among AKA-treated patients than placebo-treated patients (72.6% v. 32.9%) P-value NR • 13.4% of patients in the AKA group withdrew due to adverse event compared to 9.2% in the placebo group, but the difference was not significant ($P = 0.057$); overall discontinuation rates were similar (21.6% vs. 18.7%) • Serious infections occurred more frequently in AKA than in placebo patients (2.1% v. 0.4%), but was not statistically significantly different but may be clinically significant. ($P = 0.068$) • In patients with comorbid conditions, there were no differences between the AKA group and the placebo group in incidence of serious adverse events or overall infectious events. • In patients with comorbid conditions, the rate of serious infectious events was increased relative to placebo (2.5% vs. 0.0%; P = NR). • There is a trend towards increased risk of serious infectious events with AKA in patients with pulmonary comorbidities versus placebo (3.4% v. 1.6%), but it failed to reach statistical significance. • Neutralizing anti-ANA antibodies detected in 0.8% of AKA patients NR for patients receiving placebo. • Adverse event profiles were similar between groups taking concomitant antihypertensive, antidiabetic and statin drugs.

Authors: Fleischmann et al. and Schiff et al. and Tesser et al. **Year: 2003 and 2004**		
ADVERSE EVENTS: **Overall adverse effects reported:** • Deaths • Serious adverse events • Severe adverse events • ISRs • Infectious episode • Serious infection • URTI • Sinusitis • Influenza-like • UTI • Bronchitis • Infection (resistance mechanism body system)	**AKA** 1,027 (92.0%) 4 (0.4%) 86 (7.7%) 15.5% 72.6% 41.2% 2.1% 13.3 6.7 5.8 4.6 3.4 2.9	**Placebo** 261 (92.2%) 1 (0.4%) 22 (7.8%) 13.1% 32.9% 43.5% 0.4% 18.4 6.0 6.4 5.3 4.6 3.2
Significant differences in adverse events:	• No significant differences reported. (No P-value was reported for ISRs.)	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (15/1414)	
ADEQUATE RANDOMIZATION:	NR	
ADEQUATE ALLOCATION CONCEALMENT:	NR	
BLINDING OF OUTCOME ASSESSORS:	Yes	
ATTRITION (*overall*):	**Overall loss to follow-up:** 394 (21%) **Loss to follow-up differential high:** No	
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**AKA** 21.6% 13.4%	**Placebo** 18.7% 9.2%
QUALITY RATING:	**Fair**	

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Genevay et al.**[196] **Year: 2007** **Country:** Switzerland	
FUNDING:	University and grants	
RESEARCH OBJECTIVE:	To evaluate the tolerance to and effectiveness of anti–tumor necrosis factor (anti-TNF) agents in elderly patients (>65 years old) with RA (ERA) in comparison with younger patients (YRA)	
DESIGN:	**Study design:** Observational cohort **Setting:** Multicenter **Sample size:** 1571	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**YRA** various median 3 years 1227	**ERA** various median 3 years 344
INCLUSION CRITERIA:	All patients have been diagnosed as having RA according to the clinical judgment of their rheumatologist.	
EXCLUSION CRITERIA:	N/A	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

Authors: Genevay et al. **Year: 2007**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **Disease severity:** Mild-moderate-severe	
	YRA	**ERA**
Median age (years):	51	71
Sex (% female):	75	78.5
Ethnicity:	NR	NR
Other germane population qualities:		
• Mean disease duration	11.5	14.3
• DMARD use (%)		
• MTX use (%)	42	35.2
• Corticosteroids use (%)	48.8	59.9
• DAS score	4.2	4.5
• HAQ score	1.23	1.4
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** DAS28 **Secondary Outcome Measures:** EULAR and HAQ **Timing of assessments:** Annually and when changes were made in treatment	
RESULTS:	**Health Outcome Measures:** • Mean change in DAS28 scores at 2 years (–0.65 versus –0.58) P = NS • Mean change in HAQ score ERA (– 0.02) than in YRA (– 0.1) $P < 0.001$ • EULAR good responders criteria at 1 year ERA 7.2% versus YRA 11.2%; $P < 0.05$ • EULAR poor responders ERA 60.2% versus YRA 51.5%; $P < 0.01$.	

Authors: Genevay et al. **Year: 2007**		
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	**NR**	
Significant differences in adverse events:	NR	
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:**	
ARE GROUPS COMPARABLE AT BASELINE:	No	
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes	
STATISTICAL ANALYIS ADEQUATE:	Yes	
ATTRITION (*overall*):	**Overall attrition:** 128 (8%) **Attrition differential high:** No	
ATTRITION (*treatment specific*):	**drug 1**	**drug 2**
Attrition overall:	8%	8%
Attrition due to adverse events:	NR	NR
QUALITY RATING:	**Fair**	

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Genovese et al.**[21] **Year: 2004** **Country:** US		
FUNDING:	Amgen, Inc., Thousand Oaks, CA		
RESEARCH OBJECTIVE:	To determine the potential for additive or synergistic effects of combination therapy with the selective anti-TNF-α agent etanercept and the anti-IL1 agent anakinra.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter, specialty clinic **Sample size:** 242		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg *twice* per week 24 weeks 80	**½ ETA + AKA** 25 mg *once* per week; 100 mg/day 24 weeks 81	**ETA + AKA** 25 mg *twice* per week; 100 mg/day 24 weeks 81
INCLUSION CRITERIA:	Age 18 or greater; greater than 6-month history of RA diagnosed by ACR criteria; 6+ swollen joints; 9+ tender/painful joints; at least 2 of: morning stiffness lasting 45 or more minutes, serum CRP of ≥ 1.5 mg/dl, or ESR ≥28 mm/hr; and, received MTX for at least 16 weeks, with a stable dose in the range of 10-25 mg/week for at least 8 weeks.		
EXCLUSION CRITERIA:	Any DMARD other than MTX within the past 4 weeks; treatment with AKA or any protein-based TNF-alpha inhibitor; received any intraarticular or systemic corticosteroid injections within past 4 weeks; or, had a recent history of significant infection or other important concurrent illness.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Continued treatment with stable doses of MTX and other stable medications, such as corticosteroids.		

Authors: Genovese, et al.
Year: 2004

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes, but there is a slight overall trend to more severe disease in full ETA + AKA group.
Disease severity: Moderate

	ETA	½ ETA + AKA	ETA + AKA
Mean age (years):	54.4	53.8	55.7
Sex (% female):	82.5	71.6	77.8
Ethnicity (% white race):	86.3	77.8	75.3
Other germane population qualities:			
• TJC	31.0	31.0	35.9
• SJC	21.4	19.8	23.4
• MTX use (%)	100	100	100
• Corticosteroids use (%)	48.8	54.3	44.4
• HAQ score	1.5	1.5	1.6

OUTCOME ASSESSMENT:

Primary Outcome Measures: ACR50 at week 24.
Secondary Outcome Measures: ACR20 and ACR70 at week 24; sustained ACR20 response ("response for at least 4 monthly measurements, not necessarily consecutive, with 1 occurring at month 6"); good or moderate EULAR response at week 24; improvement in the ACR core criteria components; duration of morning stiffness; the DAS; and the SF-36; plasma AKA and ETA concentrations and anti-AKA and anti-ETA antibody concentrations.
Timing of assessments: Baseline and weeks 2, 4, 8, 12, 16, 20, and 24; plasma concentrations at weeks 4, 12, and 24; antibody concentrations at weeks 12 and 24.

RESULTS:

Health Outcome Measures (ETA v. ½ ETA + AKA v. ETA + AKA), measure (95% CI):

- At week 24 there were no significant differences in outcomes between the treatment groups
  ACR50 at week 24: 41% v. 39% v. 31% ($P = 0.914$, by 1-tailed t-test)
  - OR (ETA + AKA v. ETA alone) 0.64 (90% CI: 0.37 to 1.09)
  - Sensitivity analysis yielded similar results.
- **ACR20 at week 24:**
  - 68% v. 51% v. 62% Only significant difference is between ETA alone and the ½ ETA + AKA group ($P = 0.037$).
- ACR70 at week 24: 21% v. 24% v. 14% (*P*-value NR)
- Sustained ACR20 response: between 43% and 54% of subjects in each group (specifics NR).
- EULAR response at week 24: 79% v. 66% v. 73% (*P*-value NR)
- Mean % reduction in DAS: 39% v. 41% v. 40% (*P*-value NR)

Authors: Genovese et al. **Year: 2004**			
ADVERSE EVENTS:	**ETA**	**½ ETA + AKA**	**ETA + AKA**
Overall adverse effects reported, %:	90.0	95.1	93.8
• Infections	40.0	37.0	46.9
• URTI	20.0	11.1	13.6
• ISR	40.0	67.9	70.4
• Any serious adverse event	2.5	4.9	14.8
• Serious infection	0.0	3.7	7.4
Significant differences in adverse events:	Patients receiving ETA (any dosage) + AKA experienced more ISRs and serious adverse events than patients receiving ETA alone. *P*-values NR.		
ANALYSIS:	**ITT:** YES **Post randomization exclusions:** 2		
ADEQUATE RANDOMIZATION:	**YES**		
ADEQUATE ALLOCATION CONCEALMENT:	Unknown		
BLINDING OF OUTCOME ASSESSORS:	YES		
ATTRITION (*overall*):	**Overall loss to follow-up:** 15.7% **Loss to follow-up differential high:** 15% between ETA alone and ½ ETA + AKA		
ATTRITION (*treatment specific*):	**ETA**	**½ ETA + AKA**	**ETA + AKA**
Loss to follow-up:	7%	22%	20%
Withdrawals due to adverse events:	0%	8.6%	7.4%
QUALITY RATING:	**Fair**		

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Gottlieb et al.**[197] **Year: 2005** **Country:**		
FUNDING:	Biogen Idec, Inc.		
RESEARCH OBJECTIVE:	To assess safety & efficacy of alefacept in elderly, obese, and diabetic patients with moderate to severe chronic plaque psoriasis by integrating data from 9 phase 2 & 3 clinical studies and their extensions.		
DESIGN:	**Study design:** Pooled analysis of RCTs **Setting:** Multicenter **Sample size:** 1,473		
INTERVENTION: N/A	**ALE in phase 2 studies**	**ALE in phase 3 studies**	**Placebo**
Dose:	0.025, 0.075, or 0.15mg/kg, or 7.5 mg IV	10 or 15mg IM, or 7.5 mg IV	N/A
Duration:	12 weeks	12 weeks	NR
Sample size:	NR	NR	NR
INCLUSION CRITERIA:	Participation in any of 9 multicenter, randomized, clinical studies; at least 16 years old; chronic plaque psoriasis for ≥ 12 months, involving ≥ 10% body surface area; CD4+ lymphocyte count above 400 cells/uL; no serious local or systemic infection within last 3 months.		
EXCLUSION CRITERIA:	History of malignancy, other than basal cell carcinomas or ≤ 3 cutaneous squamous cell carcinomas; use of phototherapy, systemic retinoids / steroids / fumarates, immunosuppressants, and high-potency corticosteroids within last 4 weeks.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Moderate-potency topical corticosteroids, vitamin D analogs, keratolytics, and coal tar on scalp, palms, groin, and soles only, and not within 2 weeks of study drug administration.		

<table>
<tr><td colspan="4">Authors: Gottlieb et al.
Year: 2005</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:

Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: NR</td></tr>
<tr><td>NR</td><td></td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: PASI 75 (75% reduction from baseline); Physician Global Assessment (PGA)

Timing of assessments: Adverse events collected during monthly interim visits.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
ALE was associated with substantial clinical improvement in the elderly, obese, & diabetic.
ALE- treated patients had numerically higher degree of clinical improvement vs. placebo.
24%-33% of ALE-treated patients achieved PASI 75 at any time during 1st course, with 17%-26% achieving a PGA of “clear” or “almost clear.”
Among those who received 3 courses of ALE, 41-58% achieved a PASI 75, and 33-37% achieved a PGA or “clear” or “almost clear.”</td></tr>
</table>

Authors: Gottlieb et al. **Year: 2005**			
ADVERSE EVENTS in 1st course: **Overall adverse effects reported:** • Accidental injury • Headache • Pharyngitis • Rhinitis • Infection • Any malignancy	**Elderly (n=99)** NR 15.2% 14.1% 13.1% 12.1% 11.1% 6.1%	**Obese (n=652)** NR 16.7% 16.6% 16.4% 12.3% 12.1% 1.2%	**Diabetic (n=122)** NR 18.9% 13.9% 12.3% 12.3% NR 1.6%
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** No **Post randomization exclusions:** N/A		
ADEQUATE RANDOMIZATION:	N/A		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	NR		
QUALITY RATING:	**Fair**		

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Kristensen et al.**[198] **Year: 2008** **Country:** Sweden		
FUNDING:	Grants from Osterlund and Kock Foundations, King Gustav V 80 year fund, and Reumatikerforbundet.		
RESEARCH OBJECTIVE:	To identify factors predicting response to first TNF blocking treatment course in patients with established RA with a special focus on gender differences		
DESIGN:	**Study design:** Observational **Setting:** Multicenter- primary **Sample size:** 1565		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Males** Various 3 months 353	**Females** Various 3 months 1212	
INCLUSION CRITERIA:	A diagnosis of RA according to clinical judgment of the treating physician		
EXCLUSION CRITERIA:	Patients with <3 month of follow-up or having received previous courses of biologic therapy		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs and MTX		

Authors: Kristensen et al.
Year: 2008

POPULATION CHARACTERISTICS:

Groups similar at baseline:
Disease severity: Mild-moderate-severe

	Males	**Females**
Mean age (years):	58	55
Sex (% female):	0	100
Ethnicity:	NR	NR
Other germane population qualities:		
• Tender joint count	7.7	9.4
• Swollen joint count	9.9	9.7
• Mean disease duration	11 yrs	12 yrs
• DMARD use (%)	15	13
• MTX use (%)	66	61
• Corticosteroids use (%)	NR	NR
• DAS score	5.36	5.62
• HAQ score	1.12	1.42
• ADA	12%	16%
• ETA	34%	40%
• INF	54%	44%

OUTCOME ASSESSMENT:

Primary Outcome Measures: EULAR and ACR
Timing of assessments: Baseline, 3 months and 6 months

RESULTS:

Health Outcome Measures:

	Males		Females		Level of significance
	3 months n=353 (%)	6 months n = 308 (%)	3 months n = 1212 (%)	6 months n = 1020 (%)	
EULAR Good	21	22	19	21	NS
EULAR remission (DAS28<2.6)	18	18	16	17	NS
EULAR Good	21	22	19	21	NS
EULAR remission (DAS28<2.6)	18	18	16	17	NS
ACR50	22	24	25	24	NS
ACR70	8	9	8	8	NS

Authors: Kristensen et al. **Year: 2008**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	NR		
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** No **Post randomization exclusions:** NR		
ARE GROUPS COMPARABLE AT BASELINE:	No		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall attrition:** 59 (3.7%) **Attrition differential high:** No		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	NR		
QUALITY RATING:	**Fair**		

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Takeuchi et al.**[186] **Year: 2008** **Country:** Japan
FUNDING:	Tanabe Seiyaku Co., Ltd
RESEARCH OBJECTIVE:	Safety of INF in patients with RA
DESIGN:	**Study design:** Observational – postmarketing surveillance study **Setting:** Multicenter **Sample size:** 5000
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 3 mg/kg at weeks 0,2,6 and then every 8 weeks 6 months 5000
INCLUSION CRITERIA:	All patients treated with INF between July /2003 and Dec 2004 with active disease despite treatment with MTX of greater than 6 mg /week for at least 3 months
EXCLUSION CRITERIA:	N/A – but in order for institutions to prescribe INF they had to agree to participate fully in this study.
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes

Authors: Takeuchi et al. **Year: 2008**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe
	INF
Mean age (years):	55.1 years
Sex (% female):	79
Ethnicity:	NR – assume Asian 100%
Other germane population qualities:	
• Hepatic disorder	3.1
• Cardiac disorder	2.5
• Diabetes Mellitus	9.4
• Respiratory disease	4.7
• Haematological disease	1.2
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Adverse events and adverse drug reactions were compared to a clinical trial that was conducted in Japan
RESULTS:	**Health Outcome Measures:** **See adverse events and risk factors for bacterial pneumonia** OR 95% CI Comorbid Respiratory disease Yes vs. none 3.90 (2.35–6.47) $P < 0.001$ Male vs. female 1.94 (1.29–2.93) $P = 0.001$ 40s and under vs. 50s 0.25 (0.10–0.66) 50s 1.00 (reference) , $P < 0.001$ 60s vs. 50s 1.90 (1.18–3.07) 70s and over vs. 50s 2.57 (1.48–4.45)

Authors: Takeuchi et al. **Year: 2008**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Serious ADRs • ADRs Per 100 pt/yrs • infections • Serious infections	**PMS n = 5000** 28% 6.2 59.38 (59.07 to 59.69) 18.35 (18.18 to 18.52) 8.56 (8.44-8.68)	**Japanese clinical trial n = 141** 67.4 10.6 72.16 (70.1 to 73.61) 39.50 (38.4 to 40.57) 8.36 (7.87-8.85)	**drug 3**
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	Yes		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	NR		
STATISTICAL ANALYIS ADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall attrition:** N/A **Attrition differential high:** N/A		
ATTRITION (*treatment specific*): **Attrition overall:** **Attrition due to adverse events:**	N/A		
QUALITY RATING:	N/A		

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Weaver et al.**[53] **Year: 2006** **Country:** US				
FUNDING:	Immunex Corporation				
RESEARCH OBJECTIVE:	To evaluate the effectiveness of select biologics, methotrexate, and DMARDs in the management of adult RA in routine clinical practice.				
DESIGN:	**Study design:** Prospective observational **Setting:** 509 rheumatology practices **Sample size:** 5397 (includes 762 patients whose treatment strategies were not of interest to this review)				
INTERVENTION: **Dose (median wkly at baseline):** **Duration:** **Sample size:**	**MTX** 10 mg 12 months 941	**ETA** 50 mg 12 months 1251	**INF** 3.8 mg/kg every 8 wks 12 months 120	**ETA+MTX** 50 mg+15 mg 12 months 1783	**INF+MTX** 3.8mg/kg every 8 wks+15mg 12 months 540
INCLUSION CRITERIA:	Patients requiring a change in their existing RA treatment: ≥ 18 years; met ACR criteria for RA.				
EXCLUSION CRITERIA:	Active infection; pregnancy; concurrent enrollment in a clinical trial				
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes				

Authors: Weaver et al.
Year: 2006

POPULATION CHARACTERISTICS:

Groups similar at baseline: No
Disease severity: Mild-moderate-severe

	MTX	ETA	INF	ETA+MTX	INF+MTX
Mean age (years):	56.8	53.2	60.2	52.6	58.5
Sex (% female):	75	75	71	79	77
Ethnicity:	77	81	78	81	81
Other germane population qualities:					
• TJC	13.0	13.4	10.6	13.3	13.9
• SJC	11.3	11.1	14.8	11.5	12.0
• Mean disease duration	3.5	9.2	10.6	7.7	9.5
• DMARD naive (%)	75	65	15	4	4
• Corticosteroids use (%)	NR	NR	NR	NR	NR
• DAS score	N/A	N/A	N/A	N/A	N/A
• HAQ score	1.3	1.4	1.5	1.3	1.4

OUTCOME ASSESSMENT:

Primary Outcome Measures: Modified ACR 20 (doesn't include ESR or CRP)
Secondary Outcome Measures: HAQ, patient global and pain assessments, physician global assessment and 28-count swollen and tender joints
Timing of assessments: 12 months (± 1 month)

RESULTS:

Health Outcome Measures:

- Unadjusted mACR20 ETA+MTX 43% ETA 41% INF+MTX 35% INF 26% MTX 37%
- After adjusting for baseline covariates, ETA + MTX vs MTX OR 1.29, 95% CI 1.09-1.52; $P < 0.01$
- ETA vs. MTX OR 1.23, 95% CI 1.02-1.47; $P < 0.05$
- Significant differences were not observed between patients receiving MTX vs. INF + MTX (OR 0.96 CI 0.76-1.21 $P = 0.72$) or INF monotherapy (OR 0.66 95% CI 0.43-1.02 $P = 0.06$)
- Percent improvement on HAQ (vs MTX) MTX 7% (N/A) ETA 17% ($P < 0.001$) INF 1% (P =NS) ETA+MTX 17% ($P < 0.0001$) INF+MTX 3% (P = NS)

Authors: Weaver et al. **Year: 2006**					
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	**MTX** NR	**ETA**	**INF**	**ETA+MTX**	**INF+MTX**
Significant differences in adverse events:	NR				
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A				
ARE GROUPS COMPARABLE AT BASELINE:	No				
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes				
STATISTICAL ANALYIS ADEQUATE:	Yes				
ATTRITION (*overall*):	**Overall loss to follow-up:** No **Loss to follow-up differential high:** Yes				
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**MTX** 23% 4%	**ETA** 31% 6%	**INF** 33% 11%	**ETA+MTX** 39% 8%	**INF+MTX** 29% 9%
QUALITY RATING:	**Fair**				

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Weinblatt et al.**[199] **Year: 2006** **Country:** USA and Canada			
FUNDING:	Bristol-Myers Squibb			
RESEARCH OBJECTIVE:	To assess the safety of ABA in patients with RA who have been receiving treatment with DMARDs and/or biologics for 3 months or more			
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 1441			
INTERVENTION:	**Nonbiologic background therapy**		**Biologic background therapy**	
	ABA	**Placebo**	**ABA**	**Placebo**
Dose:	10 mg/kg days 1, 15, and 29, then every 4 weeks a total of 14 doses.	N/A	10 mg/kg days 1, 15, and 29, then every 4 weeks a total of 14 doses.	N/A
Duration:	1 year	1 year	1 year	1 year
Sample size:	856	418	103	64
INCLUSION CRITERIA:	Men and women at least 18 years of age who met the 1987 ACR; criteria for the diagnosis of RA and the 1991 ACR criteria for RA functional classes I, II, III, or IV; active disease despite receiving background DMARDs and/or biologic therapy, warranting additional therapy at the discretion of the investigator; the average score for the patient's global assessment of disease activity, as assessed by VAS measurements at screening and randomization (day 1), was required to be >20 mm; at least 1 biologic and/or nonbiologic DMARD approved for RA for at least 3 months, and at a stable dose for at least 28 days prior to day 1; stable medical conditions such as congestive heart failure (CHF), asthma, COPD, and diabetes mellitus			
EXCLUSION CRITERIA:	Unstable or uncontrolled renal, endocrine, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, or neurologic diseases, or any autoimmune disorder other than RA as the main diagnosis; active or chronic recurrent bacterial infections unless treated and resolved, active herpes zoster infection within the previous 2 months, hepatitis B or hepatitis C virus infection, and active or latent tuberculosis; pregnant or nursing.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Approved biologic and nonbiologic DMARDs, MTX, hydroxychloroquine, leflunomide, gold, azathioprine, AKA, ETA, INF, and ADA; stable, low-dose oral corticosteroids (10 mg/day or less) and/or stable doses of NSAIDs, including aspirin			

Authors: Weinblatt et al.
Year: 2006

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: Moderate-severe

	Nonbiologic background therapy		Biologic background therapy	
	ABA	**Placebo**	**ABA**	**Placebo**
Mean age (years):	52.2	52.0	54.6	52.8
Sex (% female):	83.1	83.7	75.7	75.0
Ethnicity (%white):	83.9	83.3	97.1	92.2
Other germane population qualities:				
• Pain, 100-mm VAS	61.1	61.3	62.2	61.5
• HAQ - DI	1.5	1.5	1.5	1.6
• Mean disease duration – years	9.5	9.5	11.3	11.3
• MTX	80.7	80.4	56.3	56.3
• Corticosteroids	71.6	73.7	74.8	79.7

OUTCOME ASSESSMENT:

Primary Outcome Measures: Safety- adverse events and infusion reactions
Secondary Outcome Measures: HAQ-DI; Patient's global assessment of disease activity, and physician's global assessment of disease activity
Timing of assessments: days 1, 85, 169, and 253.

RESULTS:

Health Outcome Measures: ABA vs. placebo
HAQ-DI; -0.46 versus -0.25; $P < 0.001$
Patient's assessment of pain -26.3 vs. -16.4 $P < 0.001$
Patient's global assessment of disease activity -27.2 vs. -17.4 $P < 0.001$
Physician's global assessment of disease activity -33.5 vs. -23.6 $P < 0.001$

Patients w/COPD overall AEs ABA 97.3% (n = 37) and placebo 88.2% (n = 17).
AEs involving the respiratory system ABA 43.2% versus placebo 23.5%
SAEs ABA 27% versus placebo 5.9%

Patients with DM overall AEs ABA 93.8% (n = 65) and placebo 90.3% (n = 31)
Infections ABA 50.8% vs. placebo 58.1%
SAEs ABA 21.5% vs. placebo 12.9%.

Authors: Weinblatt et al. **Year: 2006**				
ADVERSE EVENTS:	**Nonbiologic background therapy**		**Biologic background therapy**	
	ABA	**Placebo**	**ABA**	**Placebo**
Overall adverse effects reported:	89.7	86.1	95.1	89.1
• SAEs	11.7	12.2	22.3	12.5
• Neoplasms	3.2	3.8	6.8	1.6
• Infections	54.9	53.6	65.0	57.8
• Serious infections	2.6	2.4	5.8	1.6
• Death	0.6	1.0	0	0
Significant differences in adverse events:	Yes - ABA in combination with biologic background therapies was associated with an increase in the rate of serious adverse events			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 5			
ADEQUATE RANDOMIZATION:	NR			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	NR			
ATTRITION (*overall*):	**Overall attrition:** 210 (14.6%) **Attrition differential high:** No			
ATTRITION (*treatment specific*):	**Nonbiologic background therapy**		**Biologic background therapy**	
	ABA	**Placebo**	**ABA**	**Placebo**
Attrition overall:	12.8%	18%	12.8%	18%
Attrition due to adverse events:	5%	4.3%	8.7%	3.1%
QUALITY RATING:	**Fair**			

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Weisman et al.**[200] **Year: 2007** **Country:** United States		
FUNDING:	Immunex Corporation and by Wyeth Pharmaceuticals.		
RESEARCH OBJECTIVE:	To evaluate the safety of ETA in patients with rheumatoid arthritis (RA) and concomitant comorbidities		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 535		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 16 weeks 269	**ETA** 25 mg twice weekly 16 weeks 266	
INCLUSION CRITERIA:	At least 18 yrs of age, met the ACR criteria for RA [3], and had at least one qualifying comorbidity: diabetes mellitus (only patients taking insulin and/or oral hypoglycaemic agents), chronic pulmonary disease (asthma or chronic obstructive pulmonary disease), or pneumonia or recurrent infections (bronchitis, sinusitis, or urinary tract infection) in the preceding year.		
EXCLUSION CRITERIA:	Recent myocardial infarction, uncontrolled hypertension or severe pulmonary disease requiring continual oxygen therapy was excluded. A protocol amendment later excluded patients with angina pectoris.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Corticosteroids, NSAIDs, DMARDs (except azathioprine, cyclosporine and cyclophosphamide) and pain medications at the discretion of their physicians.		

Authors: Weisman et al.
Year: 2007

POPULATION CHARACTERISTICS:

Groups similar at baseline: Yes
Disease severity: Mild-moderate-severe

	Placebo	ETA
Mean age (years):	59.3	60.6
Sex (% female):	78.1	60.6
Ethnicity:	77% white, 13% Hispanic, 6.3% Black	81% white, 12% Hispanic, 6% Black
Other germane population qualities:		
• Mean disease duration	9.4 years	10.1 years
• Diabetes-insulin	16.4%	17.7%
• Diabetes-oral only	33.1%	32.0%
• Chronic pulmonary disease	40.1%	44%
• Coronary artery disease	78.4%	83.5%
• Myocardial Infarction	73.6%	80.1%
• Hypertension	56.1%	63.5%

OUTCOME ASSESSMENT:

Primary Outcome Measures: incidence of medically important infections (MIIs; defined as those resulting in hospitalization or treatment with intravenous antibiotics).

Timing of assessments: baseline, weeks 8 and 16, and 30 days post–therapy

RESULTS:

Health Outcome Measures:

	Medically important infections		Serious Adverse Events	
% of patients	Placebo	ETA	Placebo	ETA
All patients	3.7	3.0	5.9	8.6
w/ diabetes	3.8	2.3	6.8	9.1
w/o diabetes	3.7	3.7	5.1	8.2
w/ chronic pulmonary disease	5.6	4.3	6.5	10.3
w/o chronic pulmonary disease	2.5	2.0	5.6	7.4

Six patients died on study [one placebo (cardiac arrest); five ETA (cardiac arrest, cardiomyopathy, coronary artery disease, respiratory failure and subarachnoid hemorrhage)].

Authors: Weisman et al. **Year: 2007**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections	See Results		
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:**		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall attrition:** 21% **Attrition differential high:** almost – 14%		
ATTRITION (*treatment specific*):	**Placebo**	**ETA**	
Attrition overall:	27.9%	13.9%	
Attrition due to adverse events:	6.7%	4.9%	
QUALITY RATING:	**Fair**		

Evidence Table 9. Targeted Immune Modulators – Subgroups

STUDY:	**Authors: Wolfe et al.**[192] **Year: 2004** **Country:** U.S.
FUNDING:	Centocor, Inc.
RESEARCH OBJECTIVE:	To determine the frequency of heart failure in patients with RA, and to determine its predictors, particularly the use of anti-TNF therapy.
DESIGN:	**Study design:** retrospective cohort study **Setting:** Multicenter (National Data Bank for Rheumatic Diseases) **Sample size:** 13,171
INTERVENTION: **Dose:** **Duration:** **Sample size:**	Multiple
INCLUSION CRITERIA:	Participation in the National Data Bank for Rheumatic Diseases study of the outcomes of arthritis; patient at participating rheumatology clinic;
EXCLUSION CRITERIA:	NR
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A

Authors: Wolfe et al.
Year: 2004

POPULATION CHARACTERISTICS:

Groups similar at baseline: N/A
Disease severity: NR

	Total population	Anti-TNF	INF	ETA	No anti-TNF
Mean age (years):	61	60	61.5	56.7	61.5
Sex (% female):	77	78	77	80	76
Ethnicity: % white	94	95	96	92	92
Other germane population qualities:					
• Mean disease duration	14.9	14.2	13.8	15.2	15.5
• DMARD or anti-TNF use (%)	86	NR	NR	NR	NR
• MTX use (%)	56	67	76	44	47
• Prednisone use (%)	39	47	49	39	33
• DAS score	3.6	3.7	3.7	3.6	3.5
• HAQ score	1.1	1.2	1.2	1.1	1.0

OUTCOME ASSESSMENT:

Primary Outcome Measures: NR
Secondary Outcome Measures: NR
Timing of assessments: Every 6 months for a total of 2 years.

RESULTS:

Health Outcome Measures:

- There were 461 cases of heart failure in the 13,171 patients with RA (overall risk of 3.5%); after adjusting for demographic characteristics the risk was 3.9% (95% CI = 3.4% to 4.3%).
- Among all cases of heart failure, patients receiving anti-TNF therapy were less likely to have heart failure than those not receiving anti-TNF therapy (-1.2%; 95% CI -1.9 - -0.5%)
- Overall, the adjusted frequency of heart failure was 2.8% in those treated with anti-TNF vs. 3.9% in the remaining patients ($P = 0.03$).
- Frequency of heart failure was 5.2% in men and 3.0% in women.
- In examining incident cases of heart failure in patients under age 50, no increase was found (0/1569 patients using anti-TNF vs. 3/1401 most using anti-TNF therapy).

Authors: Wolfe et al. **Year: 2004**				
ADVERSE EVENTS: **Overall adverse effects reported:** • All Heart Failure: adjusted rate • Incident Heart Failure: adjusted rate	**All Anti-TNF** 2.8 0.2	**INF** 2.6 0.2	**ETA** 2.9 0.3	**No Anti-TNF** 3.4 to 3.9 0.2 to 0.3
Significant differences in adverse events:	No			
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A			
ARE GROUPS COMPARABLE AT BASELINE:	Yes			
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	Yes			
STATISTICAL ANALYIS ADEQUATE:	Yes			
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR			
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	NR			
QUALITY RATING:	**Fair**			

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