Drug Class Review
on
Targeted Immune Modulators

Final Report Update 1 Evidence Tables

January 2007

Original Report Date: December 2005
A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfmfor scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report. Please see timeline on the DERP website for details on the date of its release. Prior versions of this can be accessed at the DERP website.

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Evidence Table 1: ***Targeted Immune Modulators – Rheumatoid Arthritis***

STUDY:	**Authors: Abe et al.**[55] **Year: 2006** **Country:** Japan		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of infliximab in Japanese patients with RA already taking MTX.		
DESIGN:	**Study design:** Placebo controlled **Setting:** Multi-center **Sample size:** 147		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF (3 mg/kg)** 3 mg/kg (weeks 0,2,6) 14 weeks 47	**INF (10 mg/kg)** 10 mg/kg (weeks 0,2,6) 14 weeks 49	**placebo** N/A 14 weeks 51
INCLUSION CRITERIA:	20–75 years of age; met ARA diagnostic criteria for RA of at least 6 months prior to enrollment; Had ≥ 6 tender joints (of 68 counted) and ≥ 6 swollen joints (of 66 counted), plus at least 2 of the following: morning stiffness ≥ 45 min, erythrocyte sedimentation rate ≥ 28 mm/h, or CRP ≥ 2 mg/dl, despite treatment with MTX for more than 3 months; MTX dosage must have been stable 6 mg/week or more during the last 4 weeks. Patients receiving oral or suppository NSAIDs folic acid, oral or suppository corticosteroid (10 mg/day or less prednisolone equivalent) must have been taking a stable dose for 4 weeks prior to entry.		
EXCLUSION CRITERIA:	Use of DMARD, immunosuppressive drugs other than MTX, intraarticular, intramuscular, intravenous or epidural corticosteroids, to have arthrocentesis and plasma exchange (for 4 wks prior to entry), or use alkylating agents (for 5 yrs prior to entry); Functional class IV using Steinbrocker's criteria: Any other systemic rheumatic diseases except Sjögren's syndrome; Serious infections; Opportunistic infections (within the previous 3 mo); TB (within the previous 3 yrs); Infections of artificial joints (within the previous 5 yrs); Human immunodeficiency virus infection; Malignancies (within the previous 5 yrs); History of known allergies to human/murine chimeric antibodies; Pregnancy; Hemoglobin < 8.5 g/dl; leukocyte count < 3500 × 106/l; neutrophil count < 1500 × 106/l; platelet count < 10 × 104/μl; serum creatinine level > 1.5 mg/dl; and alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, and alkaline phosphatase (ALP) levels greater than twice the normal upper limit.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX; NSAID; folic acid, corticosteroids		

<table>
<tr><td colspan="4">Authors: Abe et al.
Year: 2006</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: NR (mean disease duration 7.9 years)</td></tr>
<tr><td></td><td><u>INF (3 mg/kg)</u></td><td><u>INF (10 mg/kg)</u></td><td><u>placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>55.2</td><td>56.8</td><td>55.1</td></tr>
<tr><td>Sex (% female):</td><td>81.6</td><td>78.4</td><td>74.5</td></tr>
<tr><td>Ethnicity:</td><td>Japanese</td><td>Japanese</td><td>Japanese</td></tr>
<tr><td>Other germane population qualities:
• TJC
• SJC
• Mean disease duration (yrs)
• MTX use (%)
• Corticosteroids use (%)</td><td>
19
15.1
9.1
100
85.7</td><td>
18.7
13.2
7.1
100
92.2</td><td>
17.8
13.5
7.5
100
89.4</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ACR20 at Week 14.

Secondary Outcome Measures: ACR50 and ACR70 and individual measurements of the ACR core set

Timing of assessments: Weeks 0, 2, 6, 10, and 14</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• ACR20 response rates at Week 14 were 23.4%, 61.2%, and 52.9% in the placebo, 3 mg/kg, and 10 mg/kg groups, respectively. Showing significantly higher response in the combined INF groups than in the placebo group ($P < 0.001$).*
• A significantly greater percentage of patients in both INF groups than in the placebo group achieved improvement of ACR20 and ACR50 at all evaluation points.
• There was not a significant difference in any outcome measure between INF groups.

Intermediate Outcome Measures:
• N/A</td></tr>
</table>

Authors: Abe et al. **Year: 2006**			
ADVERSE EVENTS:	**INF (3 mg/kg)**	**INF (10 mg/kg)**	**placebo**
Overall adverse effects reported (%):	73.5	72.5	68.1
• Infections	44.9	49	36.2
• Cold	18.4	25.5	8.5
• Fever	18.4	15.7	19.1
• Diarrhea	12.2	13.7	4.3
• Cough	6.1	13.7	10.6
• Headache	14.3	5.9	12.8
• Sputum	6.1	5.9	8.5
• Rash	8.2	5.9	0
• Pneumonia	2	5.9	0
• Hot flushes	0	5.9	2.1
• Pruritus	6.1	3.9	0
• Pain, pharynx	6.1	2	6.4
• Stomatitis	8.2	0	6.4
• Epigastralgia	6.1	0	0
Significant differences in adverse events:	None reported. Statistics not given on individual adverse events.		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** yes		
ADEQUATE RANDOMIZATION:	Method NR.		
ADEQUATE ALLOCATION CONCEALMENT:	Method NR.		
BLINDING OF OUTCOME ASSESSORS:	NR.		
ATTRITION (*overall*):	**Overall loss to follow-up:** 14 (4 dropped out prior to first dose) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**INF (combined)**	**placebo**	
Loss to follow-up:	5 (5.2%)	5 (9.8%)	
Withdrawals due to adverse events:	5 (5.2%)	1 (1.9%)	
QUALITY RATING:	**Fair**		

Evidence Table 1 ***Targeted Immune Modulators – Rheumatoid Arthritis***

STUDY:	**Authors: Bathon et al.,[28] Genovese et al.,[49, 50] and Kosinski et al.[30]** **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.**[36] **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: Blumenauer et al.**[34] **Year:** 2003 **Country:** US
FUNDING:	Institute of Population Health, Canada and other sources listed on the CMSG scope
DESIGN:	**Study design:** Meta-analysis **Number of patients: 955**
AIMS OF REVIEW:	To assess the efficacy and safety of etanercept for the treatment of RA.
STUDIES INCLUDED IN META-ANALYSIS	Bathon et al. 2000, Moreland et al., 1999, and Weinblatt et al. 1999.
TIME PERIOD COVERED:	1966 to February 2003
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs or controlled clinical trials comparing ETA to placebo, ETA to MTX, or ETA plus MTX to MTX alone; at least 6 months duration; patients could be on other DMARDS, NSAIDs or corticosteroids.
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients were 16 years of age or older; met the ACR 1987 revised criteria for RA; 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.
CHARACTERISTICS OF INTERVENTIONS:	Treatment with: 1. ETA (10 or 25 mg twice weekly) versus placebo (Moreland) 2. ETA (25 mg subcutaneously twice weekly) plus MTX versus MTX alone (Weinblatt) 3. ETA (10 or 25 mg twice weekly) versus MTX (Bathon) Subcutaneous injections; minimum trial duration of 6 months.

Authors: Blumenauer et al. **Year:** 2003 **Country:** US	
MAIN RESULTS:	**6 Month Efficacy (pooled results from treatments 1 & 2)** • **ACR 20** response was significantly improved in both ETA doses compared to control at 6 months ETA 10 mg/twice weekly: 51% vs. 11% (controls); RR: 4.6 (95% CI 2.4-8.8); NNT: 3 ETA 25 mg/twice weekly: 64% vs. 15% (controls); RR: 3.8 (95% CI 2.5-6.0); NNT: 2 • **ACR 50** response was significantly improved in both ETA doses compared to control at 6 months ETA 10 mg/twice weekly: 24% vs. 5%(controls); RR 4.74 (95% CI 1.68-13.36); NNT: 5 ETA 25 mg/twice weekly: 39% vs. 4% (controls); RR 8.89 (95% CI 3.61-21.89); NNT: 3 • **ACR 70** response was significantly improved in the ETA 25 mg dose, but not with the 10 mg dose at 6 months ETA 10 mg/twice weekly: RR: 7.37 C.I.: 0.93-58.49 ETA 25 mg/twice weekly: 15% vs. 1% (controls); RR 11.31 (95% CI 2.19-58.30); NNT: 7 **6 Month Efficacy (results from treatment 3)** • **ACR 20, ACR 50, and ACR 70** response rates at 6 months were not statistically different between patients taking ETA and patients taking MTX. (no statistics given) **12 Month Efficacy (results from treatment 3)** • **ACR 20** response was not statistically different between patients taking ETA and patients taking MTX at 12 months ETA 10 mg/twice weekly: RR: 0.93 C.I.: 0.79-1.10 ETA 25 mg/twice weekly: RR: 1.12 C.I.: 0.96-1.29 • **ACR 50** response was statistically significantly greater with the 10 mg dose of ETA ($P = 0.04$), but not the 25 mg dose of ETA versus MTX at 12 months ETA 10 mg/twice weekly: RR: 0.75 C.I.: 0.58-0.98 ETA 25 mg/twice weekly: RR: 1.17 C.I.: 0.93-1.46 • **ACR 70** response was not statistically different between patients taking ETA and patients taking MTX at 12 months ETA 10 mg/twice weekly: RR: 0.74 C.I.: 0.49-1.12 ETA 25 mg/twice weekly: RR: 1.16 C.I.: 0.93-1.67 • Significantly more patients in the control groups (33%) withdrew than in the ETA 25 mg dose group (15%). RR 0.43; 95% CI 0.24-0.77 • No significant difference in withdrawal was observed between the control groups and the 10 mg dose group RR: 0.65; CI 0.34-1.26

Authors: Blumenauer et al. **Year:** 2003 **Country:** US	
ADVERSE EVENTS:	• Withdrawals due to adverse events were not statistically significantly different between the 10 mg ETA group and controls RR 0.59; 95% CI 0.31-1.10 • Fewer withdrawals due to adverse events occurred in the 25 mg ETA group versus controls RR 0.50; 95% CI 0.27-0.94 • The risk of ISR was increased in patients taking 10 mg ETA versus controls RR 3.86; 95% CI 2.59-5.77 • The risk of ISR was increased in patients taking 25 mg ETA versus controls RR 4.77; 95% CI 3.26-6.97
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: Breedveld et al.**[31] **Year: 2006** **Country:** Multinational (Europe, North America, Australia)		
FUNDING:	Abbott Laboratories		
RESEARCH OBJECTIVE:	To compare the efficacy and safety of adalimumab plus methotrexate versus methortrexate monotherapy or adalimumab monotherapy in patients with early, aggressive RA who had not previously received MTX treatment.		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (133) **Sample size:** 799		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**MTX** 20 mg/week 2 years 257	**ADA** 40 mg biweekly 2 years 274	**ADA plus MTX** 40 mg biweekly and 20 mg/week 2 years 268
INCLUSION CRITERIA:	18 years of age or older; Fulfilled ACR 1987 revised criteria for the classification of RA; Disease duration of 3 years; ≥8 swollen joints, ≥ 10 tender joints, and an erythrocyte sedimentation rate of ≥ 28 mm/hour or CRP concentration of ≥ 1.5 mg/dl; Had to either be RF positive or have had at least 1 joint erosion.		
EXCLUSION CRITERIA:	Patients who had received treatment with MTX, cyclophosphamide, cyclosporine, azathioprine, or 2 other DMARDs were excluded.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Folic acid		

<table>
<tr><td colspan="4">Authors: Breedveld et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: severe (mean disease duration 0.7 years)</td></tr>
<tr><td></td><td><u>MTX</u></td><td><u>ADA</u></td><td><u>ADA plus MTX</u></td></tr>
<tr><td>Mean age (years):</td><td>52</td><td>52.1</td><td>51.9</td></tr>
<tr><td>Sex (% female):</td><td>73.9</td><td>77.4</td><td>72.0</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>32.3</td><td>31.8</td><td>30.7</td></tr>
<tr><td>• SJC</td><td>22.1</td><td>21.8</td><td>21.1</td></tr>
<tr><td>• Mean disease duration</td><td>.8</td><td>.7</td><td>.7</td></tr>
<tr><td>• previous DMARD use (%)</td><td>31.5</td><td>33.2</td><td>32.5</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>35.4</td><td>36.5</td><td>35.8</td></tr>
<tr><td>• DAS score</td><td>6.3</td><td>6.4</td><td>6.3</td></tr>
<tr><td>• HAQ score</td><td>1.5</td><td>1.6</td><td>1.5</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Percentage of patients in whom an ACR50 response was achieved; Mean change from baseline in the modified total Sharp score comparing the combination therapy group versus the MTX monotherapy group.
Secondary Outcome Measures: Percentage of patients in whom clinical remission was achieved (defined as a DAS28 of < 2.6); Improvement in physical function (as measured by the change from baseline in the HAQ DI); % of patients with ACR20, ACR50, ACR70, or ACR90 response at year 2; Change from baseline in the modified total Sharp score at year 2; Maintained clinical response through 104 weeks, defined as an ACR70 response for ≥6 continuous months
Timing of assessments: NR</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• At 1 year, ACR50 response had been achieved in 62% ADA + MTX, 41% ADA, and 46% MTX monotherapy ($P \leq 0.001$ for both comparison treatments versus combination therapy).*
• 2year: clinical remission had been attained statistically significantly more in combination therapy than with either drug alone: ADA + MTX: 49%; ADA 25%; MTX: 25% (both $P \leq 0.001$).
Intermediate Outcome Measures:
• At 2 years, 49% ADA + MTX achieved remission (DAS20 < 2.6), compared with 23 % on ADA and 21% on MTX ($P < 0.001$).
• ADA + MTX had significantly less progression on the modified Sharp score than either drug alone (1.9 vs 5.5 vs. 10.4 Sharp units; $P < 0.002$)</td></tr>
</table>

Authors: Breedveld et al. **Year: 2006**			
ADVERSE EVENTS: **Overall adverse effects reported (events/ 100 patient-years):**	**MTX**	**ADA**	**ADA plus MTX**
• Serious adverse events	18.5	21.1	15.9
• Infectious adverse events	123	110	119
• Serious infections	2.9	0.7	1.6
• TB	0.2	0	0
• Malignancies	0.4	0.9	0.9
• Lymphoma	0	0	0.2
• Demyelination	0	0	0
Significant differences in adverse events:	Significantly more serious infections occurred in the MTX alone group than in the ADA alone group ($P < 0.05$).		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Unable to determine		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall loss to follow-up:** 260 (32%) **Loss to follow-up differential high:** Yes (Significantly more patients in the ADA + MTX group completed treatment than in the MTX or ADA group $P \leq 0.05$)		
Loss to follow-up:	**MTX**: 88 (34.2%)	**ADA**: 107 (39%)	**ADA plus MTX**: 65 (24.3%)
Withdrawals due to adverse events:	19 (7.4%)	26 (9.5%)	32 (11.9%)
QUALITY RATING:	**Good**		

Evidence Table 1 ***Targeted Immune Modulators – Rheumatoid Arthritis***

STUDY:	**Authors: Clark, et al.**[27] **Year:** 2004 **Country:** International: Europe, US, Canada, Australia
FUNDING:	Health Technology Assessment Programme (UK)
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 1007
AIMS OF REVIEW:	To review the evidence on the clinical benefits and hazards of using anakinra in adult RA patients.
STUDIES INCLUDED IN META-ANALYSIS	• ***Efficacy Trials*** ▪ Bresnihan (1998); Cohen (2001); Cohen (2002); Unpublished report by Amgen (2001; STN 103950 Clinical Review; low-dose for 3 months) • ***Safety Trial*** ▪ Fleischmann (2001) Efficacy data not released to authors with the statement that as the trial was not designed to evaluate efficacy and the varied patient population it enrolled, "it would be inappropriate and misleading to draw any conclusions from any efficacy assessments taken from this study." (p. 30)
TIME PERIOD COVERED:	Through 2002.
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized placebo-controlled (except 1) trials of AKA or AKA plus MTX in patients with highly active RA. Fleischmann study control arm consisted of placebo plus current DMARD treatment.
CHARACTERISTICS OF INCLUDED POPULATIONS:	Mean ages in the 50s; duration of disease from 6 months to over 10 years; majority had failed at least one DMARD and some were taking MTX up to trial start; majority of patients were taking low-dose steroids and NSAIDs.

Authors: Clark et al. **Year:** 2004 **Country:** International: Europe, US, Canada, Australia	
CHARACTERISTICS OF INTERVENTIONS:	AKA alone: AKA from 2.5 mg/day to 150 mg/day AKA + MTX: AKA 0.04 mg/kg per day to 2.0 mg/kg per day or fixed dose 100 mg/day
MAIN RESULTS:	• Combined Data at 6 months (N = 1007): measure AKA 100mg/d versus control (95% CI); significantly greater response rates for AKA- than placebo-treated patients: ▪ ACR20: RR 1.61 (1.31 to 1.97); RD 0.14 (0.09 to 0.20); NNT 7.1 ▪ ACR50: RR 2.26 (1.53 to 3.32); RD 0.09 (0.05 to 0.13); NNT 11.1 ▪ ACR70: RR 3.06 (1.28 to 7.33); RD 0.03 (0.01 to 0.05); NNT 33.3 ▪ HAQ: -0.18 (-0.24 to -0.12) ▪ Patient Global Assessment: -10.37 (-14.41 to -6.33) ▪ SJC: -1.53 (-2.68 to -0.38) • Adjusted indirect comparisons with anti TNF agents (ETA, INF) suggested that AKA may be significantly less effective at relieving clinical symptoms than anti-TNF agents (-0.21; 95% CI: -0.32- -0.10).
ADVERSE EVENTS:	• Withdrawals due to adverse events: Control: 4.1% to 9%; AKA: 5% to 13% • Specific adverse events ▪ Serious adverse events: Control: 3.2% to 11.6%; AKA: 4.4% to 12.8% ▪ Malignancy: Control: 0% to 1.8%; AKA: 0% to 1.1% ▪ ISRs: Control: 3% (low-dose study) to 33%; AKA: 19.8% (low-dose study) to 73% ▪ Any infection: Control: 13.3% (low-dose study) to 50%; AKA: 13.5% (low-dose study) to 48.4% ▪ Serious infections: Control: 0.4% to 1.4%; AKA: 0.8% to 2.1% ▪ Neutropenia: Control: 0% to 4%; AKA: 0% to 9% ▪ Antibodies to IL-1Ra: Control: 0% to 1.8%; AKA: 0.9% to 5%
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: Cohen et al.**[48] **Year: 2004** **Country:** Multinational		
FUNDING:	Amgen, Thousand Oaks, CA, US		
RESEARCH OBJECTIVE:	To evaluate effects of anakinra 100 mg injection daily vs. placebo injection in combination with methotrexate in patients with persistent RA activity after treatment with methotrexate alone.		
DESIGN:	**Study design**: RCT **Setting:** Multicenter, university clinic **Sample size:** 501		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**AKA** 100 mg/day 24 weeks 250	**Placebo** N/A 24 weeks 251	
INCLUSION CRITERIA:	At least 18 years old; diagnosis of RA according to ACR criteria; disease duration of at least 24 weeks before study entry; radiographic evidence of bone erosion in the hands, wrists, or feet; currently active RA. (Active RA defined as six or more swollen joints, nine or more tender of painful joints, and either a C reactive protein level of at least 15 mg/l or an ESR of at least 28 mm/1st hour. Must also be treated with stable dosing of either MTX 10-25 mg/week for at least 24 consecutive weeks or MTX 25-50 mg/every other week for at least 24 weeks.		
EXCLUSION CRITERIA:	Presence of significant systemic disease or autoimmune disease other than RA; serious infection; leukopenia; allergy to products derived from Eschericia coli; were being considered for surgery to their hands, wrists, or feet; treated with intra-articular or systemic corticosteroid injections within 4 weeks before the study; being treated with DMARDs other than MTX (60 day washout period required before randomization); requiring narcotic analgesics for pain; or previous treatment with IL1 receptor antagonist.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX, NSAIDs, or oral corticosteroids (≤ 10 mg/day of prednisone equivalent) if the dose has been stable for at least 4 weeks before randomization.		

Authors: Cohen et al. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** moderate		
	AKA	**Placebo**	
Mean age (years):	56	57	
Sex (% female):	79	75	
Ethnicity:			
Caucasian	86	87	
African American	5	6	
Latino	6	4	
Other	3	2	
Other germane population qualities:			
• Corticosteroid Use (%)	53	52	
• MTX dose (mg/week), mean	16	16	
• SJC (0-66)	20.1	20.0	
• Tender/painful joint count (0-68)	26.8	24.5	
• Physician's assessment of disease severity (0-100)	53.2	52.3	
• Patient's assessment of pain (0-100)	59.2	55.7	
• HAQ score (0-3)	1.4	1.3	

Authors: Cohen et al. **Year: 2004**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Proportion of subjects who attained an ACR20 response at week 24. **Secondary Outcome Measures:** Change from baseline in individual ACR components, including patient's assessment of disease activity, patient's assessment of pain, HAQ score, plasma CRP level, and ESR; ACR50 and ACR70 responses; and sustainability of the ACR20 responses (response for minimum of 4 out of 6 months). **Timing of assessments:** One week after randomization (evaluation of tolerability and adverse events) and every 4 weeks after randomization through week 24
RESULTS:	**Health Outcome Measures: (AKA compared to placebo)** • ACR50 response at week 24: 17% vs. 8%, OR (95% CI) 2.61 (1.46, 4.84) ($P < 0.01$) • ACR70 response at week 24: 6% vs. 2%, OR (95% CI) 3.14 (1.16, 10.06) ($P < 0.05$) • Sustained ACR20 response: 27% vs. 12%, OR (95% CI) 3.43 (2.05, 5.90) ($P < 0.001$) • Change from baseline at week 24: o Patient's assessment of disease activity: -17.7 vs. -8.9 ($P < 0.001$) o Patient's assessment of pain: -19.0 vs. -11.7 ($P < 0.01$) o HAQ: -0.29 vs. -0.18 ($P < 0.05$) • SJC: -6.8 vs. -6.5 (not statistically significant) • Tender or painful joint count: -12.0 vs. -8.7 ($P < 0.01$) • Physician's assessment of disease activity: -25.2 vs. -20.1 ($P < 0.05$) **Intermediate Outcome Measures: (AKA compared to placebo)** • ACR20 response at week 24: 38% vs. 22%, OR (95% CI) 2.36 (1.55, 3.62); $P < 0.001$ • Log transformed CRP: -5 vs. -1 ($P < 0.001$) • ESR: -16.2 vs. – 6.0 ($P < 0.001$)

Authors: Cohen et al. **Year: 2004**			
ADVERSE EVENTS: **Overall adverse events reported:** • ISRs, % o withdrawals • Serious adverse events, % o withdrawals • Infectious events, %	**AKA** 90 65 8.4 4 0.8 33	**Placebo** 81 24 0.8 3 1 26	
Significant differences in adverse events:	None		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (AKA: 3; Placebo: 2)		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 23% **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**AKA** NR 9.2%	**Placebo** NR 1.8%	
QUALITY RATING:	**Fair**		

Evidence Table 1 ***Targeted Immune Modulators -- Rheumatoid Arthritis***

STUDY:	**Authors: Edwards et al.**[58] **Year: 2004** **Country:** Multinational			
FUNDING:	Roche			
RESEARCH OBJECTIVE:	To confirm the role of B cells in RA by evaluating the effect of rituximab 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/ week 24 weeks 40	**RIT** 1000mg on days 1&15 24 weeks 40	**RIT + CYP** RIT + 750mg on days 3&17 24 weeks 41	**RIT + MTX** RIT + ≥10 mg/week 24 weeks 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.			

<table>
<tr><td colspan="5">Authors: Edwards et al.
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="4">Groups similar at baseline: Yes
Disease severity: “highly active” (mean disease duration 10.5 years)</td></tr>
<tr><td></td><td><u>MTX</u></td><td><u>RIT</u></td><td><u>RIT + CYP</u></td><td><u>RIT + MTX</u></td></tr>
<tr><td>Mean age (years):</td><td>54</td><td>54</td><td>53</td><td>54</td></tr>
<tr><td>Sex (% female):</td><td>80</td><td>73</td><td>83</td><td>75</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>• TJC</td><td>32</td><td>34</td><td>33</td><td>32</td></tr>
<tr><td>• SJC</td><td>19</td><td>21</td><td>19</td><td>23</td></tr>
<tr><td>• Mean disease duration</td><td>11</td><td>9</td><td>10</td><td>12</td></tr>
<tr><td>• DMARD use (no.)</td><td>2.6+/- 1.3</td><td>2.5+/-1.6</td><td>2.6+/-1.4</td><td>2.5+/-1.4</td></tr>
<tr><td>• DAS score</td><td>6.9</td><td>6.8</td><td>6.9</td><td>6.8</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="4">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.</td></tr>
<tr><td>RESULTS:</td><td colspan="4">Health Outcome Measures:
• Regimens of RIT in combination with either CYP or MTX resulted in levels of ACR50 response significantly higher ($P = 0.005$) than in the control group.
• At week 24, the proportion of patients with ACR20 & ACR70 responses were higher in the RIT groups than in the control group, with statistically significant increases in the frequency of ACR20 responses in all RIT groups ($P \leq 0.025$) and ACR70 response in the RIT + MTX group.
• 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.</td></tr>
</table>

Authors: Edwards et al. **Year: 2004**				
ADVERSE EVENTS:	**MTX**	**RIT**	**RIT + CYP**	**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:**			
ATTRITION (*treatment specific*):	**MTX**	**RIT**	**RIT + CYP**	**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**			

*primary outcome measures

Evidence Table 1 ***Targeted Immune Modulators -- Rheumatoid Arthritis***

STUDY:	**Authors: Emery et al.**[59] **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 (%):	**RIT/placebo**	**RIT 500mg**	**RIT 1,000mg**
Overall adverse effects reported:	70	81	85
• Severe events	18	17	18
• RA exacerbation	30	17	14
• Headache	13	11	11
• Nausea	9	6	10
• Upper respiratory infection	6	8	6
• Nasopharyngitis	5	6	5
• Arthralgia	3	4	6
• Diarrhea	5	6	3
• Fatigue	5	4	4
• Hypertension	3	4	6
• Rigors	2	4	7
• Dizziness	4	3	5
• Serious infections	1	1	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*):	**RIT/placebo**	**RIT 500mg**	**RIT 1,000mg**
Loss to follow-up:	35%	9%	14%
Withdrawals due to adverse events:	NR	NR	NR
QUALITY RATING:	**Fair**		

Evidence Table 1 ***Targeted Immune Modulators -- Rheumatoid Arthritis***

STUDY:	**Authors: Finckh et al.**[33] **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		

Authors: Finckh et al. **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes but ETA group seems a little more severe **Disease severity:** Mild-moderate-severe		
	ETA	**ETA + DMARD**	**INF + DMARD**
Mean age (years):	53.6	54.4	53.2
Sex (% female):	79	74	82
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• TJC	6	4	3
• SJC	8	7.5	8
• Median disease duration	10.9	9.0	10.6
• DMARD use (%)	0	100	100
• MTX use (%)	0	70	92
• Corticosteroids use (%)	29	36	35
• DAS score	4.7	4.3	4.3
• HAQ score	1.46	1.29	1.40
OUTCOME ASSESSMENT:	**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.		
RESULTS:	**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).		

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: Furst et al.**[43] **Year: 2003** **Study name: STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis)** **Country:** US and Canada		
FUNDING:	Abbott Laboratories, Abbot Park, Il		
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of adalimumab when given with standard anti-rheumatic therapy in patients with active RA not adequately responding to standard therapies.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter (69 sites) **Sample size:** 636		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA** 40 mg subcutaneously every other week 24 weeks 318	**Placebo** N/A 24 weeks 318	
INCLUSION CRITERIA:	18 years of age or older; active RA at screening and baseline as defined by at least 6 swollen joints and 9 tender joints; met the 1987 revised ACR criteria for diagnosis of RA for at least 3 months		
EXCLUSION CRITERIA:	Those who participated in other trials of other biologic DMARD in RA; patients treated with Anti-CD4 therapy or biologic DMARD; history of an active inflammatory arthritide other than RA; history of active listeriosis or mycobacterial infection; major episode of infection requiring hospitalization; treatment with IV antibiotics within 30 days of screening; oral antibiotics within 14 days of screening; any uncontrolled medical condition		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Continued treatment with standard antirheumatic therapy which included traditional DMARD, low dose corticosteroids, NSAID, or analgesics		

Authors: Furst et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR		
	ADA	**Placebo**	
Mean age (years):	55.0	55.8	
Sex (% female):	79.6	79.2	
Ethnicity (%):			
White:	89	85.8	
Other:	11	14.2	
Other germane population qualities:			
• TJC	27.3	27.6	
• SJC	20.9	21.3	
• DMARD use (%)	82.1	84.9	
• MTX use (%)	56.0	62.6	
• Corticosteroids use (%)	50.9	54.4	
• DAS score	NR	NR	
• HAQ score	NR	NR	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Safety (adverse events, physical examination findings, standard laboratory results) **Secondary Outcome Measures:** ACR20; ACR50; ACR70 **Timing of assessments:** Baseline and weeks 2,4,8,12,16,20, and 24		
RESULTS:	**Health Outcome Measures:** • At endpoint, significantly more ADA (28.9%) patients achieved an ACR50 response than placebo patients (11.3%) ($P \leq 0.001$) • At endpoint, significantly more ADA (14.8%) patients achieved an ACR70 response than placebo patients (3.5%) ($P \leq 0.001$) **Intermediate Outcome Measures:** • At endpoint, significantly more ADA (52.8%) patients achieved an ACR20 response than placebo patients (34.9%) ($P \leq 0.001$)		

Authors: Furst et al. **Year: 2003**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**ADA**	**Placebo**	
• URTI	19.8%	15.1%	
• UTI	9.1%	5.7%	
• ISR	19.5%	11.6%	
• Rash	10.7%	6.0%	
• Back pain	5.3%	1.6%	
Significant differences in adverse events:	• Significantly more ADA patients reported ISR than placebo patients 19.5% vs. 11.6% ($P \leq 0.01$) • Significantly more ADA patients reported rash than placebo patients 10.7% vs. 6.0% ($P \leq 0.05$) • Significantly more ADA patients reported back pain than placebo patients 5.3% vs. 1.6% ($P \leq 0.01$) • No significant differences between ADA and placebo in overall adverse events 86.5% vs. 82.7% ($P > 0.05$) and serious infections 1.3% vs. 1.9% ($P > 0.05$)		
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:** 58 (9%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**ADA**	**Placebo**	
Loss to follow-up:	28 (9%)	30 (9%)	
Withdrawals due to adverse events:	9 (3%)	8 (3%)	
QUALITY RATING:	**Fair**		

Evidence Table 1 ***Targeted Immune Modulators – Rheumatoid Arthritis***

STUDY:	**Authors: Geborek et al.**[24] **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 1 ***Targeted Immune Modulators – Rheumatoid Arthritis***

STUDY:	**Authors: Genovese et al.**[32] **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.		

<table>
<tr><td colspan="4">Authors: Genovese, et al.
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes, but there is a slight overall trend to more severe disease in full ETA + AKA group.
Disease severity: Moderate</td></tr>
<tr><td></td><td><u>ETA</u></td><td><u>½ ETA + AKA</u></td><td><u>ETA + AKA</u></td></tr>
<tr><td>Mean age (years):</td><td>54.4</td><td>53.8</td><td>55.7</td></tr>
<tr><td>Sex (% female):</td><td>82.5</td><td>71.6</td><td>77.8</td></tr>
<tr><td>Ethnicity (% white race):</td><td>86.3</td><td>77.8</td><td>75.3</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• TJC</td><td>31.0</td><td>31.0</td><td>35.9</td></tr>
<tr><td>• SJC</td><td>21.4</td><td>19.8</td><td>23.4</td></tr>
<tr><td>• MTX use (%)</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>48.8</td><td>54.3</td><td>44.4</td></tr>
<tr><td>• HAQ score</td><td>1.5</td><td>1.5</td><td>1.6</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">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.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures (<u>ETA</u> v. <u>½ ETA + AKA</u> v. <u>ETA + AKA</u>), 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)</td></tr>
</table>

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: Genovese et al.**[37] **Year: 2005** **Country:** US		
FUNDING:	Bristol-Myers Squibb; the National Center for Research Resources, National Institutes of Health		
RESEARCH OBJECTIVE:	To evaluate efficacy and safety of abatacept in patients with active RA and an inadequate response to at least 3 months of anti-TNF α therapy.		
DESIGN:	**Study design:** RCT **Setting:** multicenter **Sample size:** 391 (393 randomized)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ABA** 10mg/kg 6 months 258	**Placebo** N/A 6 months 133	
INCLUSION CRITERIA:	Age ≥ 18 years; RA for ≥ 1 year; inadequate response to anti-TNF α therapy with ETA, INF, or both at the approved dose after ≥ 3 months of treatment; also included patients who had adverse events while on anti-TNF α therapy but who discontinued primarily due to lack of efficacy; at randomization, presence of at least 10 swollen and 12 tender joints, and CRP levels of at least 1 mg per deciliter; taking oral DMARD or AKA for ≥ 3 months with stable dose for ≥ 28 days.		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids (≤ 10 mg of prednisone or its equivalent per day) if the dose had been stable for at least 28 days		

Authors: Genovese et al.[37] **Year: 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR		
	ABA	**Placebo**	
Mean age (years):	53.4	52.7	
Sex (% female):	77.1	79.7	
Ethnicity:			
% White	96.1	93.2	
% Black	3.5	3.8	
Other germane population qualities:			
• NSAID use (%)	70.2	71.4	
• MTX use (%)	75.6	82.0	
• Corticosteroids use (%)	70.2	64.7	
• DAS28 score	6.5	6.5	
• HAQ score	1.8	1.8	
• SJC	22.3	22.0	
• TJC	31.2	32.8	
• Physician assessment of disease activity	68.8	67.3	
• Pain score	70.8	69.9	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR 20 response; HAQ disability index response (improvement of at least 0.3 from baseline) **Secondary Outcome Measures:** ACR 50 and ACR 70 at 6 months; DAS28; SF-36 at 6 months; **Timing of assessments:** NR		
RESULTS:	**Health Outcome Measures:** • At 6 months, rate of ACR 20 response was (ABA vs placebo) 50.4% vs. 19.5% ($P < 0.001$) • At 6 months, rates of ACR50 and ACR70 response were significantly higher in the ABA group than placebo group (ACR50, 20.3% vs. 3.8%, $P < 0.001$; ACR70, 10.2% vs. 1.5%, $P = 0.003$) • At 6 months, rates of remission (via DAS28) were 10.0% in ABA group vs. 0.8% in placebo group. ($P < 0.001$) • At 6 months, percentage of patients with clinically meaningful improvement in physical function (via HAQ) were 47.3% (ABA) vs. 23.3% (placebo) ($P<0.001$) • ABA group had significantly greater improvements from baseline in scores for all 8 physical and mental subscales of the SF-36.		

Authors: Genovese et al.[37] **Year: 2005**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Serious adverse events • Serious infections • Headache	**ABA** 79.5 10.5 2.3 12.4	**Placebo** 71.4 11.3 2.3 5.3	
Significant differences in adverse events:	Headache ($P = 0.03$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 2		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 17.6% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ABA** 13.6% 3.5%	**Placebo** 25.6% 3.8%	
QUALITY RATING:	**Good**		

*primary outcome measures

Evidence Table 1 ***Targeted Immune Modulators-Rheumatoid Arthritis***

STUDY:	**Authors: Hyrich et al.**[61] **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:	**ETA**	**ETA+DMARD**	**ETA+MTX**	**INF**	**INF+DMARD**	**INF+MTX**
Dose:	25 mg 2x wk	Not specified	Not specified	3mg/kg wks 0,2,6 then every 8wks	Not specified	Not specified
Duration:	6 months	6 months	6 months	6 months	6 months	6 months
Sample size:	763	245	250	128	121	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.**[35] **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.**[44] **Year: 2004** **Country:** US and Canada		
FUNDING:	Abbott Laboratories, Abbott Park, Illinois		
RESEARCH OBJECTIVE:	To investigate the ability of adalimumab to inhibit the progression of structural joint damage, reduce the signs and symptoms, and improve physical function in patients with RA receiving concomitant methotrexate treatment.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter (89 sites) **Sample size:** 619		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA 40 mg biweekly** 40 mg every other week 52 weeks 207	**ADA 20 mg weekly** 20 mg weekly 52 weeks 212	**Placebo** N/A 52 weeks 200
INCLUSION CRITERIA:	18 years of age or older; RA diagnosed according to ACR criteria; 9 or greater tender joints; 6 or greater swollen joints; CRP concentration $\geq$ 1 mg/dl; either RF positivity or at least 1 joint erosion on hand and feet radiographs; required to be on stable MTX therapy for 3 or more months		
EXCLUSION CRITERIA:	Prior use of anti-CD4 antibody therapy or TNF antagonists; active inflammatory arthritide other than RA; active listeriosis or mycobacterial infection; lymphoma or leukemia; major episode of infection; pregnant or lactating; uncontrolled medical condition		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Constant doses of concomitant RA therapies allowed (e.g. MTX, corticosteroids, NSAIDs)		

Authors: Keystone et al. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate to severe		
	ADA 40 mg biweekly	**ADA 20 mg weekly**	**Placebo**
Mean age (years):	56.1	57.3	56.1
Sex (% female):	76.3	75.5	73.0
Ethnicity: (% White)	83.6	85.4	83.0
Other germane population qualities:			
• TJC	27.3	27.9	28.1
• SJC	19.3	19.6	19.0
• DMARD use (%)	NR	NR	NR
• MTX use (%)	100	100	100
• Corticosteroids use (%)	NR	NR	NR
• Physician's assessment of disease activity	62.0	61.6	613.
• Patient's assessment of disease activity	52.7	51.9	54.3
• HAQ score	1.45	1.44	1.48
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Radiographic progression (Sharp score); ACR20; HAQ **Secondary Outcome Measures:** ACR50; ACR70; SF-36 **Timing of assessments:** Radiographs performed at baseline, week 24, and week 52; ACR responses and HAQ assessed at weeks 2, 4, 8, 12, 16, 20 ,24, 32, 40, 48, and 52;		
RESULTS:	**Health Outcome Measures at 52 weeks:** • ACR 50 response was significantly improved in ADA groups compared to placebo ($P \leq 0.001$; ADA 40 mg biweekly: 41.5%, ADA 20 mg weekly: 37.7%, placebo: 9.5%) • ACR 70 response was significantly improved in ADA groups compared to placebo ($P \leq 0.001$; ADA 40 mg biweekly: 23.2%, ADA 20 mg weekly: 20.8%, placebo: 4.5%) • Improvements in HAQ function scores were significantly better in ADA treated groups compared to placebo ($P \leq 0.001$) **Intermediate Outcome Measures at 52 weeks:** • Radiographic progression was significantly less in ADA treated groups compared to placebo. ($P \leq 0.001$) • ACR 20 response was significantly improved in both ADA groups compared to placebo ($P \leq 0.001$; ADA 40 mg biweekly: 58.9%, ADA 20 mg weekly: 54.7%, placebo: 24.0%)		

Authors: Keystone et al. **Year: 2004**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**ADA 40 mg biweekly**	**ADA 20 mg weekly**	**Placebo**
• Serious infections	5.3%	2.4%	0.5%
• ISR	26.1%	22.2%	24.0%
• URTI	19.8%	19.3%	13.5%
• Rhinitis	16.4%	17.5%	16.5%
• Sinusitis	15.9%	14.6%	13.0%
• Accidental injury	14.0%	13.2%	12.0%
Significant differences in adverse events:	• Serious infections were significantly greater in the ADA 40 mg biweekly group than placebo. ($P \leq 0.01$). • ADA was associated with statistically significant decreases ($P \leq 0.05$ compared with baseline) in mean white blood cell count, platelet count, and neutrophil percentage, and statistically significant increases ($P \leq 0.05$ compared to baseline) in the mean hemoglobin concentration, hematocrit, and lymphocyte percentage.		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 152/619 (25%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**ADA 40 mg biweekly**	**ADA 20 mg weekly**	**Placebo**
Loss to follow-up:	48 (23%)	44 (21%)	60 (30%)
Withdrawals due to adverse events:	26 (13%)	16 (7.5%)	13 (6.5%)
QUALITY RATING:	**Fair**		

Evidence Table 1 ***Targeted Immune Modulators – Rheumatoid Arthritis***

STUDY:	**Authors: Klareskog et al.**[29] **and van der Heijde et al**.[51, 52] **Study name: TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes)** **Year: 2004 and 2006** **Country:** Multinational (Europe)		
FUNDING:	Wyeth Research		
RESEARCH OBJECTIVE:	To compare safety, efficacy and patient reported outcomes of the combination of etanercept and methotrexate 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) 228	**ETA** 25 mg twice per week 52 weeks (2 yrs) 223	**MTX + ETA** Same MTX + ETA doses 52 weeks (2 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 at 52 weeks: 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 $P < 0.05$

Authors: Klareskog et al. and van der Heijde et al. **Year: 2004 and 2006**	
RESULTS (continued):	**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

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)	10 (4) (6)	10 (4) (6)
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: Kremer et al.**[39, 40] **and Emery et al.**[41] **Year: 2003, 2005, and 2006** **Country:** Multinational		
FUNDING:	Bristol-Myers Squibb		
RESEARCH OBJECTIVE:	To investigate effectiveness of cytotoxic T-lymphocyte-associated antigen 4-IgG1 (abatacept) therapy in patients with RA who had an inadequate response to methotrexate.		
DESIGN:	**Study design:** RCT, double blind, placebo-controlled **Setting:** multicenter **Sample size:** 339		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo/MTX** Mean 15mg/wk 6 months/12 months 119	**ABA2/MTX** 2mg/kg 6 months/12 months 105	**ABA10/MTX** 10mg/kg 6 months/12 months 115
INCLUSION CRITERIA:	Age 18-65 years; meeting ACR criteria for RA and in functional class I, II, or III; active disease, characterized by ≥ 10 swollen and 12 tender joints, and CRP levels of at least 1 mg per deciliter; Treatment with MTX (10-30 mg/week) for at least 6 months and have a stable dose for 28 days before enrollment;		
EXCLUSION CRITERIA:	Nursing or pregnant women		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX; stable low dose corticosteroids (≤ 10 mg / day); NSAIDS		

<table>
<tr><td colspan="4">Authors: Kremer et al. and Emery et al.
Year: 2003 and 2006</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: NR (mean disease duration 9.4 years)</td></tr>
<tr><td><u>Placebo/MTX</u></td><td><u>ABA2/MTX</u></td><td><u>ABA10/MTX</u></td></tr>
<tr><td>Mean age (years):</td><td>54.7</td><td>54.4</td><td>55.8</td></tr>
<tr><td>Sex (% female):</td><td>66</td><td>63</td><td>75</td></tr>
<tr><td>Ethnicity:</td><td></td><td></td><td></td></tr>
<tr><td>% White</td><td>87</td><td>87</td><td>87</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• MTX use (%)</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td>• SJC</td><td>21.8</td><td>20.2</td><td>21.3</td></tr>
<tr><td>• TJC</td><td>29.2</td><td>28.2</td><td>30.8</td></tr>
<tr><td>• Physician global assessment</td><td>63.3</td><td>61.0</td><td>62.1</td></tr>
<tr><td>• Pain score</td><td>65.2</td><td>65.2</td><td>62.1</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ACR 20 response at 6 months, HRQOL at 1 year
Secondary Outcome Measures: ACR 50 and ACR 70 at 6 months; Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36)
Timing of assessments: ACRs on day 1, 15, and 30 and then monthly; SF-36 at baseline, 90 days then 180 days.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• At 6 months, rate of ACR20 was significantly higher in the ABA 10mg group than placebo group: ACR 20 was 35.3% (placebo/MTX), 41.9% (ABA 2mg/MTX), and 60.0% (ABA 10mg/MTX; P < 0.001 vs. placebo).
• At 6 months, rates of ACR50 and ACR70 response were significantly higher in both ABA group than placebo group: ACR 50: 11.8% (placebo/MTX), 22.9% (ABA 2mg/MTX; P < 0.05 vs. placebo), and 36.5% (ABA 10mg/MTX; P < 0.001 vs. placebo). ACR 70: 1.7% (placebo/MTX), 10.5% (ABA 2mg/MTX; P < 0.05 vs. placebo), and 16.5% (ABA 10mg/MTX; P < 0.001 vs. placebo).
• Patients in ABA 10mg/MTX group had significant and clinically meaningful improvements from baseline scores in all 8 subscales of the SF-36, with the greatest effect in the physical-health, pain, vitality, and social function domains.
• One year HRQOL ABA10 vs. MTX (MANOVA F = 4.71, P < 0.001) and ABA2 vs. MTX MANOVA F = 1.97, P = 0.05</td></tr>
</table>

Authors: Kremer et al. and Emery et al. **Year: 2003 and 2006**			
ADVERSE EVENTS (%): **Overall adverse effects reported:**	**Placebo/MTX**	**ABA2/MTX**	**ABA10/MTX**
• Serious adverse events	10.1	11.4	2.6
• Headache	12.6	14.3	10.4
• URTI	10.1	12.4	13.0
• Musculoskeletal pain	12.6	14.1	7.0
• Nausea and vomiting	11.8	6.7	13.9
• Fatigue	8.4	9.5	5.2
• Cough	8.4	5.7	10.4
• Diarrhea	5.9	6.7	9.6
• Pharyngitis	5.9	4.8	10.4
Significant differences in adverse events:	*P* = 0.03 for serious adverse events in ABA 10mg/MTX group vs. placebo.		
ANALYSIS:	**ITT:** Yes (LOCF) **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Safety assessments unblinded.		
ATTRITION (*overall*):	**Overall loss to follow-up:** 38.9% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Placebo/MTX**	**ABA2/MTX**	**ABA10/MTX**
Loss to follow-up:	34.5%	21.9%	13.9%
Withdrawals due to adverse events:	7	7	2
QUALITY RATING:	**Fair**		

*primary outcome measures

Evidence Table 1 ***Targeted Immune Modulators—Rheumatoid Arthritis***

STUDY:	**Authors: Kremer et al.**[38] **Year: 2006** **Country:** Multinational		
FUNDING:	Bristol-Myers Squibb		
RESEARCH OBJECTIVE:	To evaluate effects of abatacept in patients with persistent, active RA despite methotrexate treatment.		
DESIGN:	**Study design:** RCT (double-blind, placebo-controlled) **Setting:** Multicenter **Sample size:** 652		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ABA + MTX** 10mg/kg per month 1 year 433	**Placebo + MTX** N/A 1 year 219	
INCLUSION CRITERIA:	Age ≥ 18 years; RA (based on ACR criteria) for ≥ 1 year that was persistent and active despite MTX treatment; treatment with MTX (≥ 15 mg/wk) for 3+ months, with a stable dose for 28 days before enrollment; and completion of 28-day DMARD washout period. At randomization, required ≥ 10 swollen or 12 tender joints; CRP ≥ 10.0 mg/L while receiving MTX.		
EXCLUSION CRITERIA:	Positive tuberculin skin test, unless patient had completed treatment for latent TB before enrollment.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Corticosteroid use, with dosages ≤ 10 mg/day of prednisone, stabilized for 25 days before randomization & stable doses of NSAIDS.		

Authors: Kremer et al. **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR (mean disease duration 8.7 years)		
	ABA + MTX	**Placebo + MTX**	
Mean age (years):	51.5	50.4	
Sex (% female):	77.8	81.7	
Ethnicity (% White):	87.5	88.1	
Other germane population qualities:			
• TJC (No.)	31.0	32.3	
• SJC (No.)	21.4	22.1	
• Mean disease duration (yrs)	8.5	8.9	
• DMARD use (%)	12.2	8.7	
• MTX use (%)	100	100	
• Corticosteroids use (%)	72.1	68.5	
• HAQ-DI score	1.7	1.7	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR 20 at 6 months; clinically meaningful improvements (≥0.3 units) in HAQ-DI at 1 year; change from baseline in joint erosion score (Genant-modified Sharp score) at 1 year. **Secondary Outcome Measures:** ACR50/ACR70 at 6 months; all ACR scores at 1 year; DAS28; SF-36. **Timing of assessments:** At enrollment & at every visit before treatment administration on days 1,15,29; every 28 days up to & including day 169 (6 months); and days 225, 281, and 365 (1 year).		
RESULTS:	**Health Outcome Measures:** • 6-month ACR 20 = 67.9% (ABA) vs. 39.7% (placebo) (difference, 28.2% [95% CI, 19.8 to 36.7]); 6-month ACR 50 = 39.9% (ABA) vs. 16.8% (placebo) (difference, 23.0% [95% CI, 15.0 to 31.1]); 6-month ACR 70 = 19.8% (ABA) vs. 6.5% (placebo) (difference, 13.3% [95% CI, 7.0 to 19.5]) • 1-year ACR 20 = 73.1% (ABA) vs. 39.7% (placebo) (difference, 33.4% [95% CI, 25.1 to 41.7]); 1-year ACR 50 = 48.3% (ABA) vs. 18.2% (placebo) (difference, 30.1% [95% CI, 21.8 to 38.5]); 1-year ACR 70 = 28.8% (ABA) vs. 6.1% (placebo) (difference, 22.7% [95% CI, 15.6 to 29.8]). All $P < 0.001$ • At 1 year, physical function improved in 63.7% (ABA) vs. 39.3% (placebo) ($P < 0.001$; difference 24.4%[95% CI, 15.9 to 32.9]). • 1 year, ABA-treated patients showed statistically significant slowing of structural damage progression: median change from baseline erosion score was 0.0 (25^{th} & 75^{th} percentiles, 0.0 and 1.0, respectively) for ABA vs. 0.27 (25^{th} & 75^{th} percentiles, 0.0 and 1.3, respectively) for placebo ($P = 0.029$) • DAS28 ≤ 3.2 achieved in 30.1% (6-month) & 42.5% (1-year) of ABA group vs. 10.0% (6-month) & 9.9% (1-year) of placebo group ($P < 0.001$).		

Authors: Kremer et al. **Year: 2006**			
ADVERSE EVENTS: **Overall adverse effects reported(%):** • Headache • Nasopharyngitis • Nausea • Diarrhea • Upper respiratory infection • Dizziness • Back pain • Hypertension • Fatigue	**ABA + MTX** 87.3 17.6 15.2 12.0 10.9 10.9 9.2 9.2 5.5 5.3	**Placebo + MTX** 84.0 11.9 11.4 11.0 9.6 9.6 7.3 5.5 1.4 6.8	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (n= 14; 1 study center was excluded because of poor adherence)		
ADEQUATE RANDOMIZATION:	**Yes**		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 16.1% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ABA + MTX** 11% 4.2%	**Placebo + MTX** 26% 1.8%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Evidence Table 1 ***Targeted Immune Modulators—Rheumatoid Arthritis***

STUDY:	**Authors: Kristensen et al.**[26] **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**		

*primary outcome measures

Evidence Table 1 ***Targeted Immune Modulators – Rheumatoid Arthritis***

STUDY:	**Authors: Moreland et al.**[53] **and Mathias et al.**[54] **Year: 1999 and 2000** **Country:** North America		
FUNDING:	Immunex Corporation, Seattle, Washington		
RESEARCH OBJECTIVE:	To compare the functional status and well-being of patients with RA who were randomized to placebo, etanercept 10 mg, or etanercept 25 mg over a 26-week period; embedded in a phase III, double-blind clinical trial (Moreland, 1999)		
DESIGN:	**Study design:** RCT **Setting:** Multicenter, specialty clinic **Sample size:** 234		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 26 weeks 80	**ETA (low dose)** 10 mg twice per week 26 weeks 76	**ETA (high dose)** 25 mg twice per week 26 weeks 78
INCLUSION CRITERIA:	Adults at least 18 years old; meet ACR criteria for RA and fall into functional class I, II, or III; discontinuation of one to four DMARDs due to lack of effect; have currently active disease defined as 12 or more tender joints, 10 or more swollen joints, and at least one of the following: ESR $\geq$ 28 mm/h, CRP $\geq$ 20 mg/dl, or morning stiffness $\geq$ 45 minutes; aminotransferase levels $\leq$ twice the upper limit of normal; hemoglobin level of $\geq$ 85 g/dl; leukocyte count of $\geq$ 125,000 cells/mm3; a serum creatinine of $\leq$ 2 mg/dl; and, no DMARDs within one month of enrollment. (From Moreland 1999.)		
EXCLUSION CRITERIA:	Intra-articular corticosteroid steroid injections within 4 weeks of enrollment; corticosteroid doses over the equivalent of 10 mg of prednisone per day; and, NSAID dosages exceeding manufacturer recommended dosing (From Moreland 1999).		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable doses of corticosteroids and NSAIDs; however, no analgesics within 24 hours preceding a joint examination; no concurrent DMARDs allowed during the study.		

Authors: Moreland et al. and Mathias et al. **Year: 1999 and 2000**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe		
	Placebo	**ETA (low dose)**	**ETA (high dose)**
Mean age (years):	51	53	53
Sex (% female):	76	84	74
Ethnicity (% white):	89	96	94
Other germane population qualities:			
• TJC	35	34	33
• SJC	25	25	25
• Prior DMARD use (%)	100	100	100
• Prior DMARDs, mean	3.0	3.4	3.3
• MTX use prior to study (%)	90	92	87
• Corticosteroids use (%)	58	66	81
• DAS score	N/A	N/A	N/A
• HAQ score	1.66	1.77	1.63
• Feeling Thermometer	47	44	48
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20/50, Paulus Index **Secondary Outcome Measures:** SF-36, HAQ, feeling thermometer **Timing of assessments:** Baseline and at weeks 2, 3, 4, 8, 12, 16, 21, and 26.		

Authors: Moreland et al. and Mathias et al. **Year: 1999 and 2000**	

RESULTS:	**Health Outcome Measures: (placebo v. ETA 10 mg v. ETA 25 mg)**
	• Significantly more patients in the ETA groups than in the placebo group achieved ACR50 response (24% vs. 40% vs. 5%; $P < 0.001$ for each ETA group compared to placebo)
	• Patients receiving ETA achieved statistically significant improvements on a variety of quality-of-life measures, including the HAQ, compared to placebo after 6 months of therapy.
	• **HAQ:**
	  • Data NR
	  • Placebo v. ETA 10 mg and placebo v. ETA 25 mg: $P < 0.05$
	• **SF-36: PCS-36 (n = 48)**
	  • Data NR
	  • At months 3 and 6, ETA groups performed significantly ($P \leq 0.01$) better than the placebo group
	• **SF-36: MCS-36 (n = 48)**
	  • Data NR
	  • At month 6, ETA groups performed significantly ($P < 0.02$) better than the placebo group
	• **MOS**
	  • Energy/Vitality: At month 6: 4.74 v. 17.38 v. 16.35 ($P < 0.01$)
	  • Mental Health: At month 6: 4.41 v. 12.95 v. 13.88 ($P < 0.01$)
	• **Feeling Thermometer:**
	  • 8.15 v. 19.97 v. 18.19
	  • ETA 10 mg v. placebo: $P = 0.019$; ETA 25 mg v. placebo: $P = 0.054$
	
	Intermediate outcome measures
	• Significantly more patients in the ETA groups than in the placebo group achieved ACR20 response (51% vs. 59% vs. 11%; $P < 0.001$ for each ETA group compared to placebo)

Authors: Moreland et al. and Mathias et al. **Year: 1999 and 2000**			
ADVERSE EVENTS: %	**Placebo**	**ETA (low dose)**	**ETA (high dose)**
Overall adverse effects reported:	NR	NR	NR
• Injection-site reaction	13	43	49
• URTI	16	29	33
• Headache	10	20	14
• Sinusitis	11	11	12
• Rhinitis	11	12	10
• Diarrhea	6	11	5
Significant differences in adverse events:	ISRs- each treatment groups vs. placebo ($P < 0.001$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (12/246)		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 41.5% **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*):	**Placebo**	**ETA (low dose)**	**ETA (high dose)**
Loss to follow-up:	67.5%	31.6%	24.4%
Withdrawals due to adverse events:	3.8%	6.6%	2.6%
Withdrawals due to lack of efficacy:	52.5%	21.1%	15.4%
QUALITY RATING:	**Fair**		

Evidence Table 1 ***Targeted Immune Modulators -- Rheumatoid Arthritis***

STUDY:	**Authors: Moreland et al.**[42] **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: St. Clair et al.**[56] **and Smolen et al.**[70, 72] **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: van de Putte et al.**[45] **Year: 2003** **Country:** Multinational (Europe)			
FUNDING:	Abbott Laboratories			
RESEARCH OBJECTIVE:	To evaluate efficacy, dose response, safety, and tolerability of adalimumab in DMARD refractory patients with longstanding, active RA			
DESIGN:	**Study design:** RCT **Setting:** Multi-center (25 sites) **Sample size:** 284			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA** 20 mg 12 weeks 72	**ADA** 40 mg 12 weeks 70	**ADA** 80 mg 12 weeks 72	**Placebo** N/A 12 weeks 70
INCLUSION CRITERIA:	Patients 18 years of age or older; a diagnosis of RA according to the revised 1987 American College of Rheumatology (ACR) criteria and active inflammatory synovitis, defined by a TJC of ≥ 12 and SJC of ≥10 based on an examination of 68 and 66 assessed joints, respectively; either an erythrocyte sedimentation rate (ESR) of ≥28 mm/1st h or a serum CRP level ≥20 mg/l; patients for whom treatment had failed with at least one traditional DMARD were eligible.			
EXCLUSION CRITERIA:	Joint surgery within two months before screening or an episode of infection requiring admission to hospital within 30 days before study entry; treatment with either intra-articular or intramuscular corticosteroids within four weeks of prescreening or an investigational chemical or biological drug within two or six months, respectively, of prescreening; patients with impaired renal or hepatic function or an abnormal serum profile; patients' body weight could not exceed 100 kg; women of childbearing potential required a negative pregnancy test; the use of a reliable contraceptive method was mandatory.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs; oral corticosteroids; propoxyphene; codeine; acetaminophen plus codeine; and aspirin			

Authors: van de Putte et al. **Year: 2003**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Severe			
	ADA 20	**ADA 40**	**ADA 80**	**Placebo**
Mean age (years):	53.7	52.6	53.2	50.2
Sex (% female):	85	81	69	81
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• TJC	31.7	31.0	32.5	30.9
• SJC	19.64	18.7	19.3	20.2
• Corticosteroids use (%)	76	70	75	77
• HAQ score (Disability Index)	1.79	1.74	1.66	1.63
• DAS score	7.0	7.1	7.0	7.1
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 **Secondary Outcome Measures:** ACR50; ACR70; TJC; SJC; DAS28; disability index of the HAQ. **Timing of assessments:** 2 and 12 weeks			

Authors: van de Putte et al. **Year: 2003**	
RESULTS:	**Health Outcome Measures: Week 12** • The ADA treatment groups all had significantly better ACR50 than placebo. ADA20 vs. Placebo 17 (23.9%) vs. 1 (1.4%) ($P \leq 0.001$) ADA40 vs. Placebo 19 (27.1%) vs. 1 (1.4%) ($P \leq 0.001$) ADA80 vs. Placebo 14 (19.4 %) vs. 1 (1.4%) ($P \leq 0.001$) • The ADA treatment groups all had significantly better ACR70 than placebo. ADA20 vs. Placebo 8 (11.3%) vs. 0 (0%) ($P \leq 0.05$) ADA40 vs. Placebo 7 (10.0%) vs. 0 (0%) ($P \leq 0.05$) ADA80 vs. Placebo 6 (8.3 %) vs. 0 (0%) ($P \leq 0.05$) • All ADA treatment groups improved significantly for both TJC and SJC. TJC changes from baseline ADA20 vs. Placebo -14 (44.2%) vs. -5.1 ($P \leq 0.001$) ADA40 vs. Placebo -15.3 (49.4%) vs. -5.1 ($P \leq 0.001$) ADA80 vs. Placebo -15.2 (46.8%) vs. -5.1 ($P \leq 0.001$) SJC changes from baseline ADA20 vs. Placebo -8.1 (41.3%) vs. -2.8 (13.9%) ($P \leq 0.001$) ADA40 vs. Placebo -9.6 (51.3%) vs. -2.8 (13.9%) ($P \leq 0.001$) ADA80 vs. Placebo -10.7 (54.6%) vs. -2.8 (13.9%) ($P \leq 0.001$) • All ADA treatment groups improved significantly on the HAQ Disability Index. ADA20 vs. Placebo 0.45 vs. 0.04 ($P \leq 0.001$) ADA40 vs. Placebo 0.47 vs. 0.04) ($P \leq 0.001$) ADA80 vs. Placebo 0.48 vs. 0.04 ($P \leq 0.001$) • All ADA treatment groups improved significantly on the DAS28. ADA20 vs. Placebo -1.8 vs. -0.5 ($P \leq 0.001$) ADA40 vs. Placebo -2.1 vs. -0.5 ($P \leq 0.001$) ADA80 vs. Placebo -2.0 vs. -0.5 ($P \leq 0.001$) **Intermediate Outcomes** • The ADA treatment groups all had significantly better ACR20, than placebo. ADA20 vs. Placebo 36 (50.7%) vs. 7 (10%) ($P \leq 0.001$) ADA40 vs. Placebo 40 (57.1%) vs. 7 (10%) ($P \leq 0.001$) ADA80 vs. Placebo 39 (54.2 %) vs. 7 (10%) ($P \leq 0.001$)

Authors: van de Putte **Year: 2003**				
ADVERSE EVENTS: **Overall adverse effects reported:** • Serious AE • Serious or intractable AE • Serious infections • ISRs • Hyperlipidamea	**ADA 20** NR 3 11 0 29 25	**ADA 40** NR 7 16 3 23 31	**ADA 80** NR 13 19 3 29 31	**Placebo** NR 10 27 0 6 19
Significant differences in adverse events:	Yes In all doses vs. placebo- Severe or intractable AE 15 vs.27 ($P \leq 0.05$) ISRs 27 vs. 6 ($P \leq 0.01$) Proteinuria 7 vs. 0 ($P \leq 0.05$)			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** yes-one with Felty Syndrome			
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:**	**Overall loss to follow-up:** 18% **Loss to follow-up differential high:** No **ADA 20** 6 0	**ADA 40** 4 4	**ADA 80** 1 3	**Placebo** 1 1
QUALITY RATING:	**Fair**			

Evidence Table 1 ***Targeted Immune Modulators – Rheumatoid Arthritis***

STUDY:	**Authors: van de Putte et al.**[46] **Year: 2004** **Country:** Multinational (3)				
FUNDING:	Abbott				
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of monotherapy with adalimumab in patients with RA for whom previous DMARD treatment failed				
DESIGN:	**Study design:** RCT **Setting:** Multicenter (52) **Sample size:** 544				
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 26 weeks 110	**ADA** 20 mg biweekly (BW) 26 weeks 106	**ADA** 20 mg week (W) 26 weeks 112	**ADA** 40 mg week 26 weeks 113	**ADA** 40 mg biweekly 26 weeks 103
INCLUSION CRITERIA:	18 years or older who met criteria for RA established by ACR; treatment with at least one DMARD had previously failed; had active disease defined as ≥12 tender joints based on a 68 joint assessment, ≥10 swollen joints based on a 66 joint evaluation, and either an ESR ≥28 mm/1st hr or a serum CRP concentration ≥20 mg/l; negative pregnancy test and the use of a reliable contraceptive method were mandatory in women of childbearing potential				
EXCLUSION CRITERIA:	Joint surgery within 2 months before screening or infection requiring admission to hospital or treatment with intravenous antibiotics within 1 month before screening; intra-articular or intramuscular corticosteriod within 1 month before the study or an investigational small molecule drug or biological agent within 2 months or 6 months before screening; patients with impaired renal or hepatic function or a history of TB as shown by radiographic				
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Propoxyphene, aspirin, codeine				

Authors: van de Putte et al. **Year: 2004**					
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Severe				
	Placebo	**ADA20BW**	**ADA20W**	**ADA40W**	**ADA 40BW**
Mean age (years):	53.5	53.1	54.4	52.7	51.8
Sex (% female):	77.3	79.2	72.3	79.6	78.6
Ethnicity:	NR	NR	NR	NR	NR
Other germane population qualities:					
• TJC	35.5	33.9	35.3	33.7	33.8
• SJC	19.8	19.6	19.8	20.5	19.3
• DMARD use	0	0	0	0	0
• MTX treatment failure (%)	86.4	88.7	93.8	92.9	87.4
• Corticosteroids use (%)	74	76	77	84	74
• DAS score	7.09	7.08	7.09	7.02	7.09
• HAQ score	1.88	1.88	1.88	1.83	1.84
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 response **Secondary Outcome Measures:** ACR50 and ACR70 response rates, improvements in ACR core components, HAQ-DI, DAS 28, EULAR response **Timing of assessments:** Baseline, biweekly during the first month, monthly thereafter, and at week 26				
RESULTS:	**Health Outcome Measures at 26 weeks (only observed values reported) :** • Patients treated with ADA 20 mg biweekly, 20 mg per week, 40 mg/wk , 40 mg biweekly achieved better improvement in mean HAQ-DI vs. those receiving placebo (-0.29, -0.39, -0.38, -.049 vs. –0.07; $P \leq 0.01$) • ACR70 response rates for ADA 40 mg biweekly were significantly better at all evaluation points and for ADA 40 mg weekly at most evaluation points compared with placebo ($P \leq 0.05$) • No significant difference in good EULAR responders between ADA regimens and placebo except for ADA 40 mg weekly (13.6% vs. 3.6%; $P < 0.01$) **Intermediate Outcome Measures at 26 weeks (only observed values reported):** • ACR20 response rates were 35.8%, 39.3%, 46.0%, and 53.4% with ADA 20 mg biweekly, 20 mg per week, 40 mg biweekly, 40 mg per week versus 19.1% with placebo ($P \leq 0.01$) • Significantly more moderate EULAR responders for ADA groups than for placebo group ($P < 0.001$)				

Authors: van de Putte et al. **Year:2004**					
ADVERSE EVENTS: **Overall adverse effects reported [%]:**	**Placebo** NR	**ADA20BW** NR	**ADA20W** NR	**ADA40W** NR	**ADA40BW** NR
• Clinical flare reaction	21.8	23.6	19.6	15.9	15.5
• Rhinitis	10.9	10.4	18.8	18.6	21.4
• Headache	10.0	20.8	17.9	21.2	20.4
• Rash	5.5	14.2	16.1	20.4	11.7
• ISR	0.9	4.7	11.6	9.7	16.5
• Sore throat	6.4	13.2	3.6	9.7	4.9
• Gastrointestinal pain	4.5	12.3	4.5	6.2	6.0
• Pruritus	0.9	10.4	7.1	11.5	8.7
Significant differences in adverse events:	• Placebo vs. all ADA : Headache (20% vs. 10%), rash (15.7% vs. 5.5%), ISRs (10.6% vs. 0.9%), and pruritus (9.4% vs. 0.9%) occurred significantly more often in ADA patients (all $P < 0.05$).				
ANALYSIS:	**ITT:** No **Post randomization exclusions:** Yes [8]				
ADEQUATE RANDOMIZATION:	Yes				
ADEQUATE ALLOCATION CONCEALMENT:	Yes				
BLINDING OF OUTCOME ASSESSORS:	Yes				
ATTRITION (*overall*):	**Overall loss to follow-up:** 33% **Loss to follow-up differential high:** yes				
ATTRITION (*treatment specific*):	**Placebo**	**Adalimumab**			
Loss to follow-up:	56.4%	27.2%			
Withdrawals due to adverse events:	0.9%	3.7%			
QUALITY RATING:	**Fair**				

Evidence Table 1 ***Targeted Immune Modulators – Rheumatoid Arthritis***

STUDY:	**Authors: Weaver et al.**[25] **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 • Y	**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**				

*primary outcome measures

Evidence Table 1 ***Targeted Immune Modulators – Rheumatoid Arthritis***

STUDY:	**Authors: Weinblatt et al.**[47, 143] **Year: 2003 and 2006** **Country:** US and Canada			
FUNDING:	Abbott Labs and Knoll Pharmaceuticals			
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of adalimumab administered subcutaneously every other week to patients with active RA despite long term therapy with methotrexate and long-term safety and efficacy in a 4 year extended study.			
DESIGN:	**Study design:** RCT and open label extension **Setting:** Multicenter (35 sites) **Sample size:** 271 (262 in extension)			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ADA** 20 mg every 2 weeks 24 weeks 69	**ADA** 40 mg every 2 weeks 24 weeks 67	**ADA** 80 mg every 2 weeks 24 weeks 73	**Placebo** N/A 24 weeks 62
INCLUSION CRITERIA:	18 years of age or older; Active RA as defined by 9 tender joints and 6 swollen joints according to ACR; treated with MTX for at least 6 months at a weekly dosage of 12.5-25 mg or 10 mg (if intolerant to higher doses) for at least 4 weeks before entering the study; must have failed treatment with at least 1 DMARD besides MTX, but no more than 4 DMARD's			
EXCLUSION CRITERIA:	Standard exclusion criteria used in trials of other biologics in patients with RA; previous treatment with anti-CD4 therapy or TNFα antagonists; history of active listeriosis or mycobacterial infection; major episode of infection requiring hospitalization; treatment with intravenous antibiotics within 30 days: oral antibiotics within 14days prior to screening			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Continued treatment with MTX, salicylates, NSAIDS, and corticosteroids			

Authors: Weinblatt et al. **Year: 2003 and 2006**					
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate				
		Placebo	**ADA20**	**ADA40**	**ADA80**
Mean age (years):		56	53.5	57.2	55.5
Sex (% female):		82.3	75.4	74.6	75.3
Ethnicity:		NR	NR	NR	NR
Other germane population qualities:					
• TJC		28.7	28.5	28.0	30.3
• SJC		16.9	17.6	17.3	17.0
• Previous # DMARDs used, mean		3.0	3.0	2.9	3.1
• MTX use dosage, mg/week		16.5	16.9	16.4	17.2
• Corticosteroids use (%)		NR	NR	NR	NR
• DAS score		58.9	60.5	58.7	62.6
• HAQ score		1.64	1.52	1.55	1.55

Authors: Weinblatt et al. **Year: 2003 and 2006**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20; And improvements in TJC, SJC, patients assessment of pain, patients global assessment of disease activity, physicians global assessment of disease activity, HAQ and serum levels of CRP. **Secondary Outcome Measures:** ACR50; ACR70; SF36 score and FACIT **Timing of assessments:** Efficacy: baseline, weekly during the first month, every other week during the second month, and monthly thereafter. Antibody assessments: baseline and weeks 4, 12, and 24
RESULTS:	**Health Outcome Measures:** • ACR50 response rates with the 20, 40, 80 mg ADA dosages (31.9%, 55.2%, 42.5%) were significantly greater than that with placebo (8.1%) ($P = 0.003$, $P < 0.001$, and $P < 0.001$) • 40 and 80 mg doses of ADA were associated with an ACR70 response (26.9%, 19.2%) that was statistically significantly greater than with placebo (4.8%) ($P < 0.001$ and $P = 0.020$) • SF-36 scores at 24 weeks compared with baseline: o ADA: statistically significant increases ($P \leq 0.05$) were achieved on 7 of 8 domains, 8 of 8 domains, and 8 of 8 domains by patients receiving 20 mg, 40 mg, and 80 mg, respectively. o Placebo: statistically significant increases ($P \leq 0.05$) were achieved on only 4 of 8 domains. o After 24 weeks, all ADA treatment groups achieved a minimum clinically important mean increase over baseline ($\geq$10 points) in 6 of 8 domains. In contrast, placebo treated patients achieved a minimally clinically important response in only 2 of 8 domains. • FACIT fatigue scale scores at 24 weeks compared with baseline: o Statistically significant improvements over baseline were observed for the ADA 40mg (8.5 points) and 80 mg (9.5 points) groups versus placebo (3.0 points) ($P = 0.001$ and $P < 0.001$) At 4 year open label extension • 147 patients completers ACR 20/50/70, 78%, 57%, and 31%; clinical remission (DAS28 <2.6) 43%; no physical function abnormalities (HAQ = 0) 22% • Serious infection rates 24 weeks vs. 4 years, 2.03 vs. 2.3 per 100 patient years **Intermediate Outcome Measures:** • ACR20 response at week 24 was achieved by a significantly greater proportion of patients in the 20, 40, 60 mg ADA plus MTX groups (47.8%, 67.2%, 65.8%) than in the placebo plus MTX group (14.5%) ($P < 0.001$)

Authors: Weinblatt et al., **Year: 2003**				
ADVERSE EVENTS: **Overall adverse effects reported (%):** • Nausea • Injection site pain • ISR • Dizziness	**ADA20** NR 18.8 8.7 4.3 11.6	**ADA40** NR 4.5 10.4 1.5 3.0	**ADA80** NR 9.6 11.0 11.0 1.4	**Placebo** NR 6.5 3.2 0 1.6
Significant differences in adverse events:	• ISRs occurred more frequently in the ADA 80 mg group compared with placebo ($P \leq 0.05$) • Dizziness and nausea occurred more frequently in the ADA 20 mg group (11.6% and 18.8%) compared with placebo (1.6% and 6.5%) ($P \leq 0.05$)			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes			
ADEQUATE RANDOMIZATION:	Yes (block size 8, stratified by center)			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	NR			
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** Withdrawals due to lack of efficacy	**Overall loss to follow-up:** 110/271 (40.6%) at 4 years LTF was 36% **Loss to follow-up differential high:** Yes **ADA** NR 2 23,27,27	**4 yr extension** 36 8 12	**Placebo** NR 5 35	***loss to follow was NR in treatment specific fashion only as overall
QUALITY RATING:	**Fair**			

Evidence Table 1 ***Targeted Immune Modulators -- Rheumatoid Arthritis***

STUDY:	**Authors: Westhovens et al.**[57] **Year: 2006** **Country:** Multinational		
FUNDING:	Centocor Research and Development, Inc		
RESEARCH OBJECTIVE:	To assess the risk of serious infections following 22 weeks of infliximab therapy		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 1084		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo + MTX** N/A 22 weeks 363	**INF 3 + MTX** 3 mg/kg wks 0,2,6,14 22 weeks 360	**INF 10 + MTX** 10 mg/kg wks 0,2,6,14 22 weeks 361
INCLUSION CRITERIA:	Diagnosis of RA according to the ACR: had active disease despite receiving MTX; patients may or may not have been treated with other concomitant DMARDs.		
EXCLUSION CRITERIA:	opportunistic infections; serious infections during the 2 months prior to screening; known HIV, active, latent or history of TB with inadequate documentation of treatment; an inability to receive prophylaxis with isoniazid; history of lymphoproliferative disease or malignancy; CHF.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Chloroquine, azathioprine, penicillamine, oral or intramuscular gold, hydroxychloroquine, sulfasalazine, leflunomide, cyclosporine, oral corticosteroids, or NSAIDs		

Authors: Westhovens et al. **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes - except for median disease duration but not statistically significant ($P = 0.083$) **Disease severity:** Moderate-severe		
	Placebo + MTX	**INF 3 + MTX**	**INF 10 + MTX**
Mean age (years):	52.0	53.0	52.0
Sex (% female):	83.2	80.0	77.8
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• TJC	22	22	22
• SJC	15	15	15
• Median disease duration	8.4	7.8	6.3
• DMARD use (%)	100	100	100
• MTX use (%)	100	100	100
• Corticosteroids use (%)	59.2	59.2	59.0
• DAS score	NR	NR	NR
• HAQ score	1.5	1.5	1.5
• Concomitant conditions predisposing to infection, no. (%)	29 (8.0)	29 (8.1)	20 (5.5)
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Rate of serious infections **Secondary Outcome Measures:** ACR 20/50/70; DAS28 **Timing of assessments:** Weeks 0,2,6,14,22		
RESULTS:	**Health Outcome Measures:** Week 22 • ACR20 INF3 58% INF10 61% MTX 26% • ACR50 INF3 32.1% INF10 35.4% MTX 9.7% • ACR70 INF3 14.0% INF10 16.1% MTX 4.7% • DAS28 response (mean) INF3 3.5 INF10 3.3 MTX 4.4 • All INF 3 or INF 10 vs. MTX had a statistical significance of $P < 0.001$		

Authors: Westhovens **Year: 2006**			
ADVERSE EVENTS (%):	**Placebo + MTX**	**INF 3 + MTX**	**INF 10 + MTX**
Overall adverse effects reported:	66.2	69.7	72.3
• Serious infections	1.7	1.7	5.0
• Pneumonia	0	0.8	1.1
• Serious AEs	7.5	7.8	7.5
• Rash	1.7	4.7	4.4
Significant differences in adverse events:	Rate of serious infections was significantly higher in the 10mg/kg group compared to placebo: RR: 3.1 95% CI 1.2 – 7.9 No significant differences in serious infections in the 3 mg/kg group: RR 1.0 95% CI 0.3 – 3.1		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 18 from efficacy analysis		
ADEQUATE RANDOMIZATION:	**Yes**		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 7.6 % **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Placebo + MTX**	**INF 3 + MTX**	**INF 10 + MTX**
Loss to follow-up:	6.3	7.2	8.9
Withdrawals due to adverse events:	2.2	5.0	5.5
QUALITY RATING:	**Good**		

Evidence Table 2 ***Targeted Immune Modulators - Juvenile Rheumatoid Arthritis***

STUDY:	**Authors: Horneff et al.**[74] **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 Rheumatoid Arthritis***

STUDY:	**Authors: Lovell et al.**[73, 142, 170] **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 3 ***Targeted Immune Modulators - Ankylosing Spondylitis***

STUDY:	**Authors: Braun et al.**[79, 84-86], **Listing et al.**[83] **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="4">Authors: Braun et al. and Listing et al.
Year: 2002, 2004, 2003</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: Severe (mean disease duration 15.6 years)</td></tr>
<tr><td></td><td><u>INF</u></td><td><u>Placebo</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>40.6</td><td>39.0</td><td></td></tr>
<tr><td>Sex (% female):</td><td>32</td><td>37</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>16.4</td><td>14.9</td><td></td></tr>
<tr><td>• BASDAI score (mean)</td><td>6.5</td><td>6.3</td><td></td></tr>
<tr><td>• BASFI score (mean)</td><td>5.4</td><td>5.1</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">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="3">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>

<table>
<tr><td colspan="4">Authors: Braun et al. and Listing et al.
Year: 2002, 2004, 2003</td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
• Infections
• Serious events</td><td><u>INF</u>
NR
18
3</td><td><u>Placebo</u>
NR
12
0</td><td></td></tr>
<tr><td>Significant differences in adverse events:</td><td colspan="3">Yes-three patients on INF had serious events and were withdrawn from the study, compared with one on placebo (P = 0.239)</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: Yes
Post randomization exclusions: No</td></tr>
<tr><td>ADEQUATE RANDOMIZATION:</td><td colspan="3">Yes</td></tr>
<tr><td>ADEQUATE ALLOCATION CONCEALMENT:</td><td colspan="3">NR</td></tr>
<tr><td>BLINDING OF OUTCOME ASSESSORS:</td><td colspan="3">NR</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: 4.2%
Loss to follow-up differential high: No</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:</td><td><u>INF</u>
0
3</td><td><u>Placebo</u>
2
0</td><td></td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

Evidence Table 3 ***Targeted Immune Modulators - Ankylosing Spondylitis***

STUDY:	**Authors: Calin et al.**[76] **Year: 2004** **Country:** Multinational		
FUNDING:	Wyeth		
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of etanercept to treat adult patients with AS		
DESIGN:	**Study design:** RCT **Setting:** Multicenter (14 sites) **Sample size:** 84		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg s.c./ twice weekly 12 weeks 45	**Placebo** N/A 12 weeks 39	
INCLUSION CRITERIA:	18-70 years with active AS; diagnosed by modified NY criteria; active disease was diagnosed if the patient had an average score of greater than or equal to 30 (on 100-point VAS) for spinal inflammation and a score of greater than or equal to 30 on at least two other domains (patient global assessment, back pain, physical function)		
EXCLUSION CRITERIA:	Complete ankylosis of the spine; previously used TNF alpha inhibitors, used DMARDs other than hydroxychoroquine, sulfasalazine, or Mtx within 4 weeks of baseline; used multiple NSAIDs; used > 10 mg prednisone daily; or changed doses of NSAIDs or prednisone within 2 weeks of baseline		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concomitant DMARDs, NSAIDs, corticosteroids, and continuation of prestudy physiotherapy		

Authors: Calin et al. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes, except age, disease duration and CRP **Disease severity:** Moderate (mean disease duration 12.5 years)		
	ETA	**Placebo**	
Mean age (years):	45.3	40.7	
Sex (% female):	20	23	
Ethnicity: white%	93	95	
Other germane population qualities:			
• Disease duration mean (years)	15	9.7	
• DMARD use (%)	36	41	
• MTX use (%)	13	13	
• Corticosteroids use (%)	16	15	
• BASDAI score (mean)	61.0	58.6	
• BASFI score (mean)	NR	NR	
• CRP (mg/dl) (median)	154	97	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ASAS 20 **Secondary Outcome Measures:** ASAS 50/70 , BASDAI, ESR, CRP **Timing of assessments:** weeks 2, 4, 8, 12		
RESULTS:	**Health Outcome Measures:** • **ASAS50** at week 12: ETA 48.9% versus placebo 10.3% ($P < 0.01$) • **ASAS70** at week 12: ETA 24.4% versus placebo 10.3% ($P < 0.05$) • More responders in ETA group at ASAS 50 at all visits ($P < 0.01$) and at ASAS 70 levels at weeks 2, 4, and 8 ($P < 0.05$) **Intermediate Outcome Measures:** • **ASAS 20** at week 12: ETA 26(60%) vs. placebo 9(23%); $P < 0.001$; 95%CI (17.4 to 56.4) ESR and CRP at week 12: Compared to placebo, ETA-treated patients achieved significant reductions in ESR and CRP ($P < 0.0001$) • **Spinal flexion** via Schober's test: ETA-treated patients achieved improved spinal flexion versus placebo-treated patients who had no improvement ($P < 0.01$)		

Authors: Calin et al. **Year: 2004**			
ADVERSE EVENTS: **Overall adverse effects reported:** • ISR • Haemorrhage, injection site • Headache • Nausea • Asthenia	**ETA** NR 15 8 6 3 5	**Placebo** NR 6 4 4 4 1	
Significant differences in adverse events:	Only ISRs.		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** None		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 2.2% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ETA** 2 0	**Placebo** 0 0	
QUALITY RATING:	**Fair**		

Evidence Table 3 ***Targeted Immune Modulators - Ankylosing Spondylitis***

STUDY:	**Authors: Davis et al.**[78] **Year: 2003** **Country:** Multinational		
FUNDING:	Immunex Corporation, Seattle, WA		
RESEARCH OBJECTIVE:	To determine the safety and efficacy of etanercept in adults with moderate to severe active AS.		
DESIGN:	**Study design:** RCT, placebo-controlled, parallel-group **Setting:** Multicenter **Sample size:** 277		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg twice weekly 24 weeks 138	**Placebo** N/A 24 weeks 139	
INCLUSION CRITERIA:	Men and women aged 18 to 70 years who satisfied the NY criteria for AS and active AS defined as: a score of $\geq$ 30 mm for morning stiffness on a 100-mm VAS analyzing duration or intensity; and scores of $\geq$ 30 mm for 2 of the following 3 parameters: patient's global assessment of disease activity, back pain, and the BASFI (all based on a 100-mm VAS).		
EXCLUSION CRITERIA:	Complete ankylosis of the spine based on radiographic assessment; previous TNF inhibitor therapy; had a serious infection (infection requiring hospitalization or intravenous antibiotics) within 4 week period prior to screening; use of DMARDs other than hydroxychloroquine, sulfasalazine, or MTX within 4 weeks of baseline evaluation.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Hydroxychloroquine, sulfasalazine, and MTX at doses stable prior to enrollment; NSAIDs and prednisone (up to 10 mg/day) if stable for 2 weeks prior to enrollment. Other analgesics (acetaminophen, codeine, hydrocodone, oxycodone, and tramadol) were permitted in standard dosages.		

Authors: Davis et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Severe (mean disease duration 10.3 years)		
	ETA	**Placebo**	
Mean age (years):	42.1	41.9	
Sex (% female):	24	24	
Ethnicity (% white):	94	91	
Other germane population qualities:			
• DMARD use (%)	32	31	
• MTX use (%)	11	12	
• Corticosteroids use (%)	13	14	
• BASDAI score (mean)	58.1	59.6	
• BASFI score (mean)	51.7	56.3	
OUTCOME ASSESSMENT:	**Primary Efficacy Outcome Measures:** ▪ ASAS20 at 12 and 24 weeks **Secondary Efficacy Outcome Measures:** ASAS50/70; BASDAI; spinal mobility (using the modified Schober test, chest expansion score, and occiput-to-wall measurements), tender and SJCs, acute-phase reactants (ESR and CRP), and assessor's global assessments (measured on a 100-mm VAS) over time. **Timing of assessments:** Efficacy: 2, 4, 8, 12, and 24 weeks. Testing for antibody to ETA occurred at baseline and week 24.		
RESULTS:	**Health Outcome Measures: (ETA v. placebo)** • **Partial remission** at 24 weeks: 17% v. 4%. (P-value NR) • At weeks 12 and 24, patients receiving ETA achieved significant improvements over those receiving placebo on the individual components of the ASAS criteria, ESR, CRP, and the BASDAI (all P-values < 0.0001). Statistically significant differences were also observed for the spinal mobility measures at 12 and 24 weeks (*P*-values ≤ 0.0014)**.** **Intermediate Outcome Measures** • **ASAS20** at 12 weeks: 59% v. 28% (*P* < 0.0001) **ASAS20** at 24 weeks: 57% v. 22% (*P* < 0.0001)		

Authors: Davis et al. **Year: 2003**			
ADVERSE EVENTS: **Overall adverse effects reported:** • URTI • Injection-site reaction • Accidental injury • Dizziness • Flu Syndrome	**ETA** NR 28% 41% 17% 8% 5%	**Placebo** NR 16% 13% 6% 3% 10%	
Significant differences in adverse events:	Injection-site reactions, URTIs, and accidental injury were the only reported adverse events achieving a statistically significant difference between the ETA and placebo groups. Patients receiving ETA experienced a statistically greater number of these adverse events.		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** None		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 11% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ETA** 14% 5.1%	**Placebo** 9% 0.7%	
QUALITY RATING:	**Good**		

Evidence Table 3 ***Targeted Immune Modulators - Ankylosing Spondylitis***

STUDY:	**Authors: Gorman et al.**[77] **Year: 2002** **Country:** US		
FUNDING:	NIH and Immunex		
RESEARCH OBJECTIVE:	To evaluate the efficacy of etanercept for the treatment of AS		
DESIGN:	**Study design:** RCT **Setting:** Rheumatology practices in Northern California **Sample size:** 40		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg s.c/twice weekly 4 months 20	**Placebo** N/A 4 months 20	
INCLUSION CRITERIA:	Meet NY clinical criteria for definite AS; evidence of active AS despite accepted treatments; and, at least 18 years old. Active spondylitis was defined as the presence of inflammatory back pain (stiffness and pain that worsened with rest and improved with exercise), morning stiffness for at least 45 minutes, and at least moderate disease activity as assessed by the patient and the physician. The physician's assessment was based on a 100-mm VAS – moderate or higher disease activity was defined as 40 mm or greater.		
EXCLUSION CRITERIA:	Had a spondylitis other than AS; clinical or radiographic evidence of complete spinal ankylosis; history of recurrent infections or cancer, serious liver, renal, hematologic or neurological disorder.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAID's, oral corticosteroids (≤ 10 mg/day), gold injections (≤ 50 mg/month), MTX(≤ 20 mg/week), and sulfasalazine (≤ 3g/day)		

Authors: Gorman et al. **Year: 2002**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No (sex, corticosteroid use, SF-36, and mean hemoglobin level) **Disease severity:** Moderate (mean disease duration 13.5 years)		
	ETA	**Placebo**	
Mean age (years):	38	39	
Sex (% female):	35	10	
Ethnicity: white %	75	70	
Other germane population qualities:			
• Mean disease duration(years)	15	12	
• DMARD use (%)	40	35	
• MTX use (%)	NR	NR	
• Corticosteroids use (%)	25	10	
• BASDAI score (mean)	NR	NR	
• BASFI score (mean)	NR	NR	
• SF-36, physical function	41.8	61.0	
• Hemoglobin, mean	12.6	13.6	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ASAS 20 **Secondary Outcome Measures:** Physician's global assessment of disease activity, measures of spinal mobility, scores for enthesitis, and peripheral-joint tenderness, BASFI, ESR, CRP **Timing of assessments:** days 1, 28, 56, 84, 112		
RESULTS:	**Health Outcome Measures:** • From baseline to the 4 month endpoint the ETA group achieved significantly better health outcomes than the placebo group **BASFI** decrease ETA 4.5 to 2.2 vs. placebo 3.2 to 3.1 ($P < 0.0001$) **Patients global assessment of disease activity** decrease ETA 3.0 to 2.0 vs. placebo remained unchanged at 3.0 ($P < 0.001$) **Score of nocturnal spinal pain** decrease ETA 65 to 15 vs. placebo 46.5 to 38 ($P < 0.001$) **Intermediate Outcome Measures:** • From baseline to the 4 month endpoint the ETA group achieved significantly better intermediate outcomes than the placebo group - **ESR** ETA 34.5 to 8.5 vs. placebo 20.0 to 16.5 ($P < 0.001$) **CRP** ETA2.0 to 0.7 vs. placebo 1.5 to 2.0. ($P = 0.003$) **ASAS20** ETA 80% vs. placebo 30% ($P = 0.004$)		

Authors: Gorman et al. **Year: 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Infections • ISRs • Diarrhea • Neurological	**ETA** NR 10 5 3 2	**Placebo** NR 12 1 1 0	
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** None		
ADEQUATE RANDOMIZATION:	**NR**		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:**	**Overall loss to follow-up:** 7.5% **Loss to follow-up differential high:** no **ETA** 1 0	**Placebo** 2 0	
QUALITY RATING:	**Fair**		

Evidence Table 3 ***Targeted Immune Modulators - Ankylosing Spondylitis***

STUDY:	**Authors: van der Heijde et al.**[80] **Year: 2005** **Country:** Multinational		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of infliximab in patients with AS.		
DESIGN:	**Study design:** RCT **Setting:** 33 sites **Sample size:** 279		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 5 mg/kg (wks 0,2,6,12,18) 24 weeks 201	**Placebo** N/A 24 weeks 78	
INCLUSION CRITERIA:	AS according to the modified NY criteria for at least 3 months; BASDAI score of ≥4 (range 0-10), and with a spinal pain assessment score of ≥4 on a VAS (range 0-10 cm); normal chest radiograph within 3 months prior to randomization and either a negative purified protein derivative (PPD) skin test result for latent TB (in the US and Canada) or adequate screening with documented negative results for latent TB using local guidelines for high-risk or immunocompromised patients (in Europe).		
EXCLUSION CRITERIA:	Total ankylosis of the spine; other inflammatory rheumatic disease; fibromyalgia; a serious infection within 2 months; TB (active or latent) or recent contact with a person with active TB; opportunistic infection within 6 months of screening, hepatitis, HIV, a transplanted organ, malignancy, multiple sclerosis, or CHF; sulfasalazine or MTX within 2 weeks prior to screening, systemic corticosteroids within 1 month prior to screening, anti-TNF therapy other than INF within 3 months prior to screening, INF at any time prior to screening, DMARDs other than sulfasalazine or MTX within 6 months prior to screening, or cytotoxic drugs within 12 months prior to screening.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable doses of NSAIDs, acetaminophen (paracetamol), or tramadol		

<table>
<tr><td colspan="4">Authors: van der Heijde et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes, but there were small differences in the sex ratio.
Disease severity: Moderate-severe (mean disease duration 10.5years)</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>INF</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>41</td><td>40</td><td></td></tr>
<tr><td>Sex (% female):</td><td>12.8</td><td>21.9</td><td></td></tr>
<tr><td>Ethnicity (% Caucasian):</td><td>97.4</td><td>98</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• DMARD use (%)</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>• MTX use (%)</td><td>0</td><td>0</td><td></td></tr>
<tr><td>• Corticosteroids use (%)</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>• BASDAI score (mean)</td><td>6.5</td><td>6.6</td><td></td></tr>
<tr><td>• BASFI score (mean)</td><td>6.0</td><td>5.7</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ASAS20
Secondary Outcome Measures: ASAS40 and ASAS partial remission; BASFI; CRP level; BASDAI, BASMI; range-of-motion assessments; SF-36
Timing of assessments: NR</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• At week 24 significantly greater number of INF patients achieved ASAS20, ASAS40, partial remission, 50% improvement on the BASDAI and improvements greater than 2 on the BASFI than placebo patients. (All $P < 0.001$)
ASAS40: INF 47.0% vs. Placebo 12.0% Partial remission: INF 22.4% vs. Placebo 1.3%
BASDAI: INF 51.0% vs. Placebo 10.7% BASFI: INF 47.5% vs. Placebo 13.3%

Intermediate Outcome Measures:
ASAS20: INF 61.2% vs. Placebo 19.2% ($P < 0.001$)</td></tr>
</table>

Authors: van der Heijde et al. **Year: 2005**			
ADVERSE EVENTS:	**Placebo**	**INF**	
Overall adverse effects reported %:	72.0	82.0	
• Any infections	36.0	42.6	
• Serious adverse event	2.7	3.5	
• Infusion reaction	9.3	10.9	
• Serious infection	0	1.0	
• Pharyngitis	2.7	10.4	
• Rhinitis	2.7	7.4	
• Pruritus	6.7	4.0	
• Nausea	10.7	3.5	
• Arthritis	5.3	3.0	
• Rash	5.3	2.5	
Significant differences in adverse events:	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:** 5 **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Placebo**	**INF**	
Loss to follow-up:	3	2	
Withdrawals due to adverse events:	1	2	
QUALITY RATING:	**Fair**		

Evidence Table 4 ***Targeted Immune Modulators - Psoriatic Arthritis***

STUDY:	**Authors: Antoni et al.**[89] and **Kavanaugh et al**.[92] **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="4">Authors: Antoni et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Generally, with the exception of CRP
Disease severity: Severe (mean disease duration 11.4 years)</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>INF</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>45.2</td><td>45.7</td><td></td></tr>
<tr><td>Sex (% female):</td><td>42.3</td><td>42.3</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>• Disease duration- years</td><td>11</td><td>11.7</td><td></td></tr>
<tr><td>• ACR 20 components</td><td></td><td></td><td></td></tr>
<tr><td># swollen joints</td><td>14.7</td><td>14.6</td><td></td></tr>
<tr><td># tender joints</td><td>20.4</td><td>23.7</td><td></td></tr>
<tr><td>• CRP mg/liter- mean(median)</td><td>31.1(14.0)</td><td>21.7(9.9)</td><td></td></tr>
<tr><td>• DAS</td><td>5.4</td><td>5.5</td><td></td></tr>
<tr><td>• PASI</td><td>4.2</td><td>5.1</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">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="3">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 (%):	**Placebo (-week 16)**	**INF 5 mg (-week 16)**	**INF 5 mg (week 16-50)**
Overall adverse effects reported:	65	73	84
• Treatment related events	47	56	69
• Infusion-associated			
All events	10	8	8
Treatment-related events	8	4	8
• Severe			
All events	4	6	12
Treatment-related events	2	4	6
• Serious			
All events	2	2	16
Treatment-related events	0	2	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*):	**Placebo**	**INF**	
Loss to follow-up:	2	3	
Withdrawals due to adverse events:	1	2	
QUALITY RATING:	**Fair**		

Evidence Table 4 ***Targeted Immune Modulators-Psoriatic Arthritis***

STUDY:	**Authors: Antoni et al.[90] and Kavanaugh et al.[91]** **Year: 2005** **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		

Authors: Antoni et al. and Kavanaugh et al. **Year: 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes, except for sex **Disease severity:** Active plaque psoriasis and PsA (mean disease duration 8 years)		
	Placebo	**INF**	
Mean age (years):	46.5	47.1	
Sex (% female):	49	29	
Ethnicity:	94	95	
Other germane population qualities:			
• Polyarticular arthritis	47	53	
• DIP joints of hand/feet	23	26	
• Asymmetric peripheral arthritis	22	18	
• NSAID use (%)	73	71	
• MTX use (%)	45	47	
• Corticosteroids use (%)	10	15	
• SF-36 score (Physical/Mental)	31/47	33/45.5	
• HAQ score	1.1	1.1	
OUTCOME ASSESSMENT:	**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		
RESULTS:	**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% ($P < 0.001$)		

Authors: Antoni et al. and Kavanaugh et al. **Year: 2005**			
ADVERSE EVENTS (%):	**Placebo n=97**	**INF n=150 (includes escape)**	
Overall adverse effects reported:	67	67	
• URTI	14	10	
• Headache	5	6	
• Increased ALT	1	6	
• Pharyngitis	4	5	
• Sinusitis	4	5	
• Dizziness	5	4	
• Serious AEs	1	4	
• Infusion reactions	6	9	
	6	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*):	**Placebo**	**INF**	
Loss to follow-up:	8%	7%	
Withdrawals due to adverse events:	1%	4%	
QUALITY RATING:	**Fair**		

Evidence Table 4 ***Targeted Immune Modulators - Psoriatic Arthritis***

STUDY:	**Authors: Mease et al.**[87] **Year: 2000** **Country:** US		
FUNDING:	Immunex		
RESEARCH OBJECTIVE:	To study the efficacy and safety of etanercept in patients with psoriatic arthritis and psoriasis		
DESIGN:	**Study design:** RCT **Setting:** Single center in Seattle **Sample size:** 60		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25mg 2x weekly 12 weeks 30	**Placebo** N/A 12 weeks 30	
INCLUSION CRITERIA:	Adults between 18 and 70 years who had active PsA (≥ 3 swollen, tender, or painful joints) at the time of enrollment; inadequate response to NSAIDs and were thought candidates for immunomodulatory therapy; hepatic transasminase concentrations no greater than 2x the upper limit of normal, hemoglobin 85 g/L or higher, platelet count 125000 per mL or more and serum creatinine 152-4 mmol/L or below		
EXCLUSION CRITERIA:	Evidence of skin conditions other than psoriasis		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX was allowed if <=25 mg/wk and stable for 4 weeks before study started; corticosteriods were allowed if the dose was less than or equal to 10 mg/day of prednisone, stable for at least 2 weeks before the first dose of study drug, and maintained at a constant dose throughout the study		

<table>
<tr><td colspan="4">Authors: Mease et al.
Year: 2000</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: NR (mean disease duration 10 years)</td></tr>
<tr><td></td><td><u>ETA</u></td><td><u>Placebo</u></td><td></td></tr>
<tr><td>Median age (years):</td><td>46</td><td>43.5</td><td></td></tr>
<tr><td>Sex (% female):</td><td>40</td><td>47</td><td></td></tr>
<tr><td>Ethnicity (% white):</td><td>83</td><td>90</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• TJC</td><td>22.5</td><td>19</td><td></td></tr>
<tr><td>• SJC</td><td>14</td><td>14.7</td><td></td></tr>
<tr><td>• DMARD # previous usage</td><td>1.5</td><td>2</td><td></td></tr>
<tr><td>• MTX use (%)</td><td>47</td><td>47</td><td></td></tr>
<tr><td>• Corticosteroids use (%)</td><td>20</td><td>40</td><td></td></tr>
<tr><td>• DAS score</td><td>N/A</td><td>N/A</td><td></td></tr>
<tr><td>• HAQ score</td><td>1.3</td><td>1.2</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: PsARC; PASI
Secondary Outcome Measures: ACR20/50/70; CRP; tender and SJC; HAQ ESR
Timing of assessments: Baseline, 4, 8, and 12 weeks</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• The ETA group had statistically better outcomes on all clinical endpoints than the placebo group.
PsARC ETA 26 (87%) vs. Placebo 7 (23%) P < 0.0001 95% CI: 44-83
ACR50 ETA 15 (50%) vs. Placebo 1 (3%) P = 0.0001 95% CI: 28-66
ACR70 ETA 4 (13%) vs. Placebo 0 (0%) P = 0.0403 95% CI: 1-26
HAQ ETA 0.1 (0,1) vs. Placebo 1.3 (0.9,1.6) P < 0.001
Intermediate Outcome Measures:
• ACR20 was achieved by 73% ETA treated patients compared with 13% placebo treated patients (P < 0.0001)
• CRP ETA 4 (3,11) vs. Placebo 14 (4,23) P<0.001</td></tr>
</table>

Authors: Mease et al. **Year: 2000**			
ADVERSE EVENTS: **Overall adverse effects reported:** • URI • Pharynigitis • Rhinitis • Sinusitis • Influenza syndrome • Injection site bruise • ISR • Fatigue	**ETA** NR 17(57%) 5 (17%) 5 (17%) 3 (10%) 0 6 (20%) 6 (20%) 4 (13%)	**Placebo** NR 17(57%) 3 (10%) 4 (13%) 2 (7%) 6 (20%) 5 (17%) 1 (3%) 0	
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 6.6% (4) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ETA** 0 0	**Placebo** 4 0	**Placebo**—3 for lack of efficacy and 1 lost to follow-up
QUALITY RATING:	**Fair**		

Evidence Table 4 ***Targeted Immune Modulators - Psoriatic Arthritis***

STUDY:	**Authors: Mease et al.**[88] **Year: 2004** **Country:** US		
FUNDING:	Immunex		
RESEARCH OBJECTIVE:	To evaluate the safety, efficacy, and effect on radiographic progression of etanercept in patients with psoriatic arthritis		
DESIGN:	**Study design:** RCT **Setting:** 17 sites **Sample size:** 205		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 24 weeks 104	**ETA** 25 mg/2x weekly (subcutaneous) 24 weeks 101	
INCLUSION CRITERIA:	18-70 years and had active psoriatic arthritis (PsA) with at least 3 swollen and 3 tender joints at screening and a previous inadequate response to NSAID; had at lease one of the PsA subtypes: distal interphalangeal joint involvement, polyarticular arthritis, arthritis mutilans, asymmetric peripheral arthritis, or AS-like arthritis; stable plaque psoriasis with a qualifying lesion		
EXCLUSION CRITERIA:	Oral retinoids, topical vitamin A or D analog preparations, and anthralin		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX therapy (stable 2 month at <=25 mg/week); corticosteriods (stable 4 weeks continued at <=10 mg/day of prednisone)		

Authors: Mease et al. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR (mean disease duration 9.1 years)		
	Placebo	**ETA**	
Mean age (years):			
Sex (% female):	47.3	47.6	
Ethnicity: (% white)	55	43	
Other germane population qualities:	91	90	
• Polyarticular arthritis			
• DIP joints of hand/feet	83	86	
• Asymmetric peripheral arthritis	50 38	51 41	
• NSAID use (%)	83	88	
• MTX use (%)	41	42	
• Corticosteroids use (%)	15	19	
• DAS score	N/A	N/A	
• HAQ score	NR	NR	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 **Secondary Outcome Measures:** ACR 50; ACR70: HAQ; SF-36; PsARC; PASI **Timing of assessments:** screening, baseline, weeks 4, 12, 24, and every 12 weeks thereafter		
RESULTS:	**Health Outcome Measures:** • 59% of ETA patients met ACR20 criteria compared with 15% placebo patients ($P < 0.0001$) • 23% of ETA patients eligible for psoriasis evaluation achieved at least 75% improvement in the psoriasis area and severity index, compared with 3% of placebo patients ($P = 0.001$) • Radiographic disease progression was inhibited in the ETA group at 12 months; the mean annualized rate of change over one year of treatment in the modified Sharp score was –0.03 unit, compared with 1.00 unit in the placebo ($P = 0.0001$) • HAQ- improvement from baseline in ETA group 54% vs. 6% of placebo group ($P < 0.0001$)		

Authors: Mease et al. **Year: 2004**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • ISR • URTI • Injection site ecchymosis • Accidental injury • Headache • Sinusitis • UTI • Rash	**Placebo** NR 9 23 11 5 5 8 6 7	**ETA** NR 36 21 12 8 8 6 6 5	
Significant differences in adverse events:	Yes- ISR ($P < 0.001$)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 40 (19.5%) **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Placebo** 31% 1%	**ETA** 8% 1%	
QUALITY RATING:	**Fair**		

Evidence Table 4 ***Targeted Immune Modulators-Psoriatic Arthritis***

STUDY:	**Authors: Mease et al.**[93] **Year: 2005** **Country:** Multi-national		
FUNDING:	Abbott Laboratories		
RESEARCH OBJECTIVE:	Evaluation of efficacy and safety of adalimumab in patients with moderately to severely active PsA.		
DESIGN:	**Study design:** RCT **Setting:** Clinical- 50 sites **Sample size:** 313		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 24 weeks 162	**ADA** 40 mg every other week 24 weeks 151	
INCLUSION CRITERIA:	At least 18 years old; moderately to severely active PsA (defined as having at least 3 swollen joints and 3 tender or painful joints); either active psoriatic skin lesions or a documented history of psoriasis; a history of an inadequate response or intolerance to NSAID therapy for PsA.		
EXCLUSION CRITERIA:	Treatment within 4 weeks of the baseline visit with cyclosporine, tacrolimus, DMARDs other than MTX, or oral retinoids; topical treatments for psoriasis within 2 weeks of baseline, other than medicated shampoos or low-potency topical steroids; concurrent treatment with MTX at dosages >30 mg/week and/or corticosteroids in a prednisone-equivalent dosage of >10 mg/day; and anti-TNF therapy at any time; a history of neurologic symptoms suggestive of central nervous system demyelinating disease; history of active TB or listeriosis; presence of a severe infection requiring hospitalization or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days of study entry.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX use was allowed during the study only if it had been taken for at least 3 months previously, with the dosage stable for at least 4 weeks prior to the baseline visit; after 12 weeks, patients who failed to have at least a 20% decrease in both swollen and TJCs on 2 consecutive visits could receive rescue therapy with corticosteroids or DMARDs.		

Authors: Mease et al. **Year: 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe (mean disease duration 9.5 years)		
	Placebo	**ADA**	
Mean age (years):	49.2	48.6	
Sex (% female):	45.1	43.7	
Ethnicity (% white):	93.8	97.4	
Other germane population qualities:			
• Polyarticular arthritis (%)	69.8	64.2	
• DIP joints of hand/feet	NR	NR	
• Asymmetric peripheral arthritis (%)	24.7	24.5	
• NSAID use (%)	NR	NR	
• MTX use (%)	50	51	
• Corticosteroids use (%)	NR	NR	
• HAQ-DI score	1	1	
• Modified total Sharp score	19.1	22.7	
• PASI	8.3	7.4	
• Mean disease duration (years)	9.2	9.8	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20 at week 12; change in modified total Sharp score at week 24 **Secondary Outcome Measures:** ACR20 response rate at week 24; ACR50 and 70 at weeks 12 and 24; PsARC; HAQ DI; SF-36 (physical and mental component summaries, PCS and MCS); PASI **Timing of assessments:** Baseline, 12 and 24 weeks		
RESULTS:	**Health Outcome Measures (ADA vs. placebo at 24 weeks):** • ACR50 39% vs. 6% ($P < 0.001$) • ACR70 23% vs. 1% ($P < 0.001$) • PASI75 59% vs. 1% ($P < 0.001$) (n=69 per group) • PsARC response rate 60% vs. 23% ($P <$ NR) • HAQ DI change -0.4 vs. -0.1 ($P < 0.001$) • SF-36 PCS change 9.3 vs. 1.4 ($P < 0.001$) • SF-36 MCS change 1.8 vs. 0.6 ($P = 0.288$) **Intermediate Outcome Measures:** • ACR20 57% vs. 15% ($P < 0.001$)		

Authors: Mease et al. **Year: 2005**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Serious adverse events • URTI • Nasopharyngitis • ISR • Headache • Hypertension • Psoriatic arthropathy aggravated • Arthralgia • Psoriasis aggravated • Diarrhea	**Placebo** NR 4.3 14.8 9.3 8.6 3.1 6.8 5.6 6.2 5.6	**ADA** NR 3.3 12.6 9.9 6.6 6.0 5.3 3.3 2.0 2.0 2.0	
Significant differences in adverse events:	None reported		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes-2 ADA patients prior to drug administration		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 7.6% **Loss to follow-up differential high: No**		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events (includes AEs and abnormal lab values):**	**Placebo** 13 (8%) 5 (3.1%)	**ADA** 11 (7.3%) 5(3.3%)	
QUALITY RATING:	**Fair**		

Evidence Table 4 ***Targeted Immune Modulators – Psoriatic Arthritis***

STUDY:	**Authors: Mease et al.**[94] **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="4">Authors: Mease et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">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><td></td></tr>
<tr><td>Mean age (years):</td><td>45.6</td><td>45.5</td><td></td></tr>
<tr><td>Sex (% female):</td><td>50</td><td>63</td><td></td></tr>
<tr><td>Ethnicity:</td><td>98% white</td><td>98% white</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• NSAID use (%) diclofenac</td><td>41</td><td>24</td><td></td></tr>
<tr><td>• MTX use (mean dose/week)</td><td>13.7</td><td>14.6</td><td></td></tr>
<tr><td>• Corticosteroids use (%)</td><td>8</td><td>15</td><td></td></tr>
<tr><td>• HAQ score</td><td>1.0</td><td>1.1</td><td></td></tr>
<tr><td>• PASI</td><td>10.2</td><td>9.6</td><td></td></tr>
<tr><td>• BSA $\geq$ 3 % (%)</td><td>47</td><td>47</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">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="3">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**		

*primary outcome measures

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

STUDY:	**Authors: D'Haens et al.**[99] **Year: 1999** **Country:** Multinational (Europe)			
FUNDING:	Centocor Inc.			
RESEARCH OBJECTIVE:	Efficacy of one-time use of infliximab in refractory Crohn's disease.			
DESIGN:	**Study design:** RCT **Setting:** Multi-center (4 sites) **Sample size:** 30			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 4 weeks 8	**INF5** 5 mg/kg 4 weeks 7	**INF10** 10 mg/kg 4 weeks 7	**INF20** 20 mg/kg 4 weeks 8
INCLUSION CRITERIA:	Crohn's disease for at least 6 months; CDAI between 220 and 400; disease was refractory to any of the following: mesalamine (8 weeks-4 stable) corticosteroids up to the equivalent of 40 mg prednisone (8 weeks- 2 stable), and mercaptopurine or azathioprine (6 months- 8 weeks stable)			
EXCLUSION CRITERIA:	Cyclosporine, MTX or experimental agents within 3 months; symptomatic stenosis or strictures, stoma, proctocolectomy ot total colectomy or treatment with paenteral corticosteroids within 4 weeks			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Azathioprine; mesalamine; mercaptopurine; and steroids			

<table>
<tr><td colspan="5">Authors: D’Haens et al.
Year: 1999</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="4">Groups similar at baseline: Yes
Disease severity: Moderate - severe</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>INF 5</u></td><td><u>INF 10</u></td><td><u>INF 20</u></td></tr>
<tr><td></td><td>Mean age (years):</td><td>34.4</td><td>30.1</td><td>30.7</td><td>33.1</td></tr>
<tr><td></td><td>Sex (% female):</td><td>63</td><td>57</td><td>57</td><td>63</td></tr>
<tr><td></td><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td></td><td>Other germane population qualities:</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>• Mean baseline CDAI</td><td>276.9</td><td>314.4</td><td>336.8</td><td>300.9</td></tr>
<tr><td></td><td>• Azathioprine use (%)</td><td>38</td><td>43</td><td>14</td><td>63</td></tr>
<tr><td></td><td>• Corticosteroids use (%)</td><td>63</td><td>57</td><td>43</td><td>50</td></tr>
<tr><td></td><td>• Mean baseline CDEIS</td><td>8.4</td><td>15.1</td><td>10.6</td><td>13.3</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="4">Primary Outcome Measures:
CDEIS

Secondary Outcome Measures:
CDAI and CRP

Timing of assessments:
Baseline and 4 weeks after injection</td></tr>
<tr><td>RESULTS:</td><td colspan="4">Health Outcome Measures:
• The INF treatment groups all showed a significant improvement compared to the placebo group on the CDEIS at week 4: INF5 6.4 (P < 0.01 vs. placebo); INF10 4.3 (P < 0.01 vs. placebo); INF20 5.2 (P < 0.01 vs. placebo); placebo 7.5
• INF better than placebo on CDAI: INF5 122.8 (P < 0.01 vs. placebo); INF10 220.5 (P < 0.05 vs. placebo); INF20 161.9 (P < 0.01 vs. placebo); placebo 261.3
Intermediate Outcome Measures:
• The INF treatment groups all showed a significant improvement compared to the placebo group in their CRP (mg/dL) at week 4 (P <0.01).</td></tr>
</table>

Authors: D'Haens et al. **Year: 1999**				
ADVERSE EVENTS: **Overall adverse effects reported:** • None specified	**Placebo** 2 (inferred)	**INF 5** NR	**INF 10** NR	**INF 20** NR
Significant differences in adverse events:	NR			
ANALYSIS:	**ITT: Yes** **Post randomization exclusions:** No			
ADEQUATE RANDOMIZATION:	**Yes**			
ADEQUATE ALLOCATION CONCEALMENT:	Unable to assess			
BLINDING OF OUTCOME ASSESSORS:	Yes			
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR			
ATTRITION (*treatment specific*):	**Placebo**	**INF5**	**INF10**	**INF20**
Loss to follow-up:	2	NR	NR	NR
Withdrawals due to adverse events:	1 (inferred)	NR	NR	NR
QUALITY RATING:	**Fair**			

Evidence Table XX ***Targeted Immune Modulators – Crohn's Disease***

STUDY:	**Authors: Hanauer et al.**[95] **Year: 2006** **Country:** Multinational			
FUNDING:	Abbott			
RESEARCH OBJECTIVE:	Evaluate the efficacy of adalimumab induction therapy in patients with CD.			
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 299			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 4 weeks 74	**ADA 40** 40mg wk 0; 20mg wk 2 4 weeks 74	**ADA 80** 80mg wk 0; 40mg wk 2 4 weeks 75	**ADA 160** 160mg wk 0; 80mg wk 2 4 weeks 76
INCLUSION CRITERIA:	18–75 years of age; CD for at least 4 months who had moderate to severe disease as defined by a CDAI score of 220–450 points; radiologic or endoscopic studies were required to confirm the diagnosis of CD.			
EXCLUSION CRITERIA:	history of malignancy or active TB, listeriosis, or HIV; ulcerative colitis; symptomatic obstructive strictures; underwent surgical bowel resection within 6 months; ostomy; underwent extensive bowel resection (>100 cm) or had short bowel syndrome; currently receiving total parenteral nutrition; received investigational chemical agents within 30 days; received investigational biologic therapy within 4 months; had antibiotic treatment within 3 weeks for infections not related to CD; pregnant or breast-feeding; history of clinically significant drug or alcohol abuse within 1 year; poorly controlled medical conditions (including diabetes with history of recurrent infections or cerebrovascular accident within 3 months); previously received INF or any other anti-TNF therapy; enema therapy within 2 weeks; cyclosporine or tacrolimus within 8 weeks; positive *Clostridium difficile* stool assay; clinically significant deviations in prespecified laboratory parameters.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	5-aminosalicylates, prednisone (≤20 mg/day), budesonide (≤9 mg/day), azathioprine, 6-mercaptopurine, MTX, and antibiotics, were permitted at stable dosages.			

<table>
<tr><td colspan="5">Authors: Hanauer et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="4">Groups similar at baseline: Yes
Disease severity: moderate - severe</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>ADA 40</u></td><td><u>ADA 80</u></td><td><u>ADA 160</u></td></tr>
<tr><td>Mean age (years):</td><td>37</td><td>39</td><td>38</td><td>39</td></tr>
<tr><td>Sex (% female):</td><td>50</td><td>47</td><td>67</td><td>53</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>• Previous surgery for CD (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Patients with fistulae (%)</td><td>8</td><td>5</td><td>13</td><td>16</td></tr>
<tr><td>• Mean baseline CDAI</td><td>296</td><td>299</td><td>301</td><td>295</td></tr>
<tr><td>• Mercaptopurine/Azathioprine use (%)</td><td>11/18</td><td>18/8</td><td>12/13</td><td>14/29</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>34</td><td>23</td><td>43</td><td>32</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="4">Primary Outcome Measures: CDAI remission rates (CDAI < 150 points)

Secondary Outcome Measures: IBDQ; safety; CRP; CDAI response (≤70 point or ≤ 100 point change)

Timing of assessments: weeks 0, 1, 2, 4</td></tr>
<tr><td>RESULTS:</td><td colspan="4">Health Outcome Measures:
• Remission- placebo 12% [9/74] vs. ADA 40 18% [13/74] vs. ADA 80 24% [18/75] vs. ADA 160 mg 36% [27/76]; P = 0.004 for comparison of ADA 80 and 160 with placebo
• IBDQ- ADA 80 and ADA 160 were statistically different (better) than placebo P < 0.05 for both comparisons (Data = NR)
• No statistically significant relationship between CRP concentrations and remission
• More ADA patients (all doses) than placebo patients had at least a 70-point CDAI reduction (P<0.05); only the ADA 160 group had statistically significant differences in the percentage of patients having a 100-point reduction.</td></tr>
</table>

Authors: Hanauer et al. **Year: 2006**				
ADVERSE EVENTS (%):	**Placebo**	**ADA 40**	**ADA 80**	**ADA 160**
Overall adverse effects reported:	74	68	68	75
• Abdominal tenderness	1	1	0	5
• CD aggravated	5	3	4	3
• CD	3	5	3	4
• Nausea	1	7	5	8
• Flatulence	4	3	3	5
• Nasopharyngitis	1	3	5	5
• Pharyngitis	3	1	1	7
• Headache	5	4	5	9
• ISR	16	26	24	38
Significant differences in adverse events:	Not according to authors but abdominal tenderness and pharyngitis were more common in ADA 160 than the other groups			
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:** 5% **Loss to follow-up differential high:** No			
ATTRITION (*treatment specific*):	**Placebo**	**ADA 20**	**ADA 80**	**ADA 160**
Loss to follow-up:	6 (8%)	2 (3%)	5 (7%)	2 (3%)
Withdrawals due to adverse events:	2 (3%)	1 (1%)	1 (1%)	0 (0%)
QUALITY RATING:	**Good**			

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

STUDY:	**Authors: Hanauer et al.,[100] Lichtenstein et al.,[107] Feagan et al.,[108] Geboes et al.,[106] and Rutgeerts et al.[109]** **Year: 2002, 2003, 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. **Year: 2002**	
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 ≥ 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. **Year: 2002**	
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. **Year: 2002**			
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: Ljung et al.**[96] **Year: 2004** **Country:** Sweden
FUNDING:	NR
RESEARCH OBJECTIVE:	To assess the use of infliximab in inflammatory bowel disease (IBD) in a population based cohort, with special emphasis on the occurrence of severe adverse events and mortality.
DESIGN:	**Study design:** Case series **Setting:** Multicenter (11 medical centers) **Sample size:** 217
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 5 mg/kg 2 hour IV infusion N/A 217
INCLUSION CRITERIA:	All patients with IBD including Crohn's disease, ulcerative colitis, and indeterminate colitis treated with INF in Stockholm, Sweden between Jan 1999 and Apr 2001.
EXCLUSION CRITERIA:	N/A
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes

Authors: Ljung et al. **Year: 2004**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** NR
	INF
Mean age (years):	37.6
Sex (% female):	48%
Ethnicity:	NR
Other germane population qualities:	
• Crohn's disease	191 (88%)
• Ulcerative Colitis	22 (10%)
• Indeterminate Colitis	4 (2%)
• Mean # of infusions (range)	2.6 (1-11)
• Mercaptopurine/Azathioprine use (%)	54%
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Number of severe adverse events; number of mortalities **Secondary Outcome Measures:** Response rate **Timing of assessments:** N/A
RESULTS:	**Health Outcome Measures:** • 42 severe adverse events occurred in 41 patients (19%). • Six fatal adverse events occurred (3%). • The response rate was 75% in all forms of IBD • Remission in 48% • Failure to respond in 25%

Authors: Ljung et al. **Year: 2004**			
ADVERSE EVENTS: **Overall adverse effects reported (severe):** • Lymphoma • Infection • Postoperative infection • Thromboembolitic event • Hypersensitivity • Anaphylactic reaction • Urticaria • Miscellaneous	**INF** 42 events in 18.9% of patients 3 (1.4%) 11 (5.1%) 7 (3.2%) 5 (2.3%) 5 (2.3%) 3 (1.4%) 5 (2.3%) 3 (1.4%)		
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 ANALYSIS ADEQUATE:	No		
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 5 ***Targeted Immune Modulators – Crohn's Disease***

STUDY:	**Authors: Present et al.**[101] **Year: 1999** **Country:** Multinational		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To determine the efficacy of using infliximab to treat Crohn's disease		
DESIGN:	**Study design:** RCT **Setting:** 12 centers (US and Europe) **Sample size:** 94		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 34 weeks 31	**INF** 5 mg/kg 34 weeks 31	**INF** 10 mg/kg 34 weeks 32
INCLUSION CRITERIA:	18-65 years of age who had single or multiple draining abdominal or perianal fistulas of at least 3 months' duration as a complication of Crohn's disease that had been confirmed by radiography, endoscopy, or pathological exams.		
EXCLUSION CRITERIA:	Using cyclosporine or investigational agents or the use of any medication to reduce the concentration of TNF alpha was not allowed within 3 months before enrollment; CD complications such as current strictures or abscesses, presence of a stoma created less than 6 months before enrollment; history of allergy to murine proteins; previous treatment with INFL		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Aminosalicylates at a dosage that had been stable for more than 4 weeks before screening, oral corticosteroids at a dosage of 40 mg or less per day that had been stable for more than 3 weeks; MTX given for at least three months at a dosage that had been stable for more than 4 weeks; azathioprine or mercaptopurine given for at least 6 months at a dosage that had been stable for more than 4 weeks		

<table>
<tr><td colspan="4">Authors: Present et al.,
Year: 1999</td></tr>
<tr><td rowspan="2">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 (5 mg/kg)</u></td><td><u>INF (5 and 10 mg/kg)</u></td></tr>
<tr><td></td><td>Mean age (years):
Sex (% female):
Ethnicity: % white
% black
Other germane population qualities:
• Previous surgery for CD (%)
• Mean baseline CDAI</td><td>35.4
45
94
6

39
192.9</td><td>41.2
52
90
10

68
184.8</td><td>35.0
62
91
9

53
184.9</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Reduction of 50% or more from baseline in the number of draining fistulas observed at 2 or more consecutive study visits
Secondary Outcome Measures: Closure of all fistulas; length of time to beginning of response; duration of response; change in CDAI and PDAI
Timing of assessments: Weeks 0, 2, 6 for administration; assessment at 2, 6, 10, 14, 18, 26, 34</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• 68% of patients on 5 mg INF/kg and 56% of those on 10mg.kg achieved the primary endpoint vs. 26% of patients in placebo group $P = 0.002$ and $P = 0.02$ respectively
• 55% of patients on 5 mg INF/kg and 38% on 10 mg/kg had closure of all fistulas vs. 13% of patients assigned to placebo $P = 0.001$ and $P = 0.04$ respectively
• Median time to onset of response was shorter for INF (2 weeks) than for placebo (6 weeks) (P = NR)
• Duration of response approximately 3 months for INF and placebo
Intermediate Outcome Measures:
• At week 18 changes in the CDAI were not significantly different between either dose of INF and placebo; compared to placebo, PDAI scores were significantly better for 5mg/kg but not 10mg/kg ($P < 0.05$)</td></tr>
</table>

Authors: Present et al. **Year:1999**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Upper respiratory infections • Headache • Abscess • Fatigue	**Placebo** 21 (65%) 2 (6%) 7 (23% 1 (3%) 2 (6%	**INF (5 mg/kg)** 21 (65%) 1 (3%) 5 (16%) 2 (6%) 2 (6%)	**INF(10 mg/kg)** 27 (84%) 5 (16%) 6 (19%) 5 (16% 4 (12%)
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 6 (6.4%) **Loss to follow-up differential high: No**		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**placebo** 4 (13%) 0 (0%)	**INF** 2 (3%) 1 (2%	
QUALITY RATING:	**Fair**		

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

STUDY:	**Authors: Rutgeerts et al.**[102] **Year: 1999** **Country:** Multinational		
FUNDING	Not specified but it is a continuation of a study (Targan 1997) that was funded by Centocor; at least two authors affiliated with Centocor		
RESEARCH OBJECTIVE:	To determine whether repeated infusions of infliximab would effectively and safely maintain the remitting benefit		
DESIGN:	**Study design:** randomized, double-blind, placebo-controlled, parallel group clinical trial **Setting:** 17 clinical sites **Sample size:** 73		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 10 mg/kg every 8 weeks 36 weeks 37	**Placebo** 0 mg/kg every 8 weeks 36 weeks 36	
INCLUSION CRITERIA:	Crohn's disease for at least 6 months, with a CDAI between 220 and 400. Extension of earlier study, see Targan et al. (1997)		
EXCLUSION CRITERIA:	Symptomatic stenosis or ileal strictures; proctocolectomy, total colectomy, or stoma; a history of allergy to murine proteins; prior administration of murine, chimeric, or humanized monoclonal antibodies; or treatment with parenteral corticosteroids or adrenocorticotrophic hormone within 4 weeks before screening; treatment with MTX, cyclosporine, or experimental agents		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Mesalamine ≥8 weeks' duration and at a stable dosage for 4 weeks before screening; Oral corticosteroids ≥8 weeks' duration at a stable dosage for 2 weeks, with a maximum dosage of 40 mg/day; and 6-mercaptopurine or azathioprine ≥6 months' duration at a stable dosage for 8 weeks.		

<table>
<tr><td colspan="4">Authors: Rutgeerts et al.
Year: 1999</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No; more women in INF group (P = 0.05)
Disease severity: Moderate - severe</td></tr>
<tr><td></td><td><u>INF</u></td><td><u>Placebo</u></td><td></td></tr>
<tr><td>Median age (years (range)):</td><td>34 (20-64)</td><td>39 (20-65)</td><td></td></tr>
<tr><td>Sex (% female):</td><td>59.5</td><td>36.1</td><td></td></tr>
<tr><td>Ethnicity (% white):</td><td>100</td><td>100</td><td></td></tr>
<tr><td>Other germane population qualities:
• Previous surgery for CD (%)</td><td>51.4</td><td>44.4</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: maintained treatment response as assessed by the CDAI, remission defined as CDAI < 150; inflammatory bowel disease questionnaire (IBDQ) score

Secondary Outcome Measures: serum concentrations of CRP

Timing of assessments: Every 4 weeks; initial randomization at 12 weeks</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Retreatment with INF maintained the initial treatment benefit in 62% of patients compared to 37% of placebo-treated patients (P = 0.160)
• 53% of INF patient in clinical remission at 44 weeks compared to 20% for placebo (P = 0.013)
• IBDQ scores improved for INF compared to placebo (P = NR)

Intermediate Outcome Measures:
• CRP concentrations improved for INF compared to placebo (P = NR)</td></tr>
</table>

Authors: Rutgeerts et al. **Year: 1999**			
ADVERSE EVENTS: **Overall adverse effects reported (# patients reporting 1 or more AE):** • URTI • Headache • Abdominal pain • Nausea • Fever • Bronchitis • Pharngytis	**INF** 35 (94.6%) 9 (24.3%) 6 (16.2%) 5 (13.5%) 7 (18.9%) 4 (10.8%) 6 (16.2%) 7 (18.9%)	**Placebo** 35 (97.2%) 6 (16.7%) 4 (11.1%) 5 (13.9%) 3 (8.3%) 5 (13.9%) 3 (8.3%) 1 (2.8%)	
Significant differences in adverse events:	No		
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:** 24 (33%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**INF** 10 (27%) 6 (16%)	**Placebo** 14 (39%) 0 (0%)	
QUALITY RATING:	**Fair**		

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

STUDY:	**Authors: Sample et al.**[97] **Year: 2002** **Country:** Canada		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To determine whether the clinical efficacy and safety of infliximab in diverse clinical referral practices was similar to that seen in RCT for CD.		
DESIGN:	**Study design:** Observational **Setting:** Multicenter **Sample size:** 109		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 5 mg/kg N/A 109		
INCLUSION CRITERIA:	Patients of gastroenterologists in Edmonton, Can treated with INF for CD; charts were reviewed for patients with at least one follow-up visit after infusion		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Any concomitant therapy allowed		

<table>
<tr><td colspan="4">Authors: Sample et al.
Year: 2002</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: NR</td></tr>
<tr><td></td><td><u>INF</u></td><td></td><td></td></tr>
<tr><td>Median age (years):</td><td>42.5</td><td></td><td></td></tr>
<tr><td>Sex (% female):</td><td>48%</td><td></td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td></td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• MTX use (%)</td><td>26%</td><td></td><td></td></tr>
<tr><td>• Corticosteroids use (%)</td><td>95%</td><td></td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Complete and partial response to treatment

Secondary Outcome Measures: None

Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• 19 patients (17%) had a complete response to INF.
• 61 patients (55%) showed a partial response to INF
• 29 patients (27%) had no response to INF.
• The overall response rate was similar to previously published studies; however, the complete response rate was slightly lower than previously published studies.</td></tr>
</table>

Authors: Sample et al. **Year: 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Total number reported • Immediate adverse events	**INF** 16 8 (7%)		
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 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:**	N/A		
QUALITY RATING:	**N/A**		

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

STUDY:	**Authors: Sandborn et al.**[98] **Year: 2001** **Country:** US	
FUNDING:	Immunex Corporation	
RESEARCH OBJECTIVE:	Evaluation of etanercept for the treatment of active Crohn's disease	
DESIGN:	**Study design:** RCT **Setting:** Multi-center (6 sites) outpatient **Sample size:** 43	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** 25 mg sq twice weekly 8 weeks 23	**Placebo** N/A 8 weeks 20
INCLUSION CRITERIA:	Patients were at least 12 years of age; with moderate to severe Crohn's Disease as defined by a CDAI of 220-450 and confirmed by radiologic, endoscopic or histologic criteria	
EXCLUSION CRITERIA:	Patients with ileostomy or colostomy; those in immediate need of surgery for gastrointestinal bleeding; local or systemic infections; confirmed bowel obstruction in the last 6 months; planned inpatient hospitalizations; clinically important active diseases (ie. Renal or hepatic conditions); cancer in the last 5 years; pregnancy and breastfeeding; active fistula; dysplasia of colon within 5 years; history of drug/alcohol abuse; infl or investigational therapy within 12 weeks; corticosteroids within 2 weeks.	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Prednisone and budesonide for 4 weeks with a stable dose for 2 weeks; mercaptopurine or azathioprine for at least 12 weeks; MTX or mycophenolate for at least 8 weeks: oral or rectal 5-aminosalicylates, rectal corticosteroids and oral antibiotics.	

<table>
<tr><td colspan="3">Authors: Sandborn et al.
Year: 2001</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: Yes
Disease severity: Moderate - severe</td></tr>
<tr><td><u>ETA</u></td><td><u>Placebo</u></td></tr>
<tr><td>Median age (years (Range)):
Sex (% female):
Ethnicity:
Other germane population qualities:
• Previous surgery for CD (%)
• Patients with fistulae (%)
• Median baseline CDAI (range)</td><td>37.4
50
N/ R

57
17
303 (226-499)</td><td>39.3
30.4
N/R

45
5
265 (115-453)</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: Clinical response, a decrease in the baseline Crohn's Disease Activity Index score > or = 70 points; clinical remission, a CDAI score < 150 points.

Secondary Outcome Measures: The rate of fistula improvement (≥ 50% of fistula improvement); Fistula remission (closure of all fistulas); IBDQ scores

Timing of assessments: Primary- 4 weeks
Secondary- 2 and 8 weeks for clinical response, others were assessed at each visit (twice weekly)</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
• Only 4 ETA and 1 placebo patient had fistulas; only 1 ETA patient (and no placebo patient) improved and no patient had remission
• No differences in IBDQ scores at 8 weeks

Intermediate Outcome Measures:
• There were no differences in CDAI response at week 8 between ETA (30%) and placebo (30%) ($P > 0.05$)
• No differences in CDAI remission at 8 weeks (ETA 13%; placebo 25%; $P = 0.44$)</td></tr>
</table>

Authors: Sandborn et al. **Year: 2001**		
ADVERSE EVENTS: **Overall adverse effects reported:** • Headache • New ISRs • Asthenia • Abdominal pain • Mild anemia • Skin disorders	**ETA (%)** 17 (74%) 3 (13%) 3 (13%) 2 (9%) 0 (0%) 2 (9%) 2 (9%)	**Placebo (%)** 10 (50%) 1 (5%0 1 (5%) 0 (0%) 2 (10%) 0 (0%) 0 (0%)
Significant differences in adverse events:	No	
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR	
ADEQUATE RANDOMIZATION:	Method NR but it was done by Immunex Corporation	
ADEQUATE ALLOCATION CONCEALMENT:	Method NR	
BLINDING OF OUTCOME ASSESSORS:	NR	
ATTRITION (*overall*):	**Overall loss to follow-up:** 23 (53%) **Loss to follow-up differential high: Yes**	
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**ETA** 14(61%) 2 (9%)	**Placebo** 9 (45%) 0 (0%)
QUALITY RATING:	**Fair**	

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

STUDY:	**Authors: Sands et al.,**[103, 110, 112] **Lichtenstein et al.**[111] **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: 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			

<table>
<tr><td colspan="5">Authors: Targan et al. and Lichtenstein et al.
Year: 1997 and 2002</td></tr>
<tr><td rowspan="6">POPULATION CHARACTERISTICS:</td><td colspan="4">Groups similar at baseline: Yes
Disease severity: Moderate - severe</td></tr>
<tr><td></td><td><u>INF 5</u></td><td><u>INF10</u></td><td><u>INF20</u></td><td><u>Placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>37.0</td><td>39.3</td><td>36.0</td><td>38.5</td></tr>
<tr><td>Sex (% female):</td><td>48</td><td>54</td><td>54</td><td>40</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>• Previous surgery for CD (%)
• Mean baseline CDAI</td><td>44
312</td><td>50
318</td><td>50
307</td><td>52
288</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="4">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</td></tr>
<tr><td>RESULTS:</td><td colspan="4">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</td></tr>
</table>

Authors: Targan et al. and Lichtenstein et al. **Year: 1997 and 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Headache • Nausea • URTI • Fatigue	**One dose (n = 102)** 76 (75%) 19 (19% 11 (11%) 8 (8%) 6 (6%)	**Two doses (n = 29)** 23 (79%) 3 (10%) 5 (17%) 4 (14%) 3 (10%)	**Placebo (n = 25)** 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:**	**One dose** NR NR	**Two doses** NR 2 (7%)	**Placebo** 0 NR
QUALITY RATING:	**Fair**		

Evidence Table 6 ***Targeted Immune Modulators – Ulcerative Colitis***

STUDY:	**Authors: Jarnerot et al.** [114] **Year: 2005** **Country:** Sweden and Denmark		
FUNDING:	Schering-Plough		
RESEARCH OBJECTIVE:	Efficacy of infliximab in the rescue treatment of acute severe or moderately attack of UC that did not respond to IIVT.		
DESIGN:	**Study design:** Double–blind RCT **Setting:** Multicenter **Sample size: 45**		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 5 mg/kg 3 months 24	**Placebo** NA 3 months 21	
INCLUSION CRITERIA:	18–75 years; certain or probable UC verified by a typical clinical history, appearance on endoscopy, and exclusion of an infectious cause; severe or moderately severe attack of UC according to the Seo index; fulminant colitis index ≥8.0 on day 3 after institution of IIVT or a Seo index on day 5, 6, or 7 that was compatible with a severe or moderately severe attack of UC that was not responding to corticosteroid treatment.		
EXCLUSION CRITERIA:	Pregnancy or lactation; known or probable Crohn's colitis, infectious colitis, ongoing infection such as an abscess, central line infection; febrile UTI, active TB, or exposure to TB; multiple sclerosis; malignancy; heart failure or treated heart failure, earlier treatment with INF or another antibody, another disease according to the investigator's judgment, psychiatric disease, alcoholism, or anything else whereby the patient was judged incapable of completing the trial.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Jarnerot et al. **Year: 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **Disease severity:** severe		
	INF	**Placebo**	
Mean age (years):	37.5	36.2	
Sex (% female):	50	33	
Ethnicity (% white):	NR	NR	
Other germane population qualities:			
• Duration of disease (%)	NR	NR	
• Left-side involvement (%)	NR	NR	
• Extensive involvement (%)	9/24	8/21	
• Distal colitis	6/24	2/21	
• Prednisolone use (%)	NR	NR	
• Azathioprine use (%)	NR	NR	
• Corticosteroid use (%)	NR	NR	
• Duration of steroid use	NR	NR	
• CRP level (Median)	65	44	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Colectomy or death **Timing of assessments:** within 3 months of treatment		
RESULTS:	**Health Outcome Measures:** • Colectomy- INF 7/24 (29%) Placebo 14/21 (67%) (P = 0.017) OR 4.9 (95% CI 1.4-17) in favor of INF • No patients died		

<table>
<tr><td colspan="4">Authors: Jarnerot et al.
Year: 2005</td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported: NR</td><td><u>INF</u>
Central venous line septicemia; coagulase-negative staphylococci (n = 1)
Arthralgia, knee joints (n = 2)
Upper respiratory infection (n = 2)
Pneumothorax when adopting central venous line (n = 1)
Discrete exanthema, probably trimetoprim/sulphonamide (n = 1)
Pruritus during infusion (n = 1)
Perspiration day 30 (n = 1)</td><td colspan="2"><u>Placebo</u>
Exanthema, probably trimetoprim/sulfamethoxazole (n = 2)
Epigastralgia, reflux, abnormal liver tests 50 days after infusion, probably azathioprine (n = 1)
Headache, 38.5°C 14 days after infusion, negative lumbar puncture (n = 1)
Ptosis, right eyelid, 32 days after infusion (n = 1)
Dermal sensations during infusion (n = 1)
Arthralgia 90 days after infusion (n = 1)
Cardiac pacemaker 111 days after infusion (n = 1)</td></tr>
<tr><td>Significant differences in adverse events:</td><td colspan="3">Unable to tell</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: Yes
Post randomization exclusions: None</td></tr>
<tr><td>ADEQUATE RANDOMIZATION:</td><td colspan="3">Yes</td></tr>
<tr><td>ADEQUATE ALLOCATION CONCEALMENT:</td><td colspan="3">Yes</td></tr>
<tr><td>BLINDING OF OUTCOME ASSESSORS:</td><td colspan="3">NR</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: None
Loss to follow-up differential high: No</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:</td><td><u>INF</u>
0
0</td><td><u>Placebo</u>
0
0</td><td></td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

Evidence Table 6 ***Targeted Immune Modulators – Ulcerative Colitis***

STUDY:	**Authors: Rutgeerts et al.** [113] **Act 1** **Year: 2005** **Country:** Multinational		
FUNDING:	Centocor and Schering-Plough		
RESEARCH OBJECTIVE:	Efficacy of infliximab for induction and maintenance therapy in adults with ulcerative colitis.		
DESIGN:	**Study design:** Placebo-controlled RCT **Setting:** Multicenter **Sample size:** 364		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 54 weeks 121	**INF 5** 5 mg/kg 0, 2, and 6 and then every 8 weeks 54 weeks 121	**INF 10** 10 mg/kg 0, 2, and 6 and then every eight weeks 54 weeks 122
INCLUSION CRITERIA:	Established diagnosis of ulcerative colitis; Mayo score of 6 to 12 points and moderate-to-severe active disease on sigmoidoscopy (Mayo endoscopic subscore of at least 2) despite concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine Concurrent therapy was not required at enrollment for patients who had had no response to corticosteroids within the preceding 18 months or who could not tolerate corticosteroids who had had no response to azathioprine or mercaptopurine within the preceding 5 years or who could not tolerate these drugs.		
EXCLUSION CRITERIA:	Positive tuberculin skin tests; indeterminate colitis, Crohn's disease, or clinical findings suggestive of Crohn's disease		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR but doses of concomitant medications remained constant with the exception of corticosteroids which were tapered down.		

<table>
<tr><td colspan="4">Authors: Rutgeerts et al.
Year: 2005</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>INF 5</u></td><td><u>INF 10</u></td></tr>
<tr><td>Mean age (years):</td><td>41.4</td><td>42.4</td><td>41.8</td></tr>
<tr><td>Sex (% female):</td><td>40.5</td><td>35.5</td><td>92.6</td></tr>
<tr><td>Ethnicity (% white):</td><td>91.7</td><td>95.9</td><td>92.6</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Duration of disease (years)</td><td>6.2</td><td>5.9</td><td>8.4</td></tr>
<tr><td>• Left-side involvement (%)</td><td>55</td><td>52.9</td><td>55.4</td></tr>
<tr><td>• Extensive involvement (%)</td><td>45</td><td>47.1</td><td>44.6</td></tr>
<tr><td>• Distal colitis</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Prednisolone use (%)</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Azathioprine use (%)</td><td>29.8</td><td>37.2</td><td>36.1</td></tr>
<tr><td>• Corticosteroid use (%)</td><td>65.3</td><td>57.9</td><td>59.8</td></tr>
<tr><td>• Duration of steroid use</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• CRP level</td><td>1.7</td><td>1.4</td><td>1.6</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: clinical response at week 8

Secondary Outcome Measures: clinical response or clinical remission with discontinuation of corticosteroids at week 30 and 54; clinical remission and mucosal healing at weeks 8, 30 and 54; and a clinical response at week 8 in patients with a history of disease refractory to corticosteroids.

Timing of assessments: weeks 0, 2, 6, 8, 14, 22, 30, 54</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Clinical remission at wk 54 Placebo 20 (16.5%) vs
INF5- 42 (34.7%) (P = 0.001) and INF10- 42 (34.4%) (P = 0.001)
Intermediate Outcome Measures:
• Clinical response at wk 8 Placebo 45 (37.2%) vs
INF5- 84 (69.4%) (P < 0.001) and INF10- 75 (61.5%) (P < 0.001)
• Clinical response at wk 54 Placebo 24 (19.8%) vs
INF5- 55 (45.5%) (P < 0.001) and INF10- 54 (44.3%) (P < 0.001)</td></tr>
</table>

Authors: Rutgeerts et al. **Year: 2005**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Worsening UC • Infections • Serious infections	**Placebo** 85.1 33.1 38.8 4.1	**INF 5** 87.6 19.0 43.8 2.5	**INF 10** 91.0 21.3 49.2 6.6
Significant differences in adverse events:	Not according to the authors		
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:**	**Overall loss to follow-up:** 38% **Loss to follow-up differential high:** 15% **Placebo** 47% 9.1%	**INF 5** 32% 8.3%	**INF 10** 32% 9.0%
QUALITY RATING:	**Fair**		

Evidence Table 6 ***Targeted Immune Modulators – Ulcerative Colitis***

STUDY:	**Authors: Rutgeerts et al.** [113] **Act 2** **Year: 2005** **Country:** Multinational		
FUNDING:	Centocor and Schering-Plough		
RESEARCH OBJECTIVE:	Efficacy of infliximab for induction and maintenance therapy in adults with ulcerative colitis.		
DESIGN:	**Study design:** Placebo-controlled RCT **Setting:** Multicenter **Sample size:** 364		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** NA 30 weeks 123	**INF 5** 5 mg/kg 0, 2, and 6 and then every 8 weeks 30 weeks 121	**INF 10** 10 mg/kg 0, 2, and 6 and then every eight weeks 30 weeks 120
INCLUSION CRITERIA:	Established diagnosis of ulcerative colitis; Mayo score of 6 to 12 points and moderate-to-severe active disease on sigmoidoscopy (Mayo endoscopic subscore of at least 2) despite concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine and medications containing 5-aminosalicylates; Concurrent therapy was not required at enrollment for patients who had had no response to corticosteroids within the preceding 18 months or who could not tolerate corticosteroids, patients who had had no response to azathioprine or mercaptopurine within the preceding 5 years or who could not tolerate these drugs, and patients who had had no response to medications containing 5-aminosalicylates within the preceding 18 months or who could not tolerate such drugs.		
EXCLUSION CRITERIA:	Positive tuberculin skin tests; indeterminate colitis, Crohn's disease, or clinical findings suggestive of Crohn's disease		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR but doses of concomitant medications remained constant with the exception of corticosteroids which were tapered down.		

Authors: Rutgeerts et al. **Year: 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** moderate – severe		
	Placebo	**INF 5**	**INF 10**
Mean age (years):	39.3	40.5	40.3
Sex (% female):	42.3	37.2	43.3
Ethnicity (% white):	95.1	95.9	92.5
Other germane population qualities:			
• Duration of disease (%)	6.5	6.7	6.5
• Left-side involvement (%)	58.3	59.3	62.5
• Extensive involvement (%)	41.7	40.7	37.5
• Distal colitis	NR	NR	NR
• Prednisolone use (%)	NR	NR	NR
• Azathioprine use (%)	28.5	33.9	30.8
• Corticosteroid use (%)	48.8	49.6	55.0
• Duration of steroid use	NR	NR	NR
• CRP level	1.6	1.3	1.4
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** clinical response at week 8 **Secondary Outcome Measures:** clinical response or clinical remission with discontinuation of corticosteroids at week 30; a clinical remission and mucosal healing at weeks 8 and 30; and a clinical response at week 8 in patients with a history of disease refractory to corticosteroids. **Timing of assessments:** weeks 0, 2, 6, 8, 14, 22, and 30		
RESULTS:	**Health Outcome Measures:** • Clinical remission at wk 30 Placebo 13 (10.6%) vs INF5- 31 (25.6%) (P = 0.003) and INF10- 43 (35.8%) (P < 0.001) **Intermediate Outcome Measures:** • Clinical response at wk 8 Placebo 36 (29.3%) vs INF5- 57 (47.1%) (P < 0.001) and INF10- 54 (60.0%) (P < 0.001) • Clinical response at wk 30 Placebo 32 (26.0%) vs INF5- 78 (64.5%) (P < 0.001) and INF10- 83 (69.2%) (P < 0.001)		

Authors: Rutgeerts et al. **Year: 2005**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Worsening UC • Infections • Serious infections	**Placebo** 73.2 16.3 23.6 0.8	**INF 5** 81.8 9.1 27.3 1.7	**INF 10** 80.0 10.0 28.3 2.5
Significant differences in adverse events:	No		
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:** 27% **Loss to follow-up differential high:** 21%		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Placebo** 41% 9.8%	**INF 5** 20% 1.7%	**INF 10** 20% 4.2%
QUALITY RATING:	**Fair**		

Evidence Table 7 ***Targeted Immune Modulators-Plaque Psoriasis***

STUDY:	**Authors: Ellis et al.**[116, 118, 119] **Year: 2001** **Country:** US			
FUNDING:	Biogen; grant from the National Institutes of Health.			
RESEARCH OBJECTIVE:	To evaluate the use of alefacept as immunomodulatory therapy for psoriasis[116], assess the remission period following alefacept therapy[119], and assess health related QoL.[118]			
DESIGN:	**Study design:** RCT, placebo-controlled, double-blind **Setting:** Multicenter **Sample size:** 229 (205 in QoL analysis)			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ALE 0.025** 0.025 mg/kg 12 weeks 57	**ALE 0.075** 0.075 mg/kg 12 weeks 55	**ALE 0.150** 0.150 mg/kg 12 weeks 58	**Placebo** N/A 12 weeks 59
INCLUSION CRITERIA:	Age 18 to 70; chronic plaque psoriasis diagnosed ≥ 12 months prior to screening that involved ≥ 10% of body-surface area; previous systemic treatment or phototherapy, or candidates for such treatment;			
EXCLUSION CRITERIA:	Serious hepatic or renal disease; history of cancer (except basal cell carcinoma or < 3 squamous carcinomas of the skin); weight ≥ 75% above ideal body weight; serious infection within previous 3 months; women of child-bearing potential who didn't agree to use contraception.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Allowed the restricted use of moderate-potency topical corticosteroids, keratolytics, coal, tar, or calcipotriene on the groin and scalp; emollients permitted, but not within 12hrs before each assessment.			

Authors: Ellis et al. **Year: 2001**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Majority moderate-severe			
	ALE 0.025	**ALE 0.075**	**ALE 0.150**	**Placebo**
***Median* age (years):**	50	44	44	42
Sex (% female):	21.1	25.4	27.6	40.7
Ethnicity (% White):	87.7	81.8	82.3	95
Other germane population qualities:				
• Duration of disease (median)	15	19	18	18
• PASI score (median)	14	15	20	15
• Physician global assessment:				
Moderate / severe (%)	89	91	91	81
Mild / Moderate (%)	11	9	9	19
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PASI; physician global assessment; SF-36 Health Survey; Dermatology Life Quality Index (DLQI); Dermatology Quality of Life Scales (DQOLS) **Secondary Outcome Measures:** serum ALE levels; T- and B- cell quantifications **Timing of assessments:** Every 2 weeks during treatment phase (12 weeks), and weeks 1,2,4,8, & 24 during follow-up.			

Authors: Ellis et al. **Year: 2001**	
RESULTS:	**Health Outcome Measures:** • During 12-week treatment phase, patients on ALE had greater decrease in PASI than placebo. • At 2 weeks post-treatment, mean PASI scores were 38%, 53%, & 53% lower in groups receiving 0.025, 0.075, and 0.150 mg/kg of ALE, respectively vs. 21% in placebo group ($P < 0.001$) • At 12 weeks post-treatment, 47%, 63%, and 42% of patients in the ALE groups, respectively had at least 50% reduction in baseline score, compared to 32% in placebo group ($P = 0.02$). • At 12 weeks post-treatment, 33%, 31%, and 19% of patients in the ALE groups, respectively had at least 75% reduction in baseline score, compared to 11% in placebo group ($P = 0.02$). • No reports of a flare or rebound of psoriasis after the cessation of ALE therapy. • Responses were sustained for a median of 10 months, and for up to 18 months. • No correlation between the dose of ALE and length of remission ($P = 0.28$): Mean length of remission in days was 291 +/- 108, 338 +/- 128, and 377 +/- 92 in groups receiving 0.025, 0.075, and 0.150 mg/kg of ALE, respectively. • Patients treated with ALE had significantly greater improvements on dermatology-specific QoL scales compared with patients receiving placebo ($P < 0.05$). • Patients achieving a $\geq$ 50% or $\geq$75% reduction in PASI reported similar improvement in QoL. • During therapy there was little observed change in SF-36 scores. • Significant differences from baseline to last observed QoL endpoint were found for the DLQI overall scale ($P = 0.04$) & the DQOLS symptom scale ($P = 0.01$). • % improvement in DLQI overall scale from baseline = 47, 49, & 17% for 0.025mg/kg, 0.075mg/kg, and placebo, respectively. • % improvement in DQOLS symptoms scale from baseline = 47, 45, & 16% for 0.025mg/kg, 0.075mg/kg, and placebo, respectively

Authors: Ellis et al. **Year: 2001**				
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Unrelated accidental injury • Dizziness • Nausea • Chills • Cough	**ALE treatment** NR 13 9 6 5 5		**Placebo** NR 5 2 0 0 0	
Significant differences in adverse events:	No			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR			
ADEQUATE RANDOMIZATION:	Yes			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	Yes			
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:**	**Overall loss to follow-up:** 14% **Loss to follow-up differential high:** NR			
	ALE 0.025 NR	**ALE 0.075** NR	**ALE 0.150** NR	**Placebo** NR
QUALITY RATING:	**Fair**			

*primary outcome measures

Evidence Table 7 ***Targeted Immune Modulators-Plaque Psoriasis***

STUDY:	**Authors: Gordon, et al.**[123, 136] **Year: 2003** **Country:** US		
FUNDING:	Genentech, Inc.		
RESEARCH OBJECTIVE:	To assess safety & efficacy of efalizumab in patients with moderate to severe plaque psoriasis.		
DESIGN:	**Study design:** RCT; uncontrolled open-label trial after 12 weeks **Setting:** Multicenter **Sample size:** 556		
INTERVENTION: N/A **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 12 weeks 187	**EFA** 1mg/kg 12 weeks 369	
INCLUSION CRITERIA:	Age 18-75 years; diagnosed with plaque psoriasis for ≥ 6 months; minimum PASI score of 12.0; & candidates for systemic therapy.		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Emollients, tar, salicylic acid, & low-potency topical corticosteroids on face, hands, feet, groin, and axillae.		

<table>
<tr><td colspan="4">Authors: Gordon et al.
Year: 2003</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: Moderate-to-severe</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>EFA</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>45</td><td>45</td><td></td></tr>
<tr><td>Sex (% female):</td><td>29</td><td>32</td><td></td></tr>
<tr><td>Ethnicity (% white):</td><td>89</td><td>90</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• PASI score</td><td>19</td><td>19</td><td></td></tr>
<tr><td>• DLQI</td><td>12</td><td>12</td><td></td></tr>
<tr><td>• Itching VAS</td><td>6</td><td>6</td><td></td></tr>
<tr><td>• Body surface area, mean (%)</td><td>27.3</td><td>28.3</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: PASI 75 (75% reduction from baseline) at week 12.

Secondary Outcome Measures: Static Physician Global Assessment (sPGA) at weeks 12 & 24; PASI 50; Patient-reported outcome scales (DLQI, itching VAS, & Psoriasis Symptom Assessment (PSA))

Timing of assessments: Baseline, & every other week (weeks 0-16), then every 4 weeks (PASI); baseline & weeks 2,4,8,12,14,16,20, & 24 (sPGA); baseline, & every 4 weeks (patient-reported outcomes)</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• At week 12, PASI 50 response achieved by 58.5% (EFA) vs. 13.9% (placebo) (P < 0.001).
• At week 12, PASI 75 response achieved by 26.6% (EFA) vs. 4.3% (placebo) (P < 0.001).
• At week 12, PASI 90 response achieved by 5.1% (EFA) vs. 0.5% (placebo). (P value NR)
• The mean % improvement in all patient-reported outcomes at week 12 was maintained at week 24 (DLQI, 49.2%; itching scale, 42.2%; PSA frequency, 47.6%; and PSA severity, 47.3%).</td></tr>
</table>

Authors: Gordon et al. **Year: 2002**				
ADVERSE EVENTS (%):	Weeks 1-12		Weeks 13-24	
Overall adverse events reported[1]:	**Placebo (n=187)**	**EFA (n=368)**	**Placebo/EFA (n=174)**	**EFA/EFA (n=342)**
• Headache[2]	71.1	80.4	70.7	63.2
• Infection	20.9	33.4	25.3	6.1
• Chills[3]	12.3	12.5	9.8	11.1
• Nausea	5.3	12.0	5.7	1.5
• Myalgia[4]	7.0	10.6	5.2	3.8
• Generalized pain[5]	4.3	10.3	4.0	2.6
• Pharyngitis	4.8	10.1	9.8	3.2
• Flu-like syndrome	5.3	7.3	4.0	2.9
• Fever[6]	3.7	7.3	4.6	2.9
• Rhinitis	1.6	6.8	3.4	0.9
• Diarrhea	5.9	6.3	4.6	2.0
	5.3	5.4	6.3	4.1
Significant differences in adverse events:	P values for weeks 1-12 = 0.02[1]; 0.002[2]; 0.01[3]; 0.01[4]; 0.03[5];0.007[6]			
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:** 6.5% (at 12 weeks) **Loss to follow-up differential high:** No (at 12 weeks)			
ATTRITION (*treatment specific*):	**Placebo**	**EFA**		
Loss to follow-up:	7% (at 12 weeks)	7% (at 12 weeks)		
Withdrawals due to adverse events:	2 (at 12 weeks)	7 (at 12 weeks)		
QUALITY RATING:	**Good**			

Evidence Table 7 ***Targeted Immune Modulators-Plaque Psoriasis***

STUDY:	**Authors: Gottlieb et al.**[131] **and Feldman et al.**[134] **Year: 2004, 2005** **Country:** US		
FUNDING:	Centocor, Inc		
RESEARCH OBJECTIVE:	To evaluate the effect of infliximab on the HQL of patients with severe plaque psoriasis (*Feldman)*; to evaluate the safety and efficacy of INF induction therapy for treatment of psoriasis (G*ottlieb).*		
DESIGN:	**Study design:** RCT (double-blind, placebo controlled) **Setting:** Multicenter **Sample size:** 249		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A Given at week 0,2,6 51	**INF-3** 3 mg/kg Given at week 0,2,6 99	**INF-5** 5 mg/kg Given at week 0,2,6 99
INCLUSION CRITERIA:	Age ≥ 18 yrs; diagnosis of plaque psoriasis for ≥ 6 months; previous receipt of psoralen and long wave ultraviolet radiation or systemic therapy; PASI score ≥ 12 or more; and ≥ 10% of total body surface area involved.		
EXCLUSION CRITERIA:	Nonplaque forms of psoriasis; history of chronic infectious disease or opportunistic infection; serious infection within 2 months of enrollment; active or latent TB; pregnancy or planned pregnancy within 12 months of enrollment; history of lymphoproliferative disease; active malignancy or history of malignancy within previous 5 years (except basal cell carcinoma of the skin previously excised with no evidence of recurrence).		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Emollients and shampoos containing tar or salicylic acid		

Authors: Feldman et al. & Gottlieb et al. **Year: 2005, 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** yes **Disease severity:** Severe		
	Placebo	**INF-3**	**INF-5**
Mean age (years):	45	45	44
Sex (% female):	39.2	29.3	26.3
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• Psoriasis disease duration (yrs)	16	18	16
• Body surface area (%)	26	29	25
• PASI	18	20	20
• DLQI	14	11	11
• Prior systemic agents (%)	82.4	86.9	88.9
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PASI-75 **Secondary Outcome Measures:** DLQI; static PGA; PASI-50; PASI-90 **Timing of assessments:** Baseline, biweekly for 1st 10 weeks, then every 4 weeks through week 30. (DLQI at baseline & week 10 only)		
RESULTS:	**Health Outcome Measures:** • At week 10, PASI-75 achieved in 6% (placebo) 72% (INF-3) and 88% (INF-5); P < 0.001. • At week 10, PASI-50 achieved in 22% (placebo) 84% (INF-3) and 97% (INF-5); P < 0.001. • At week 10, PASI-90 achieved in 2% (placebo) 46% (INF-3) and 58% (INF-5); P < 0.001. • At week 10, median decrease from baseline DLQI was significantly greater among INF groups [8.0 in INF-3 group (P < 0.001) and 10.0 in INF-5 group (P < 0.001)] than placebo [0]. • At week 10, median percentage improvement from baseline DLQI was significantly greater among INF groups [84% in INF-3 group (P < 0.001) and 91% in INF-5 group (P < 0.001)] than placebo [0%]. • The median percentage improvement from baseline to week 10 for each individual component of the DLQI except symptoms and feelings was 100% in INF groups vs. 0% in placebo. • At week 10, PGA was minimal or cleared in 10% (placebo) 72% (INF-3) and 90% (INF-5); P < 0.001.		

Authors: Feldman et al. & Gottlieb et al. **Year: 2005, 2004**			
ADVERSE EVENTS: **Overall adverse effects reported %** • Serious adverse events • Serious infections • Infusion reactions • Antibodies to INF • Newly positive ANA	**Placebo** 62.7 0.0 0.0 2.0 N/A 2.3	**INF-3** 77.6 4.1 0.0 18.4 27.6 22.9	**INF-5** 78.8 8.1 1.0 22.2 19.5 25.0
Significant differences in adverse events:	NR		
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:**	**Overall loss to follow-up:** NR (for 10 weeks) **Loss to follow-up differential high:** Yes **Placebo** NR 1	**INF-3** NR 7	**INF-5** NR 3
QUALITY RATING:	**Fair**		

*primary outcome measures

Evidence Table 7 ***Targeted Immune Modulators-Plaque Psoriasis***

STUDY:	**Authors: Gottlieb et al.**[127] **Year: 2003** **Country:** US		
FUNDING:	Immunex, Corp.		
RESEARCH OBJECTIVE:	To determine safety & efficacy of monotherapy with etanercept in patients with plaque psoriasis.		
DESIGN:	**Study design:** RCT (double-blind, placebo-controlled) **Setting:** Multicenter **Sample size:** 112		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 24 weeks 55	**ETA** 25mg twice weekly 24 weeks 57	
INCLUSION CRITERIA:	Age ≥ 18 years; active, stable plaque psoriasis involving ≥ 10% total body surface area; ≥ 1 previous phototherapy or systemic therapy (such as methoxsalen plus UV-A, UV-B, oral retinoids, cyclosporine, or MTX)		
EXCLUSION CRITERIA:	Administration of systemic psoriasis therapy or psoralen UV- A phototherapy within 4 weeks of study drug; topical corticosteroids, vitamin A or D analogues, anthralin, or UV-B phototherapy within 2 weeks of baseline measurements; Active guttate, erythrodermic, or pustular psoriasis; other skin conditions; or other significant medical conditions that might interfere with study evaluation.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Lower-potency topical corticosteroids or tar-based shampoo on the scalp, axilla, and groin.		

Authors: Gottlieb et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR		
	Placebo	**ETA**	
Mean age (years):	46.5	48.2	
Sex (% female):	33	42	
Ethnicity (% White):	95	89	
Other germane population qualities:			
• MTX use (%)	20	22	
• Corticosteroids use (%)	5	8	
• Duration of disease (yrs)	20	23	
• Mean PASI score	19.5	17.8	
• Mean % body surface area	34	30	
• Mean physician's global score	2.9	2.8	
• Mean patient's global score	4.2	4.1	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PASI 75 (a ≥ 75% improvement from baseline PASI) at week 12. **Secondary Outcome Measures:** PASI 50; PASI 90; Physician's & patient's global scores; DLQI. **Timing of assessments:** Screening, baseline, and weeks 2, 4, 8, 12, 16, 20, & 24. (DLQI at baseline and weeks 4,8,12,&24)		
RESULTS:	**Health Outcome Measures:** • At week 12, PASI 75 achieved by 30% of ETA-treated vs. 2% of placebo group ($P< 0.001$; difference 28%, 95% CI 16%-40%). • At week 24, PASI 75 achieved by 56% of ETA-treated vs. 5% of placebo group ($P< 0.001$; difference 51%, 95% CI 36%-65%). • Week 24 PASI 50 = 77% (ETA) vs. 13% (placebo) ($P < 0.001$). • Week 24 PASI 90 = 21% (ETA) vs. 0% (placebo) ($P < 0.001$). • Week 24 physician global score % mean improvement = -2 (placebo) vs. 46 (ETA) ($P < 0.001$). • Week 24 patient global score % mean improvement = 7 (placebo) vs. 62 (ETA) ($P < 0.001$). • Week 24 BSA affected % mean improvement = -12 (placebo) vs. 63 (ETA) ($P < 0.001$). • Week 24 composite DLQI % mean improvement = 7 (placebo) vs. 64 (ETA) ($P < 0.001$).		

Authors: Gottlieb et al. **Year:2003**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Upper respiratory infection • Headache • Bruise at injection site • Sinusitis • Pain • Peripheral edema • Hypertension • Accidental injury	**Placebo** NR 20 13 9 4 7 9 4 4	**ETA** NR 35 16 11 14 7 2 7 7	
Significant differences in adverse events:	NR		
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:**6.7% at 12 weeks and 49.1% at 24 weeks. **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Placebo (12 wk / 24 wk)** 27% / 78% 6	**ETA (12 wk / 24 wk)** 7% / 16% 2	
QUALITY RATING:	**Fair**		

*primary outcome measures

Evidence Table 7 ***Targeted Immune Modulators – Plaque Psoriasis***

STUDY:	**Authors: Lebwohl et al.,[115] Finlay et al.,[117] and Ortonne[135]** **Year: 2003** **Country:** Multinational		
FUNDING:	Biogen Inc., Cambridge, Mass		
RESEARCH OBJECTIVE:	To examine effects of a 12 week course of intramuscular alefacept on QoL in 507 patients with chronic plaque psoriasis using both dermatology-specific questionnaires and the Short Form-36 Health Survey (SF-36).		
DESIGN:	**Study design:** Placebo-controlled, 12-week RCT followed by additional 12 weeks of observation **Setting:** Multicenter (64) **Sample size:** 507		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 12 weeks 168	**ALE 10mg** 10 mg 12 weeks 173	**Alefacet 15mg** 15 mg 12 weeks 166
INCLUSION CRITERIA:	Adult ≥ 18 years old; diagnosis of chronic plaque psoriasis for a minimum of 12 months, involving at least 10% body surface area; CD4+ lymphocyte counts above the lower limits of normal.		
EXCLUSION CRITERIA:	Erythrodermic, guttate or generalized pustular forms of psoriasis; serious infection in last 3 months; history of malignancy other than basal cell carcinoma or fewer than 3 squamous cell carcinomas.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Moderate-potency topical corticosteroids, vitamin D analogues, keratolytics and coal tar were prohibited within 2 weeks of study drug administration and throughout study, except on the scalp, palms, groin, anal fold, and soles; low-potency topical corticosteroids and emollients were allowed but not within 12 hours of efficacy assessments.		

<table>
<tr><td colspan="4">Authors: Finlay et al., Lebwohl et al. and Ortonne
Year: 2003</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: severe(10%), moderate-severe(36%), moderate(39%), mild-moderate(13%), mild(2%)</td></tr>
<tr><td><u>Placebo</u></td><td><u>ALE 10mg</u></td><td><u>ALE 15mg</u></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• DLQI</td><td>46.5
35
88

10.9(7.4)</td><td>44.0
31
92

10.7(6.4)</td><td>45.3
38
90

11.9(7.1)</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Dermatology Life Quality Index (DLQI), PASI
Secondary Outcome Measures: Dermatology Quality of Life Scales (DQOLS) and the Short Form-36 Health Survey (SF-36)
Timing of assessments: baseline, 2 weeks after last dose (week 14), and 12 weeks after last dose (week 24)</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• There were dose-dependent improvements in overall DLQI scores at week 14; mean reductions from baseline DLQI scores were 2.7 (placebo) and 4.9 (ALE 15mg) (P < 0.001). The 10mg groups showed improvement trend compared to placebo, but not statistically significant.
• At week 24, each treatment group had greater mean improvement in DLQI compared to placebo, but not statistically significant.
• Responders with reductions in disease severity at week 14 achieved and maintained significantly greater improvements in DLQI scores than nonresponders.
• Patients with ≥ 50% to < 75% reduction in PASI at week 14 had a 5.1 mean reduction in DLQI score 2 weeks post-treatment and a 4.4 mean reduction 12 weeks post-treatment. These reductions were significantly greater than those in patients achieving a ≥ 75% reduction in PASI (P<0.001)
• Results of DQOLS similar to those of DQLI
• Week 14: patients on ALE 15mg had significantly greater improvement on QoL compared to placebo on these SF-36 scales: general health, vitality, role emotional, physical component summary, and mental component summary (all P < 0.025)
• No statistically significant differences in SF-36 between patients on ALE 10mg vs. placebo.
• Mean reductions in PASI in the 15-mg ALE, 10-mg ALE, and placebo groups reached a maximum of 46%, 41%, and 25%, respectively, at 6 weeks postdosing.</td></tr>
</table>

Authors: Finlay et al., Lebwohl et al. and Ortonne **Year: 2003**			
ADVERSE EVENTS (%):	**Placebo**	**ALE 10mg**	**ALE 15mg**
Overall adverse effects reported:	NR	NR	NR
• Infection	11	14	16
• Headache	15	20	18
• Pruritus	10	14	18
• Serious adverse events	6	5	4
• Cancer	1- prostate	0	2- basal cell
Significant differences in adverse events:	No		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 19		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 12.2% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Placebo**	**ALE 10mg**	**ALE 15mg**
Loss to follow-up:	15.5%	12.1%	9.0%
Withdrawals due to adverse events:	2.4%	2.3%	1.2%
QUALITY RATING:	**Good**		

*primary outcome measures

Evidence Table 7 ***Targeted Immune Modulators-Plaque Psoriasis***

STUDY:	**Authors: Lebwohl et al.**[120] **Year: 2003** **Country:** United States		
FUNDING:	Supported by Genentech		
RESEARCH OBJECTIVE:	To evaluate efficacy and safety of Efalizumab (EFA) in subjects with moderate-to-severe plaque psoriasis.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 597		
INTERVENTION: **Phase 1 (weeks 1-12)** **Dose:** **Duration:** **Sample size**	**Placebo** N/A 12 weeks 122	**EFA-1** 1 mg/kg per week 12 weeks only 232	**EFA-2** 2 mg/kg per week 12 weeks 243
INCLUSION CRITERIA:	Age ≥ 18-70 y.o.; plaque psoriasis that had been clinically stable for ≥ 3 months and moderate to severe for ≥ 6 months; PASI ≥ 12.0 at screening; plaque psoriasis covering at least 10% of body surface area; candidacy for systemic therapy.		
EXCLUSION CRITERIA:	Patient with a history of cancer or ongoing uncontrolled infection; presence of cancer over past 5 years; hepatic or renal dysfunction; WBC count less than 4,000 or more than 14,000 per cubic millimeter; history of severe allergic or anaphylactic reaction to humanized monoclonal antibodies; previous treatment with EFA.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Eucerin cream, tar or salicylic acid preparations on scalp; limited application of low-potency corticosteroids; and oral antipruritic agents.		

Authors: Lebwohl et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR **Disease severity:** moderate-severe		
	Total population		
Mean age (years):	46		
Sex (% female):	35%		
Ethnicity:	NR		
Other germane population qualities:			
• Mean disease duration (yrs)	19		
• Mean psoriasis index (%)	20		
• Previous treatment (%)	67		
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PASI **Timing of assessments:** NR		
RESULTS:	**Health Outcome Measures:** • Patients in both EFA groups had significantly better responses than placebo ($P < 0.001$) • At week 12, mean PASI = 9 in EFA group vs. 17 in placebo group ($P < 0.001$) • At week 12, mean improvement = 51%(EFA 1mg), 52% (EFA 2 mg), &17% (placebo)($P < 0.001$)		

Authors: Lebwohl et al. **Year: 2003**			
ADVERSE EVENTS:	**Placebo**	**Efalizumab-2**	**Efalizumab-1**
Overall adverse effects reported (%)*	75	86	85
• Headache**	24	38	31
• Infections	16	18	12
• Nausea	9	14	15
• Fever#	5	12	11
• Pain+	3	12	15
• Chills++	2	16	13
• Rhinitis	7	5	8
• Back pain^	1	4	7
• Worsening psoriasis	2	3	5
Significant differences in adverse events:	* P = 0.006; ** P = 0.02; #P = 0.03; +P < 0.001; ++P < 0.001; ^P = 0.03		
ANALYSIS:	**ITT:**Yes **Post randomization exclusions:** Cannot tell; 8 discontinued due to "investigator decision"		
ADEQUATE RANDOMIZATION:	Yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (%)(*overall*):	**Overall loss to follow-up:** 23% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*) (%):	**Placebo**	**EFA-1**	**EFA-2**
Phase 1 (n = 597)			
Loss to follow-up:	9	9	6.6
Withdrawals due to adverse events:	0.8	3	2.5
QUALITY RATING:	**Fair**		

Evidence Table 7 ***Targeted Immune Modulators-Plaque Psoriasis***

STUDY:	**Authors: Leonardi et al.**[125] and **Feldman et al**.[126] **Year: 2003 and 2005** **Country:** US			
FUNDING:	Immunex, Seattle			
RESEARCH OBJECTIVE:	To evaluate safety, efficacy and HRQOL of 3 different regimens of etanercept in patients with moderate-to-severe psoriasis			
DESIGN:	**Study design:** **Setting:** Multi-center **Sample size:** 672			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A, then ETA 25mg biweekly 12wks, then 12wks ETA 166	**ETA low-dose** 25mg / week 12 weeks 160	**ETA medium-dose** 25mg twice weekly 12 weeks 162	**ETA high-dose** 50mg twice weekly 12 weeks 164
INCLUSION CRITERIA:	Age ≥ 18 years; active, clinically stable plaque psoriasis involving ≥ 10% total body surface area; PASI ≥ 10; Receipt of ≥ 1 previous phototherapy or systemic therapy (or candidate for such treatment)			
EXCLUSION CRITERIA:	Active guttate, erythrodermic, or pustular psoriasis , or other active skin conditions that would interfere with study; Receipt of ETA or anti-TNFα antibody at any time; Receipt of anti-CD4 antibodies or interleukin-2-diptheria-toxin fusion protein in previous 6 months; Receipt of any biologic or investigational drug, psoralen ultraviolet(UV) A phototherapy, systemic corticosteroids, or systemic psoriasis therapy within previous 4 weeks; Receipt of topical corticosteroids, vitamin A or D analogues, or UVB phototherapy within last 2 weeks; Receipt of antibiotics within the last week			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Topical corticosteroids (low or moderate strength) on the scalp, axilla, and groin.			

Authors: Leonardi et al. and Feldman et al. **Year: 2003 and 2005**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe			
	Placebo	**ETA (low-dose)**	**ETA (medium-dose)**	**ETA (high dose)**
Mean age (years):	45.6	44.4	45.4	44.8
Sex (% female):	36	26	33	35
Ethnicity (% White):	90	85	85	87
Other germane population qualities:				
• Duration of disease (yrs)	18.4	19.3	18.5	18.6
• Affected body surface area (%)	28.8	27.7	28.5	29.9
• PASI	18.3	18.2	18.5	18.4
• Physician-rated marked or severe (%)	23	21	23	21
• Patient-rated severe (%)	75	76	74	76
• DLQI	12.8	12.2	12.7	11.3
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PASI 75 at week 12 and HRQOL at 12 weeks **Secondary Outcome Measures:** PASI 50; PASI 90; Physician's Global Assessment of Psoriasis; DLQI; Patient's Global Assessment of Psoriasis **Timing of assessments:** Weeks 2,4,8,12,16,20,& 24. (Safety at screening, baseline, & weeks 12 & 24)			
RESULTS:	**Health Outcome Measures:** • At 12 weeks, PASI 75 was achieved by 4% (placebo), 14% (low-dose), 34% (medium- dose), and 49% (high-dose) ($P < 0.001$ for all 3 comparisons with the placebo group). • PASI 50 = 14% (placebo), 41% (low-dose), 58% (medium- dose), and 74% (high-dose) ($P < 0.001$ for all 3 groups). • PASI 90 = 1% (placebo), 3% (low-dose), 12% (medium- dose), and 22% (high-dose) ($P < 0.001$ for medium and high-dose groups vs. placebo). • At 12 weeks, physician rating of "clear" or "almost clear" of psoriasis in 5% (placebo), 23% (low-dose), 34% (medium- dose), and 49% (high-dose) ($P < 0.001$ for all 3 ETA groups vs. placebo). • At week 12, mean improvement in DLQI was 10.9% (placebo), 47.2% (low-dose), 50.8% (medium- dose), and 61.0% (high-dose) ($P < 0.001$ for all 3 ETA groups vs. placebo). • Patient global assessment significantly better in all ETA groups vs. placebo ($P < 0.001$). • At 12 wks significantly more ETA patients had a clinically significant change in DLQI than placebo 28% (placebo), 50% (low-dose), 54% (medium- dose), and 63% (high-dose) $P < 0.001$			

Authors: Leonardi et al. and Feldman et al. **Year: 2003 and 2005**				
ADVERSE EVENTS (%):	**Placebo**	**ETA low-dose**	**ETA medium-dose**	**ETA high-dose**
Overall adverse effects reported :	NR	NR	NR	NR
• ISR	7	11	17	13
• Headache	7	3	12	7
• Upper respiratory infection	11	10	9	5
• Injection-site ecchymosis	4	7	2	5
• Asthenia	3	4	4	2
• Myalgia	2	2	4	2
• Accidental injury	4	4	3	4
• Sinusitis	1	0	0	0
• Nausea	1	3	2	2
• Rash	2	3	2	3
Significant differences in adverse events:	No			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (20 did not receive any intervention)			
ADEQUATE RANDOMIZATION:	NR			
ADEQUATE ALLOCATION CONCEALMENT:	NR			
BLINDING OF OUTCOME ASSESSORS:	Yes			
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR			
ATTRITION (*treatment specific*):	**Placebo**	**ETA low-dose**	**ETA medium-dose**	**ETA high-dose**
Loss to follow-up:	NR	NR	NR	NR
Withdrawals due to adverse events:	NR	NR	NR	NR
QUALITY RATING:	**Fair**			

Evidence Table 7 *Targeted Immune Modulators – Plaque Psoriasis*

STUDY:	**Authors: Leonardi et al.**[121] **Year: 2005** **Country:**		
FUNDING:	Genentech Inc.		
RESEARCH OBJECTIVE:	Efficacy and safety of efalizumab therapy for psoriasis		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 498		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Efalizumab 1 mg/kg** 1 mg/kg weekly 12 162	**Efalizumab 2 mg/kg** 2 mg/kg weekly 12 166	**Placebo** N/A 12 170
INCLUSION CRITERIA:	18-70 years of age diagnosed with moderate to severe plaque psoriasis for at least 6 months, with clinically stable disease for at least 3 months; PASI ≥12, had a body surface area (BSA) involvement ≥10% at screening.		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Leonardi et al. **Year: 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes		
	Placebo	**Efalizumab 1mg/kg**	**Efalizumab 2mg/kg**
Mean age (years):	41.7	45.2	45.5
Sex (% female):	27.1	27.2	28.9
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• Mean PASI	19.0	18.6	18.9
• Mean body surface area involvement	29.4	29.6	29.9
• Mean duration of psoriasis	18.5	19.1	16.7
• Received prior systemic therapy (%)	NR	NR	NR
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PASI-75 at week 12 **Secondary Outcome Measures:** Minimal or clear on the static Physician's Global Assessment (sPGA). PGA of change rating of excellent or cleared. **Timing of assessments:** every two weeks in first phase, then monthly.		
RESULTS:	**Health Outcome Measures:** • PASI-50 Placebo- 25 (14.7%) vs. EFA1-99 (61.1%) P < 0.001 or EFA2-85 (51.2%) P < 0.001 Overall EFA- 184 (56.1%) • PASI-75 Placebo- 4 (2.4%) vs. EFA1- 63 (38.9%) P < 0.001 or EFA2- 44 (26.5%) P < 0.001 • PASI-90 Placebo- 2 (1.2%) vs. EFA1- 20 (12.3%) or EFA2- 8 (4.8%) Overall EFA28 (8.5%) Not analyzed • sPGA minimal or clear Placebo- 5 (2.9%) vs. EFA1-52 (32.1%) P < 0.001 or EFA2-37 (22.3%) P < 0.001 or Overall EFA 89 (27.1%) • PGA excellent or clear Placebo- 7 (4.1%) vs. EFA1- 63 (38.9%) P < 0.001 or EFA2-50 (30.1%) P < 0.001 Overall EFA- 113 (34.5%) • EFA patients not achieving PASI-75 at week 12 were re-randomized to receive EFA (n = 123) or placebo (n = 60) during extended treatment. At week 24, EFA 20.3% (25/123) vs. placebo 6.7% (4/60) (P = .018).		

Authors: Leonardi et al. **Year: 2005**			
ADVERSE EVENTS:	**Placebo**	**EFA 1 mg/kg**	**EFA 2 mg/kg**
Overall adverse effects reported:	76.5	83.3	89.2
• Headache	30.0	35.2	35.5
• Nonspecific pain	9.4	13.0	9.6
• Chills	5.9	12.3	13.3
• Nausea	9.4	8.6	12.7
• Serious AEs	1.2	1.9	3.0
• Infection related AEs	22.9	27.2	24.7
Significant differences in adverse events:	Headache, fever, chills, nausea and myalgia occurred more frequently in EFA-treated patients following the first 2 injections but were similar to placebo after that.		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	**Yes**		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 11% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Placebo**	**EFA 1 mg/kg**	**EFA 2 mg/kg**
Loss to follow-up:	11%	8%	13%
Withdrawals due to adverse events:	3%	3%	5%
QUALITY RATING:	**Fair**		

*primary outcome measures

Evidence Table 7 ***Targeted Immune Modulators – Plaque Psoriasis***

STUDY:	**Authors: Menter et al.**[132] **Year: 2006** **Country:** Multinational		
FUNDING:	Centocor and Schering-Plough		
RESEARCH OBJECTIVE:	The efficacy and safety of infliximab vs. placebo were compared in a 10 week induction phase followed by 40 weeks of continuous (every 8-week) and intermittent (as-needed) maintenance regimens		
DESIGN:	**Study design:** RCT **Setting:** 63 sites **Sample size:** 835		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Infliximab 3mg** 3 mg/kg at wks 0, 2, 6 10 weeks (50 weeks) 313	**Infliximab 5mg** 5 mg/kg at wks 0, 2, 6 10 weeks (50 weeks) 314	**Placebo** N/A 10 weeks (50 weeks) 208
INCLUSION CRITERIA:	Candidates for phototherapy or systemic therapy; PASI score ≥12 with at least 10% total BSA		
EXCLUSION CRITERIA:	History of serious infection, lymphoproliferative disease, or active TB; previous treatment with infliximab		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Low potency topical corticosteroids for the face and groin after week 10; stable NSAIDs throughout		

Authors: Menter et al. **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:**		
	Infliximab 3mg	**Infliximab 5mg**	**Placebo**
Mean age (years):	43.4	44.5	44.4
Sex (% female):	34.2	35.0	30.8
Ethnicity (% white):	93	93.3	90.9
Other germane population qualities:			
• Mean PASI	20.1	20.4	19.8
• Mean body surface area involvement	28.0	28.7	28.4
• Mean duration of psoriasis	18.1	19.1	17.8
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PASI 75 at week 10 **Secondary Outcome Measures:** PGA, DLQI, PASI 90 **Timing of assessments:** weeks 10, 16, 30, 50		
RESULTS:	**Health Outcome Measures:** **10 weeks** • PASI 75- INF3 70.3% and INF5 75.5% versus placebo 1.9% ($P < .001$) • PGA score of clear or excellent- INF3 69.8% and INF5 76.0% versus placebo 1.0% ($P < .001$) • Change in DLQI score- INF3 9.0 and Inf5 9.0 versus placebo no change ($P < .001$) • PASI 90- INF3 37.1% and INF5 45.2% versus placebo 0.5% ($P < .001$) • Continuous maintenance regimens were more efficacious than intermittent regimens.		

Authors: Menter et al. **Year: 2006**			
ADVERSE EVENTS:	**Infliximab 3mg**	**Infliximab 5mg**	**Placebo**
Overall adverse effects reported:	62.6	68.8	56.0
• Infections	33.9	30.9	30.0
• Rhinitis	3.2	2.9	0.5
• Sinusitis	2.9	6.4	1.4
Significant differences in adverse events:	Rhinitis was significantly more common in active treatment groups. Also there were 2 cases of TB and 12 malignancies in infliximab groups and none in placebo		
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:** 30% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Infliximab 3**	**Infliximab 5**	**Placebo**
Loss to follow-up:	7%	5%	12%
Withdrawals due to adverse events:	4%	4%	2%
QUALITY RATING:	**Fair**		

Evidence Table 7 ***Targeted Immune Modulators-Plaque Psoriasis***

STUDY:	**Authors: Ortonne et al.**[122] **Year: 2005** **Country:** Multinational		
FUNDING:	Serono International S.A.		
RESEARCH OBJECTIVE:	To evaluate impact of efalizumab (EFA) on HQL and other patient-reported outcomes in patients with moderate to severe plaque psoriasis, including a large cohort of High-Need patients for whom at least 2 other systemic therapies were unsuitable because of lack of efficacy, intolerance, or contraindication.		
DESIGN:	**Study design:** RCT (double-blind, placebo-controlled, parallel-group) **Setting:** Multicenter **Sample size:** 793		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**EFA** 1 mg/kg per week 12 weeks 526	**Placebo** N/A 12 weeks 264	
INCLUSION CRITERIA:	Age 18-75 years; ≥ 6-month history of plaque psoriasis, with >10% of total body area involved; minimum PASI of 12.0 at screening; previous systemic treatment for psoriasis or treatment-naïve candidates for such therapy. * A mid-study protocol amendment limited enrollment to patients meeting the "High-Need" criteria: patients for whom ≥ 2 current systemic therapies (e.g., photochemotherapy [PUVA], cyclosporine, corticosteroids, MTX, oral retinoids, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine, 6-mercaptopurine) were ineffective, poorly tolerated, or contraindicated.		
EXCLUSION CRITERIA:	Clinically significant disease flare at screening or enrollment; major concomitant illness, immune disorder, or organ dysfunction.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Emollients and tar or salicylic acid preparations for scalp lesions; small quantities of group VI or VII topical corticosteroids for lesions on face, hands, feet, groin, or axillae, except on day of a scheduled PASI assessment.		

<table>
<tr><td colspan="3">Authors: Ortonne et al.
Year: 2005</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: NR
Disease severity: moderate-to-severe</td></tr>
<tr><td><u>EFA</u>
NR</td><td><u>Placebo</u>
NR</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: SF-36; DLQI
Secondary Outcome Measures: PSA; Itching visual analog scale (VAS); PGPA
Timing of assessments: Baseline, 4, 8, and 12 weeks.</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
At week 12, EFA group had significantly greater improvements from baseline than placebo ($P \leq 0.05$) in each SF-36 component except the Physical Functioning Index.
SF-36 overall summary score improved by 59.7 points (EFA) vs. 10.4 points (placebo) ($P = 0.002$)
At week 12, EFA group had significantly greater improvements from baseline in DLQI total score than placebo (5.7 points (5.4 in High Need group) vs. 2.3 points, respectively; $P < 0.001$).
At week 12, PSA Frequency had improved by 5.7 & 5.8 points (EFA total population & High Need population, respectively) vs. 2.0 & 2.1 (placebo total population & High Need population, respectively) ($P < 0.001$ for both analyses).
At week 12, PSA Severity had improved by 6.2 & 6.3 points (EFA total population & High Need population, respectively) vs. 1.9 (placebo both populations) ($P < 0.001$ for both analyses).
At week 12, itching VAS score had improved by 2.5 & 2.4 points (EFA total population & High Need population, respectively) vs. 0.6 & 0.4 (placebo total population & High Need population, respectively) ($P < 0.001$ for both analyses).
At week 12, mean improvement in PGPA was 2.8 points (EFA) vs. 0.4 points (placebo) ($P < 0.001$)</td></tr>
</table>

Authors: Ortonne et al. **Year: 2005**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**EFA**	**Placebo**	
• Headache	26.1	14.0	
• Influenza-like illness	9.6	7.2	
• Arthralgia	7.4	3.0	
• Rigors	6.2	5.3	
• Pyrexia	7.9	1.1	
• Nasopharyngitis	5.3	4.2	
• Myalgia	5.5	2.7	
• Pruritus	3.6	5.7	
• Serious adverse events	5.5	5.7	
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Cannot tell		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:**		
ATTRITION (*treatment specific*):	**EFA**	**Placebo**	
Loss to follow-up:	NR	NR	
Withdrawals due to adverse events:	5.7%	2.7%	
QUALITY RATING:	**Fair**		

*primary outcome measures

Evidence Table 7 ***Targeted Immune Modulators-Plaque Psoriasis***

STUDY:	**Authors: Papp et al.**[128, 129] **Year: 2005** **Country:** Multinational		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To assess patient-reported outcomes (PROs) in patients with psoriasis receiving etanercept therapy; to examine efficacy & safety of etanercept and to assess maintenance of treatment effect after dose reduction.		
DESIGN:	**Study design:** RCT(double blind) followed by open label **Setting:** Multicenter **Sample size:** 611 (583 for ITT)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 12 weeks 193	**ETA 25** 25 mg twice weekly (BIW) 12 weeks 196	**ETA 50** 50 mg twice weekly (BIW) 12 weeks 194
INCLUSION CRITERIA:	Active, clinically stable plaque psoriasis involving ≥ 10% of body surface area; minimum PASI score of 10; received at least 1 course of previous phototherapy or systemic therapy for psoriasis (or a candidate for such therapy); and at least 18 years old.		
EXCLUSION CRITERIA:	Active, guttate, erythrodermic or pustular psoriasis; other skin conditions that would interfere; active infection within 4 weeks of study; receipt of antibiotics within 1 week of study drug initiation; vitamin A or D analogue preparations, dithranol, or UV B phototherapy within 2 weeks; or systemic psoriasis therapy or psoralen plus UVA photochemotherapy within 4 weeks; ETA or an anti-TNF at any time		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Topical steroids of moderate strength on the scalp, axilla, and groin, or tar compound or steroid-free topical emollients.		

Authors: Papp et al. **Year: 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR		
	Placebo	**ETA 25**	**ETA 50**
Mean age (years):	44	45.4	45.2
Sex (% female):	36	35	33
Ethnicity (% white):	91	92	89
Other germane population qualities:			
• Mean duration of disease	19.4	22.2	19.9
• Mean PASI score	18.6	19.1	19.5
• Mean DLQI total score	12.2	11.5	11.4
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Dermatology Life Quality Index (DLQI); SF-36; patient rating of pruritis; patient global assessment of psoriasis; PASI 75 (≥ 75% improvement from baseline) **Secondary Outcome Measures:** PASI 50; PASI 90 **Timing of assessments:** Weeks 2,4,8, & 12 of double-blind period, and then every 4 weeks during open-label extension; SF-36 assessed at 12-week intervals		

Authors: Papp et al. **Year: 2005**	
RESULTS:	**Health Outcome Measures:** • Response to ETA was dose dependent. • In ITT population, the PASI 75 response was achieved at week 12 by 49% (ETA 50mg BIW), 34% (ETA 25mg BIW), and 3% (placebo) of patients (P < 0.0001). • In ITT population, PASI 50 response was achieved at week 12 by 77% (ETA 50mg BIW), 64% (ETA 25mg BIW), and 9% (placebo) of patients (P < 0.0001). • In ITT population, PASI 90 response was achieved at week 12 by 21% (ETA 50mg BIW), 11% (ETA 25mg BIW), and 1% (placebo) of patients (P < 0.0001). • In ITT population, at week 24, PASI 75 response was achieved by 54% of patients following dose reduction from 50mg BIW to 25mg BIW (n = 194), by 45% after continuous treatment with ETA 25mg BIW (n = 196), and by 28% of patients in group that began receiving ETA 25mg BIW after initial 12 weeks of placebo (n = 193). • Of the 91 patients who were PASI 75 responders at week 12, 77% maintained the PASI 75 response at 24 weeks, and only 3 did not maintain a PASI 50 response. • Treatment with ETA rapidly improved health-related QoL. • At week 12, improvement in DLQI total score was 65-70% in patients receiving ETA vs. 6% in those receiving placebo (P < 0.0001). • At 12 weeks, 72-77% of patients on ETA had achieved a clinically meaningful DLQI response vs. 26% of those on placebo (P < 0.0001). During open label, response was maintained. • At 12 weeks, 81-86% of patients on ETA improved by at least 1 DLQI band vs. 36% in placebo group (P < 0.0001). • The DLQI subscales showing greatest magnitude of improvement = symptoms and feelings subscale (placebo 6%, ETA 60-62%; P < 0.0001), and daily activities subscale (placebo 1%, ETA 56-62%; P < 0.0001). • Significantly greater improvement in the SF-36 physical and mental component summary scores at week 12 for ETA vs. placebo (mean PCS: placebo, 49.6; ETA, 52.7-52.8, *P* <0.01; mean MCS: placebo, 46.5; ETA, 50.6-51.1, *P* ,0.01) • **Intermediate Outcome Measures:** • Most lab abnormalities observed throughout the study were mild to moderate. • Anti-ETA antibodies were observed in 6 patients during the initial 12 weeks and an additional nine patients by week 24.

Authors: Papp et al. **Year: 2005**			
ADVERSE EVENTS (at week 12): **Overall adverse effects reported:**	**Placebo**	**ETA 25**	**ETA 50**
• ISR	11	26	35
• Upper respiratory infection	25	26	25
• Headache	15	23	21
• Injection site ecchymosis	22	24	15
• Accidental injury	12	8	13
• Flu syndrome	3	9	8
Significant differences in adverse events:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 11.9% (by week 24) **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*):	**Placebo**	**ETA 25**	**ETA 50**
Loss to follow-up:	NR	NR	NR
Withdrawals due to adverse events:	NR	NR	NR
QUALITY RATING:	**Fair**		

*primary outcome measures

Evidence Table 7 ***Targeted Immune Modulators-Plaque Psoriasis***

STUDY:	**Authors: Reich et al.**[130, 133] **Year: 2005 and 2006** **Country:** NR		
FUNDING:	Centocor and Schering-Plough		
RESEARCH OBJECTIVE:	To present the results of a phase III study, addressing the long-term safety and efficacy 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="4">Authors: Reich et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">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><td></td></tr>
<tr><td>Mean age (years):</td><td>43.8</td><td>42.6</td><td></td></tr>
<tr><td>Sex (% female):</td><td>21</td><td>31</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>• Psoriasis duration (yrs)</td><td>17.3</td><td>19.1</td><td></td></tr>
<tr><td>• Body surface area (%)</td><td>18</td><td>19</td><td></td></tr>
<tr><td>• PASI</td><td>22.8</td><td>22.9</td><td></td></tr>
<tr><td>• Patients with nail psoriasis (%)</td><td>86</td><td>81</td><td></td></tr>
<tr><td>• MTX use (%)</td><td>46</td><td>42</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: PASI 75 (≥ 75% improvement in baseline PASI) at week 10 and Quality of life DLQI and 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="3">Health Outcome Measures:
• At week 10, PASI 75 achieved by 80% (INF) vs. 3% (placebo) (P < 0.0001)
• At week 10, PASI 75 achieved by 57% (INF) vs. 1% (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)
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**			
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**		

*primary outcome measures

Evidence Table 7 ***Targeted Immune Modulators-Plaque Psoriasis***

STUDY:	**Authors: Tyring et al.**[124] **Year: 2006** **Country:** US & Canada		
FUNDING:	Presumed Immunex & Amgen		
RESEARCH OBJECTIVE:	To assess the effect of etanercept on fatigue and symptoms of depression in patients with psoriasis.		
DESIGN:	**Study design:** RCT, placebo-controlled, double-blind **Setting:** Multicenter **Sample size:** 618		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 12 weeks 309	**ETA** 50 mg twice weekly 12 weeks 311	
INCLUSION CRITERIA:	Age ≥ 18 years; Active, clinically stable plaque psoriasis involving ≥ 10% total body surface area; Minimum PASI score of 10; Receipt of ≥ 1 previous phototherapy or systemic therapy (or candidate for such treatment); Adequate renal, hepatic, and hematological function.		
EXCLUSION CRITERIA:	History of psychiatric disease that would interfere with study; Skin conditions other than psoriasis; Active guttate, erythrodermic, or pustular psoriasis; Receipt of systemic psoriasis therapy or psoralen ultraviolet(UV) A phototherapy within last 4 weeks; Topical corticosteroids, vitamin A or D analogue preparations, dithanol, or UVB phototherapy within last 2 weeks; Receipt of ETA or anti-TNFalpha antibody at any time.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Topical corticosteroids of no more than moderate strength on the scalp, axilla, and groin.		

Authors: Tyring et al. **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR		
	Placebo	**ETA**	
Mean age (years):	45.6	45.8	
Sex (% female):	30	35	
Ethnicity (% White):	88	90	
Other germane population qualities:			
• Mean disease duration (yrs.)	19.7	20.1	
• Mean PASI score	18.1	18.3	
• Mean DLQI total score	12.5	12.1	
• Mean HAM-D score	4.5	4.5	
• Mean BDI score	8.4	8.1	
• Mean FACIT-F score	38.1	37.5	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PASI 75 (a ≥ 75% improvement from baseline PASI) at week 12. **Secondary Outcome Measures:** DLQI; joint pain; skin pain; and the functional assessment of chronic illness therapy fatigue (FACIT-F) scale. all at week 12. Other endpoints were PASI 50, PASI 90, Hamilton rating scale for depression (HAM-D), and Beck Depression Inventory (BDI). **Timing of assessments:** Baseline (day 1), and weeks 1,2,4,8, & 12.		
RESULTS:	**Health Outcome Measures:** • At week 12, PASI 75 achieved by 47% of ETA-treated vs. 5% of placebo group ($P < 0.0001$; difference 42%, 95% CI 36-48). • Week 12 PASI 50 = 74% (ETA) vs. 14% (placebo) (difference 60%, 95% CI 53-66) • Week 12 PASI 90 = 21% (ETA) vs. 1% (placebo) ($P < 0.0001$; difference 20%, 95% CI 15-24) • At week 4, BDI response rates were 45% (ETA) vs. 36% (placebo) (P =0.0153). Rates were 55% & 39%, respectively at week 12. • At week 12, BDI difference between groups was 1.8 (95% CI 0.6-2.9), thus effect size = 0.22. • At week 12, HAM-D response rates were 43% (ETA) vs. 32% (placebo) (P =0.0048). • Mean improvement from baseline HAM-D was significantly greater in ETA group (1.5) vs. placebo (0.4) (P = 0.0012; difference 1.2, 95% CI 0.4-1.9), thus effect size = 0.25. • At week 12, mean improvement in FACIT-F was 5.0 (ETA) vs. 1.9 (placebo) ($P < 0.0001$; mean difference 2.0, 95% CI 1.6-4.5; effect size = 0.27)		

Authors: Tyring et al. **Year: 2006**			
ADVERSE EVENTS:	**Placebo**	**ETA**	
Overall adverse effects reported(%):	44.8	49.0	
• At least 1 infection	23.2	27.9	
• Nasopharyngitis	4.2	7.1	
• Upper respiratory	4.6	3.8	
• Sinusitis	1.3	3.5	
• Headache	5.9	6.4	
• Injection site bruising	4.2	6.4	
• Fatigue	1.3	4.2	
• Arthralgia	3.3	3.5	
• ≥ 1 ISR	0.7	10.9	
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 loss to follow-up:** 3.7% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Placebo**	**ETA**	
Loss to follow-up:	5%	3%	
Withdrawals due to adverse events:	3	4	
QUALITY RATING:	**Good**		

Evidence Table 8 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Askling et al.**[175] **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>

Authors: Askling et al. **Year: 2005**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	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:** NR **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Inpatient RA cohort** NR	**Early Arthritis RA cohort** NR	**TNF antagonist cohort** NR
QUALITY RATING:	**N/A**		

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Baeten et al.**[160] **Year: 2003** **Country:** Belgium
FUNDING:	NR
RESEARCH OBJECTIVE:	To report systematically the adverse events in a large cohort of patients with spondyloarthropathy treated with infliximab, with special attention to bacterial infections
DESIGN:	**Study design:** Case series based on 3 trials **Setting:** NR **Sample size:** 107
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 5 mg/kg 191.5 patients years 107
INCLUSION CRITERIA:	Patients had to fulfill the European Spondylarthropathy Study Group criteria for SpA; patients were at least 18 years old; for patients of childbearing potential, a negative pregnancy test result and adequate contraception during the study period and for six months after the last infusion were both entry criteria; active SpA, defined as the presence of at least one swollen joint, one active tendinitis or dactylitis, and/or inflammatory spinal pain (typical "night pain").
EXCLUSION CRITERIA:	Serious infections (for example, hepatitis, pneumonia, pyelonephritis) in the previous three months; opportunistic infections within two months of screening; documented HIV infection; proven urogenital or gastrointestinal reactive arthritis; known malignancy, and current signs of severe, progressive, or uncontrolled concomitant disease in the opinion of the investigator; cardiopulmonary abnormalities were excluded by obtaining a chest radiography and electrocardiogram at screening; patients who had received an investigational drug within the previous three months, or any therapeutic agent targeted at reducing TNFα within the previous six months
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Cohort 1- NSAIDs; Corticosteroids. Cohort 2- Non NSAIDs; Corticosteroids. Cohort 3- NSAIDs; Corticosteroids; MTX; Prednisone.

Authors: Baeten et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR **Disease severity:** NR		
	Cohort 1	**Cohort 2**	**Cohort 3**
Mean age (years):	43	47	46
Sex (% female):	23	30	42
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• DMARD use (%)	3	0	50
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Adverse events (see AE section)		
RESULTS:	**Health Outcome Measures:** N/A		

Authors: Baeten et al. **Year:2003**			
ADVERSE EVENTS: **Overall adverse effects reported:** Treatment related and/or serious: • Infections • Severe infections • Minor infections • Reactivation of TB • Retropharyngeal abscesses • Spinocellular carcinoma of the skin • Palmoplantar pustulosis	**All cohorts (1-3)** 20 14 8 6 2 3 1 3		
Significant differences in adverse events:	Not applicable		
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:** NR **Loss to follow-up differential high: N/A**		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Cohort 1** 2 0	**Cohort 2** 2 1	**Cohort 3** NR NR
QUALITY RATING:	**N/A**		

Evidence table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Bergstrom et al.**[165] **Year: 2004** **Country:** US		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To assess if patients who were treated with TNFα antagonists have a higher risk of developing coccidioidomycosis		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** 5 practices **Sample size:** 985		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** Various 3 years 7	**Other** N/A 3 years 4	**Control** N/A 3 years 974
INCLUSION CRITERIA:	Patients with RA, reactive arthritis, PsA, JRA		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

Authors: Bergstrom et al. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Mild-moderate-severe		
	INF	**Other**	**Control**
Mean age (years):	64.8	64.0	57.8
Sex (% female):	71	75	77
Ethnicity (% white):	86	75	
Other germane population qualities:			NR
• TJC	NR	NR	NR
• SJC	NR	NR	NR
• Mean disease duration	NR	NR	NR
• DMARD use (%)	NR	NR	50
• MTX use (%)	100	50	NR
• Corticosteroids use (%)	NR	NR	NR
• DAS score	NR	NR	NR
• HAQ score	NR	NR	NR
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Development of coccidioidomycosis.		
RESULTS:	**Health Outcome Measures:** • 7 of the 247 patients receiving INF and 4 of the 738 patients receiving other therapies developed symptomatic coccidioidomycosis (RR 5.23, 95% CI 1.54-17.71; P < 0.01).		

Authors: Bergstrom 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:	Yes
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:	**N/A**

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Bongartz et al.**[159] **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: Brown et al.**[172] **Year: 2002** **Country:** US		
FUNDING:	Authors are from FDA and National Cancer Institute		
RESEARCH OBJECTIVE:	To investigate the occurrence of lymphoproliferative disorders in patients treated with etanercept and infliximab.		
DESIGN:	**Study design:** Case series **Setting:** N/A **Sample size:** 26		
INTERVENTION: **Dose:** **Cases:**	**ETA** Various 18	**INF** Various 8	
INCLUSION CRITERIA:	MedWatch reports submitted to the FDA for the biologic products ETA and INF. All reports citing neoplasms, benign or malignant, were reviewed. Any report with a keyword of lymphoma or that mentioned lymphoma in the text was investigated further. The cases reported to MedWatch through December 2000 comprise the basis for the current summary.		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A		

Authors: Brown et al. **Year: 2002**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** NR		
	ETA	**INF**	
Median age (years):	64	62	
Sex (% female):	61	33.5	
Ethnicity:	NR	NR	
Other germane population qualities:			
• RA indication (%)	83	37.5	
• PA indication (%)	11.1	0	
• Crohn's indication (%)	0	62.5	
• Not specified indication (%)	5.6	0	
• MTX use (%)	72.2	25	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Associated lymphomas with treatment		
RESULTS:	**Health Outcome Measures:** • ETA 19 cases per 100,000 treated persons • INF 6.6 cases per 100,000 treated persons • In general, diffuse large B cell lymphoma (non-Hodgkin's) were the most common form. (21 of the 26 were non-Hodgkin's lymphomas) • The treated person rates of lymphomas in ETA and INF users is probably an underestimate based on underreporting, according to the authors (Age adjusted rate of lymphomas in US from 1992-1998 18.3 per 100,000 people) • Median time to lymphoma diagnosis was 8 weeks (range 2-52 weeks) for ETA and 6 weeks (range 2-44 weeks) for INF		

Authors: Brown et al. **Year: 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**ETA** N/A	**INF** N/A	
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** No **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	**INF** N/A	
QUALITY RATING:	**N/A**		

Evidence Table 8 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Chakravarty et al.**[177] **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:**	N/A		
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="4">Authors: Chakravarty 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>Patients with RA</u></td><td><u>Patients with OA</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>62</td><td>67</td><td></td></tr>
<tr><td>Sex (% female):</td><td>77</td><td>83</td><td></td></tr>
<tr><td>Ethnicity (% white):</td><td>91</td><td>94</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• HAQ-DI score</td><td>1.09</td><td>1.07</td><td></td></tr>
<tr><td>• Skin cancer before NDB (%)</td><td>3.8</td><td>5.8</td><td></td></tr>
<tr><td>• History of smoking (%)</td><td>56</td><td>46</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">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="3">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		

*primary outcome measures

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Cheifetz et al.**[154] **Year: 2003** **Country:** US
FUNDING:	NR
RESEARCH OBJECTIVE:	To assess the incidence and management of infusion reactions to infliximab in patients with Crohn's Disease.
DESIGN:	**Study design:** Observational – Case series **Setting:** Single center (Mt. Sinai Medical Center) **Sample size:** 165
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 5 mg/kg IV infusion N/A 165
INCLUSION CRITERIA:	Patients with Crohn's disease treated with INF infusion at Mt. Sinai Medical Center between July 1 1998 and January 23, 2001.
EXCLUSION CRITERIA:	N/A
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes

Authors: Cheifetz et al. **Year: 2003**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** NR
	INF
Mean age (years):	NR
Sex (% female):	NR
Ethnicity:	NR
Mercaptopurine/Azathioprine/MTX use (%):	6/14
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Incidence of infusion reactions **Secondary Outcome Measures:** N/A **Timing of assessments:** N/A
RESULTS:	**Health Outcome Measures:** • Incidence of infusion reactions was 6.1% (29/479) affecting 9.7% (16/ 165) of patients. • Mild reactions occurred in 3.1% of patients, moderate reactions occurred in 1.2% of patients, and severe reactions occurred in 1% of patients. • Delayed infusion reactions occurred in 0.6% of patients.

Authors: Cheifetz et al. **Year: 2003**	
ADVERSE EVENTS: **Overall adverse effects reported:**	**INF** 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 ANALYSISADEQUATE:	No
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: Chung et al.**[182] **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		

Authors: Chung et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe		
	Placebo	**INF5**	**INF10**
Mean age (years):	60 ± 12	62 ± 15	62 ± 13
Sex (% female):	24	14	16
Ethnicity (% white):	88	88	84
Current or prior angina (%):	29	18	24
Myocardial infarction (%):	63	50	67
Diabetes mellitus (%):	41	28	37
NYHA Class III/IV (%):	96/4	96/4	92/8
LVEF (%):	0.25 ± 0.07	0.23 ± 0.07	0.24 ± 0.06
OUTCOME ASSESSMENT:	**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		
RESULTS:	**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		

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 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Colombel et al.**[147] **Year: 2004** **Country:** US	
FUNDING:	NR	
RESEARCH OBJECTIVE:	Short and long term safety of infliximab treated Crohn's disease patients in clinical practice	
DESIGN:	**Study design:** Case series **Setting:** Mayo Clinic **Sample size:** 500	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 5 mg/kg Median follow-up 17 months 500	
INCLUSION CRITERIA:	Patients with CD who were treated with INF at the Mayo Clinic in Rochester, Minnesota, between October 1998 and October 2002	
EXCLUSION CRITERIA:	None	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A	

Authors: Colombel et al. **Year: 2004**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild – severe
	INF
Median age (years):	37
Sex (% female):	56
Ethnicity:	NR
Other germane population qualities:	
• Previous surgery for CD (%)	NR
• Patients with fistulae (%)	24
• Mean baseline CDAI	N/A
• Mercaptopurine/Azathioprine use (%)	75
• Corticosteroids use (%)	31
• HAQ score	N/A
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Adverse events **Timing of assessments:** N/A
RESULTS:	**Health Outcome Measures:** • See adverse events

Authors: Colombel et al. **Year: 2004**			
ADVERSE EVENTS: **Overall serious adverse effects reported:** • Serious infections • Infusion reactions • Serum sickness-like disease • Drug induced lupus • Cancer • Non-Hodgkin's lymphoma • Hodgkin's lymphoma • Demyelination • Worsening of heart failure • Deaths of other origin • Infectious events • Acute infusion reactions	**INF** 43 (8.6%) 18 2 5 3 7 1 1 1 1 4 48 19		
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** No		
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:	**N/A**		

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: 2004**			
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: 2004**			
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**		

*primary outcome measures

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Fleischmann et al.,[144] Schiff et al.,[146] Tesser et al.[145]** **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 8 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Flendrie et al.**[188] **Year: 2005** **Country:** Netherlands
FUNDING:	NR
RESEARCH OBJECTIVE:	To investigate whether dermatological conditions after TNF-α-blocking therapy are a significant and clinically important problem in RA patients receiving TNF- α -blocking therapy.
DESIGN:	**Study design:** Prospective cohort study with historic control **Setting:** Hospital rheumatology clinic **Sample size:** 578 (911 patient years)
INTERVENTION: **Dose:** **Duration:** **Sample size:**	N/A
INCLUSION CRITERIA:	Control patients selected from Nijmegen inception cohort; Patients required to meet Dutch guidelines for biological therapies: a moderate to high DAS score (DAS28 $\geq$ 3.2), and failure or intolerability of at least 2 DMARDS, including MTX, in adequate dosage regimens.
EXCLUSION CRITERIA:	NR
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Besides therapy with registrated TNF-α-blocking agents – INF, ETA, and ADA – some patients were treated in clinical trials with lenercept.

Authors: Flendrie et al. **Year: 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **Disease severity:** NR		
	TNF-α	**Control**	
Mean age (years):	NR	NR	
Sex (% female):	69%	62%	
Ethnicity: % White			
Other germane population qualities:			
• Age at diagnosis	44.5 (14.7)	54.6 (14.1)	
• DAS score	5.9 (1.1)	3.6 (1.4)	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Dermatological events / visits **Secondary Outcome Measures:** **Timing of assessments:**		
RESULTS:	**Health Outcome Measures:** • Dermatological events recorded in 72/289 (25%) of RA patients receiving TNF-α-blocking therapy and in 37 (13%) of control group. • The OR of TNF-α-blocking therapy for dermatological referral was 2.26 (95% CI 1.46 to 3.50, $P < 0.0005$). • 128 dermatological events were recorded during follow-up in RA patients on TNF-α-blocking therapy (0.14 events per patient-year).		

Authors: Flendrie et al. **Year: 2005**			
ADVERSE EVENTS (%): **Overall adverse effects reported:**	NR See results section		
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:** NR **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**			
QUALITY RATING:	**Fair**		

*primary outcome measures

Evidence Table 8 ***Targeted Immune Modulators-Adverse Events***

STUDY:	**Authors: Geborek et al.**[174] **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="4">Authors: Geborek et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">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><td></td></tr>
<tr><td>Mean age (years):</td><td>56</td><td>64</td><td></td></tr>
<tr><td>Sex (% female):</td><td>76</td><td>73</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</td><td>12</td><td>11</td><td></td></tr>
<tr><td>• Previous DMARD use (#)</td><td>3</td><td>1</td><td></td></tr>
<tr><td>• HAQ quartile > 3</td><td>61</td><td>41</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">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="3">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 • Y	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**		

*primary outcome measures

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Gomez-Reino et al.**[167] **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: Jacobsson et al.**[178] **Year: 2005** **Country:** Sweden		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To investigate the risk of cardiovascular disease (CVD) in patients with RA treated with TNF inhibitors, compared to a standard RA population.		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Population-based (2 Swedish registers) **Sample size:** 983 (combined cohort)		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Anti-TNF exposed** N/A N/A 531	**Not Anti-TNF exposed** N/A N/A 452	
INCLUSION CRITERIA:	Case cohort, the South Swedish Arthritis Treatment Group (SSATG): patients with RA treated with anti-TNF agents & included in SSATG register between 2/1/99 and 12/31/01		
EXCLUSION CRITERIA:	Previous hospital discharge due to CVD		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Jacobbson et al. **Year: 2005**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **Disease severity:** Variable		
	Anti-TNF exposed	**Not Anti-TNF exposed**	
Median age (years):	55	61	
Sex (% female):	78	75	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Mean disease duration	12	11	
• Previous DMARD use, # of drugs	4	2	
• Current prednisolone use (%)	75%	22%	
• HAQ score	1.50	1.13	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** CVD events; age-adjusted mortality rate; age-adjusted mortality rate ratio **Secondary Outcome Measures:** NR **Timing of assessments:** Subjects followed at the occurrence of a CVD event until death, or the close of the study, whichever occurred first.		
RESULTS:	**Health Outcome Measures:** • Controlling for disability, the age-sex adjusted rate ratio was 0.46 (95% CI 0.25 – 0.85; P = 0.013) in anti-TNF treated vs. not treated. • In the anti-TNF group, there were 13 CVD events (in 656 person-years at risk); age-adjusted incidence rate = 14 events per 1000 patient-years. • In the unexposed comparison group, there were 85 CVD events (in 2056 person-years at risk); age-adjusted incidence rate = 35.4 events per 1000 patient years. • RR = 0.62 (95% CI, 0.34 to 1.12; P – 0.111). • The standardized mortality ratio (SMR) revealed a significantly increased risk of new onset CVD in those not treated with TNF blockers in relation to the background population of Malmo (SMR – 228, 95% CI 179 to 277).		

Authors: Jacobbson et al. **Year: 2005**			
ADVERSE EVENTS: **Overall adverse effects reported:** • death	**Anti-TNF exposed** NR 3	**Not Anti-TNF exposed** NR 29	
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ARE GROUPS COMPARABLE AT BASELINE:	No (greater disease severity for the anti-TNF cohort)		
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:**	NR		
QUALITY RATING:	**Good**		

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Keane et al.**[139] **Year: 2001** **Country:** Multinational		
FUNDING:	National Heart, Lung and Blood Institute; Massachusetts Thoracic Society; American Lung Association of Massachusetts		
RESEARCH OBJECTIVE:	To explore the relationship between infliximab and TB based on data from MedWatch		
DESIGN:	**Study design:** Retrospective database review **Setting:** N/A **Cases:** 70		
INTERVENTION: **Dose:** **Duration:** **Cases:**	**INF** all 1 to 52 weeks 70		
INCLUSION CRITERIA:	If during or after treatment with INF, patient received a diagnosis of TB on the basis of clinical, radiologic, and laboratory findings		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Keane et al. **Year: 2001**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe		
	TB patients		
Median age (years):	57 (18-83)		
Sex (% female):	64		
Ethnicity:	NR		
Other germane population qualities:			
• Crohn's disease	26		
• RA	67		
• JRA	3		
• AS	3		
• Behcet's disease	1		
• Extrapulmonary TB	56		
• Disseminated TB	24		
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Incidence rate of TB in patients receiving INF		
RESULTS:	**Health Outcome Measures:** • Estimated incidence for patients with RA who have been treated with INF during the previous is 24.4 cases per 100,000 per year (95% CI 0.6 to 34.0). • Background incidence in the US for patients with RA not exposed to TIM therapy: 6.2 cases per 100,000 per year • TB may develop soon after treatment with INF		

Authors: Keane et al. **Year: 2001**			
ADVERSE EVENTS: **Overall adverse effects reported:**	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:**	N/A		
QUALITY RATING:	**N/A**		

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Kwon et al**.[180] **Year: 2003** **Country:** US
FUNDING:	FDA
RESEARCH OBJECTIVE:	To describe adverse event reports of heart failure after TNF antagonist therapy.
DESIGN:	**Study design:** Database review **Setting:** Multicenter (FDA's MedWatch program) **Sample size:** 47
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA or INF** Any Long term therapy 47
INCLUSION CRITERIA:	Patients who reported heart failure as an adverse event while taking ETA or INF therapy in the US since licensure of the drugs until February 2002; new onset failure and exacerbation of preexisting heart failure included
EXCLUSION CRITERIA:	Heart failure reports temporally associated with other heart failure-inciting events (such as myocardial infarction) were excluded
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A

Authors: Kwon et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe		
	New Onset Heart Failure without risk factors	**New Onset Heart Failure with risk factors**	**Heart failure exacerbation**
Median age (years):	59	67	70
Sex (% female):	74%	42%	44%
Ethnicity:	NR	NR	NR
Any:			
• RA	15	14	9
• CD	3	3	0
• Psoriatic arthritis	0	1	0
• Juvenile RA	1	0	0
• Unknown	0	1	0
Therapy:			
• ETA	12	14	3
• INF	7	5	6
Concomitant therapy:			
• Corticosteroids use	8	10	5
• NSAIDs	3	5	1
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Number of patients with new heart failure; number of patients with heart failure exacerbation **Secondary Outcome Measures:** Number of patients under 50 years of age; number of patients under 50 with heart failure resolution of discontinuation of TNF antagonist therapy		
RESULTS:	**Health Outcome Measures:** • Thirty eight patients (81%) developed new-onset heart failure; while 9 (19%) experienced heart failure exacerbation of which: 19 patients had no documented risk factors. 10 patients were under age 50. • Of the patients under 50, after cessation of TNF antagonist therapy 3 patients experienced complete resolution of heart failure, 6 patients showed improvement, and 1 patient died		

Authors: Kwon et al. **Year: 2003**			
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:	Yes		
STATISTICAL ANALYSISADEQUATE:	No		
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: Langer and Missler-Karger**[151] **Year: 2003** **Country:** Germany		
FUNDING:	Amgen, Munich		
RESEARCH OBJECTIVE:	Efficacy and safety of anakinra in patients with RA		
DESIGN:	**Study design:** Case series **Setting:** Clinical practice **Sample size:** Efficacy 166, Safety 454		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Efficacy** NR 52 weeks 166	**Safety** NR NR 454	
INCLUSION CRITERIA:	None defined but patients required to have failed 2 DMARDs previously including MTX		
EXCLUSION CRITERIA:	None defined		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Langer and Missler-Karger **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **Disease severity:** Moderate-severe		
	All (n=166)	**TNF-naïve (n=105)**	**TNF-use (n=61)**
Mean age (years):	53.7	54.7	51.9
Sex (% female):	78.9	78.1	80.3
Ethnicity:	NR	NR	NR
Other germane population qualities:			
• TJC	12.8	12.4	13.4
• SJC	10.5	10.4	10.8
• Mean disease duration	12.3	12.0	12.8
• Previous DMARD use (#)	3.6	3.0	4.4
• MTX use (%)	66.3	72.4	55.7
• Corticosteroids use (%)	84.9	81.9	90.1
• DAS score	5.8	5.6	6.1
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** DAS **Secondary Outcome Measures:** CRP; EULAR response **Timing of assessments:** baseline, follow-up visits after 1, 3, 6, 9, and 12 months		
RESULTS:	**Health Outcome Measures:** • Adverse events rates were similar to those reported in efficacy trials. • Reports that the incidence of adverse event do not increase over time • 41.2 percent experienced adverse events • Injection-site reaction was the most commonly reported adverse event (20.7%) • 7.1% withdrew because of adverse events		

Authors: Langer and Missler-Karger **Year: 2003**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • ISRs • SAEs • Skin reactions • Headache	**AKA (n=166)** 41.2 20.7 4.2 11.2 2.0		
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** No **Post randomization exclusions:** NR		
ARE GROUPS COMPARABLE AT BASELINE:	**No**		
ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:	No		
STATISTICAL ANALYIS ADEQUATE:	No		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:**	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR **AKA** NR 32/454 (7.1%)		
QUALITY RATING:	N/A		

*primary outcome measures

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Lebwohl et al**.[176] **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="4">Authors: Lebwohl et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: NR (probably at least moderate disease)</td></tr>
<tr><td></td><td><u>ETA</u></td><td></td><td></td></tr>
<tr><td>Mean age (years):</td><td>49.9</td><td></td><td></td></tr>
<tr><td>Sex (% female):</td><td>76.5</td><td></td><td></td></tr>
<tr><td>Ethnicity (% white):</td><td>87.4</td><td></td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Duration of disease, mean yrs</td><td>7.1</td><td></td><td></td></tr>
<tr><td>• Prior # DMARDs used</td><td>2.1</td><td></td><td></td></tr>
<tr><td>• Duration ETA exposure</td><td></td><td></td><td></td></tr>
<tr><td>o Mean</td><td>3.7</td><td></td><td></td></tr>
<tr><td>o Maximum</td><td>5.7</td><td></td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures:
Incidence of SCC for patients receiving ETA for up to 5 years</td></tr>
<tr><td>RESULTS:</td><td colspan="3">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: Lee et al**.[141] **Year: 2002** **Country:** US (All patients from the Ohio and Mississippi River valleys.)		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To identify post-licensure cases of opportunistic histoplasmosis in patients treated with infliximab and etanercept.		
DESIGN:	**Study design:** Database analysis **Setting:** Clinics **Sample size:** 10		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** any any 9	**INF** any any 1	
INCLUSION CRITERIA:	Any report of histoplasmosis in a patient receiving ETA or INF that had been received by the Adverse Event Reporting System (AERS) by July 2001.		
EXCLUSION CRITERIA:	None		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Lee et al.
Year: 2002</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: NR</td></tr>
<tr><td></td><td><u>ETA</u></td><td><u>INF</u></td><td></td></tr>
<tr><td>Age range (years):</td><td>11-78</td><td>38</td><td></td></tr>
<tr><td>Sex (% female):</td><td>4/9</td><td>0/1</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>N/A</td><td>N/A</td><td></td></tr>
<tr><td>• % concomitant immunosuppressive</td><td>100%</td><td>100%</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures:
• Number of cases
Secondary Outcome Measures:
• Case rates/100,000 patients receiving the individual drug</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Cases of histoplasmosis reported to the AERS by July 2001
o Nine cases among patients receiving INF
o One case among patients receiving ETA
• Through August 2001, number of patients treated
o With INF: ~150,000
o With ETA: ~96,500
• Histoplasmosis case rates per 100,000 patients receiving drug
o INF: ~6/100,000
o ETA: ~1/100,000
• Deaths due to histoplasmosis
o INF: 1/10
o ETA 0/1
Summary: More cases of histoplasmosis were reported to the AERS by July 2001 among patients receiving INF than for those receiving ETA. When accounting for the actual number of patients taking each of the drugs, the histoplasmosis case rate was ~6 times higher among patients receiving INF than among those receiving ETA.</td></tr>
</table>

Authors: Lee et al. **Year: 2002**	
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	**N/A**
Significant differences in adverse events:	N/A
ANALYSIS:	**None**
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:	**N/A**

Evidence Table 8 ***Targeted Immune Modulators-Adverse Events***

STUDY:	**Authors: Lichtenstein et al.**[190] **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 $\geq$ 18 (although not a criterion when enrollment began).		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Lichtenstein et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">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><td></td></tr>
<tr><td>Mean age (years):</td><td>40.3</td><td>44.7</td><td></td></tr>
<tr><td>Sex (% female):</td><td>57.9</td><td>57.1</td><td></td></tr>
<tr><td>Ethnicity (% white):</td><td>88.8</td><td>89.3</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Surgical admissions (No.)</td><td>17.5</td><td>13.8</td><td></td></tr>
<tr><td>• Medical admissions (No.)</td><td>14.4</td><td>9.1</td><td></td></tr>
<tr><td>• Disease severity mild-to-moderate (%)</td><td>50.1</td><td>47.9</td><td></td></tr>
<tr><td>• Prednisone use (%)</td><td>27.4</td><td>16.1</td><td></td></tr>
<tr><td>• Immunomodulator use (%)</td><td>49.4</td><td>32.2</td><td></td></tr>
<tr><td>• Narcotic analgesics use (%)</td><td>9.8</td><td>5.4</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">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="3">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**		

*primary outcome measures

Evidence Table 8 ***Targeted Immune Modulators—Adverse Events***

STUDY:	**Authors: Listing et al.**[164] **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**		

*primary outcome measures

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Ljung et al**.[96] **Year: 2004** **Country:** Sweden
FUNDING:	NR
RESEARCH OBJECTIVE:	To assess the use of infliximab in inflammatory bowel disease (IBD) in a population based cohort, with special emphasis on the occurrence of severe adverse events and mortality.
DESIGN:	**Study design:** Observational – case series **Setting:** Multicenter (11 medical centers) **Sample size:** 217
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 5 mg/kg 2 hour IV infusion N/A 217
INCLUSION CRITERIA:	All patients with IBD including Crohn's disease, ulcerative colitis, and indeterminate colitis treated with INF in Stockholm, Sweden between Jan 1999 and Apr 2001.
EXCLUSION CRITERIA:	N/A
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes

Authors: Ljung et al. **Year: 2004**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** NR
	INF
Mean age (years):	37.6
Sex (% female):	48%
Ethnicity:	NR
Other germane population qualities:	
• Crohn's disease	191 (88%)
• Ulcerative Colitis	22 (10%)
• Indeterminate Colitis	4 (2%)
• Mean # of infusions (range)	2.6 (1-11)
• Mercaptopurine/Azathioprine use (%)	54%
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Number of severe adverse events; number of mortalities **Secondary Outcome Measures:** Response rate **Timing of assessments:** N/A
RESULTS:	**Health Outcome Measures:** • 42 severe adverse events occurred in 41 patients (19%). • Six fatal adverse events occurred (3%). • The response rate was 75% in all forms of IBD • Remission in 48% • Failure to respond in 25%

Authors: Ljung et al. **Year: 2004**			
ADVERSE EVENTS: **Overall adverse effects reported (severe):** • Lymphoma • Infection • Postoperative infection • Thromboembolitic event • Hypersensitivity • Anaphylactic reaction • Urticaria • Miscellaneous	**INF** 42 events in 18.9% of patients 3 (1.4%) 11 (5.1%) 7 (3.2%) 5 (2.3%) 5 (2.3%) 3 (1.4%) 5 (2.3%) 3 (1.4%)		
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 ANALYSIS ADEQUATE:	No		
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 2 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Lovell et al.**[73, 142, 170] **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: Maini et al**.[68, 69] **Year: 2004** **Country:** Multinational				
FUNDING:	Centocor				
RESEARCH OBJECTIVE:	Efficacy and safety of repeated administration of infliximab plus methotrexate over a 2-year period in patients with RA who previously experienced an incomplete response to methotrexate.				
DESIGN:	**Study design:** Open label extension of ATTRACT (Maini 1999) **Setting:** 34 sites **Sample size: 259 (428)**				
INTERVENTION:	**Placebo + MTX**	**Infli3/8 + MTX**	**Infli3/4 + MTX**	**Infli10/8 + MTX**	**Infli10/4 + MTX**
Dose:	N/A+15 mg/wk	3 mg/kg every 8 wks+15mg/wk	3 mg/kg every 4 wks+15mg/wk	10 mg/kg every 8 wks+15mg/wk	3 mg/kg every 4 wks+15mg/wk
Duration (RCT+ follow-up):	2 years	2 years	2 years	2 years	2 years
Sample size (follow-up through 2 years):	88(51)	86(63)	86(75)	87(72)	81(70)

Authors: Maini et al. **Year: 1999 and 2004**	
INCLUSION CRITERIA:	RA according to the 1987 ACR criteria and had evidence of active disease despite treatment with MTX; oral or parenteral MTX for at least 3 months with no break in treatment of more than 2 weeks during this period, the MTX dose must have been stable at 12·5 mg/week or more, for at least 4 weeks before screening and the patient must have been on a stable dose of folic acid for the same period; haemoglobin 5·3 mmol/L or more; white blood cells 3·5X10/L or more; neutrophils 1·5X10/L; platelets 100X10/L or more; serum aminotransferase and alkaline phosphatase concentration 2 times or less the upper limit of normal; and serum creatinine 150 μmol/L or less.
EXCLUSION CRITERIA:	Little or no ability for self-care; condition with signs and symptoms that might confound the diagnosis (eg, connective tissue disease or Lyme disease); used a DMARD other than MTX or received intraarticular, intramuscular, or intravenous corticosteroids in the 4 weeks before screening; any other agent to reduce TNF or had any previous use of cyclophosphamide, nitrogen mustard, chlorambucil, or other alkylating agents; or a history of known allergies to murine proteins; infected joint prosthesis during the previous 5 years; serious infections, such as hepatitis, pneumonia, pyelonephritis in the previous 3 months; any chronic infectious disease such as renal infection, chest infection with bronchiectasis or sinusitis; active TB requiring treatment within the previous 3 years; opportunistic infections such as herpes zoster within the previous 2 months; any evidence of active cytomegalovirus; active *Pneumocystis carinii*; or drug-resistant atypical mycobacterial infection; current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease; a history of lymphoproliferative disease including lymphoma or signs suggestive of disease, such as lymphadenopathy of unusual size or location (ie, lymph nodes in the posterior triangle of the neck, infraclavicular epitrochlear, or periaortic areas); splenomegaly; any known malignant disease except basal cell carcinoma currently or in the past 5 years.
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Oral corticosteroids (10 mg/kg or less prednisone equivalent) or NSAIDs must have been on a stable dose for at least 4 weeks before screening

Authors: Maini et al.
Year: 1999 and 2004

POPULATION CHARACTERISTICS: ***From 1999, not presented in Maini 2004 for treatment groups.***

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

	Placebo + MTX	Infli3/8 + MTX	Infli3/4 + MTX	Infli10/8 + MTX	Infli10/4 + MTX
Median age (years):	51	56	51	55	52
Sex (% female):	80	81	77	77	59
Ethnicity (% white):	89	93	88	91	76
Other germane population qualities:					
• TJC	N/A	N/A	N/A	N/A	N/A
• SJC	N/A	N/A	N/A	N/A	N/A
• DMARD use (%)	0	0	0	0	0
• MTX use (%)	100	100	100	100	100
• Corticosteroids use (%)	64	63	53	57	65
• NSAID use (%)	72	79	76	77	68
• DAS score	N/A	N/A	N/A	N/A	N/A
• HAQ score	N/A	N/A	N/A	N/A	N/A

OUTCOME ASSESSMENT:

Primary Outcome Measures: ACR 20/50/70, SHS

Secondary Outcome Measures: HAQ, SF-36

Timing of assessments: 102 weeks and 52 weeks for SHS

RESULTS:

Health Outcome Measures:

- INF treated patients maintained their improvements in ACR50, HAQ, and SF-36 throughout week 102

Intermediate Outcome Measures:

- Radiographic disease progression at week 102 was significantly lower in the INF group than in the placebo group ($P < 0.001$)
- SHS

Authors: Maini et al. **Year: 1999 and 2004**					
ADVERSE EVENTS: at 30 weeks **Overall adverse effects reported:** **More than 80% in all**	**Placebo** NR	**INF 3/8 + MTX** NR	**INF 3/4 + MTX** NR	**INF 10/8 + MTX** NR	**INF 10/4 + MTX** NR
• URTI	14 (16%)	29 (33%)	17 (20%)	21 (24%)	18 (23%)
• Headache	9 (10%)	22 (25%)	17 (20%)	21 (24%)	16 (20%)
• Sinusitis	4 (5%)	10 (11%)	6 (7%)	12 (14%)	14 (18%)
• Rash	4 (5%)	5 (6%)	7 (8%)	14 (16%)	12 (15%)
• Coughing	3 (3%)	8 (9%)	6 (7%)	11 (13%)	11 (14%)
• Back pain	2 (2%)	7 (8%)	7 (8%)	6 (7%)	7 (9%)
• Abdominal pain	7 (8%)	4 (4%)	8 (9%)	7 (8%)	8 (10%)
• Pain	4 (5%)	4 (4%)	3 (3%)	7 (8%)	6 (8%)
• UTI	3 (3%)	3 (3%)	2 (2%)	6 (7%)	9 (11%)
• Fever	4 (5%)	4 (4%)	7 (8%)	3 (3%)	7 (9%)
• Any infection	34 (40%)	47 (53%)	40 (47%)	56 (64%)	58 (73%)
• Infection requiring antimicrobials	18 (21%)	20 (23%)	24 (28%)	32 (37%)	30 (38%)
• Serious infections	5 (6%)	1 (1%)	5 (6%)	5 (6%)	3 (4%)
• Serious adverse events	14 (16%)	8 (9%)	11 (13%)	8 (9%)	10 (13%)
ADVERSE EVENTS: at 2 years					
• No. (%) of patients with serious AEs	28 (33)	29 (33)	20 (23)	25 (29)	26 (32)
• No. (%) of patients with serious infections	11 (13)	10 (11)	11 (13)	11 (13)	8 (10)
• No. (%) of patients with serious infusion reactions	0	0	1 (1)	0	0
• No. (%) of patient deaths	4 (5)	3 (3)	2 (2)	1 (1)	1 (1)
• No. (%) of patients with malignancies	1 (1)	1 (1)	0	3 (3)	5 (6)
Significant differences in adverse events:	Serious adverse events were reported by similar proportions of patients who received MTX only and INF plus MTX.				

Authors: Maini et al. **Year: 1999 and 2004**					
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No				
ADEQUATE RANDOMIZATION:	NR				
ADEQUATE ALLOCATION CONCEALMENT:	Yes				
BLINDING OF OUTCOME ASSESSORS:	NR				
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** Yes				
ATTRITION (*treatment specific*):	**Placebo + MTX**	**INF 3/8 + MTX**	**INF 3/4 + MTX**	**INF 10/8 + MTX**	**INF 10/4 + MTX**
Loss to follow-up:	42%	27%	13%	28%	30%
Withdrawals due to adverse events:	NR	NR	NR	NR	NR
QUALITY RATING:	**Fair**				

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Mohan et al**.[183] **Year: 2001** **Country:** US		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To review the occurrence of neurologic events suggestive of demylenation during anti TNF alpha therapy for inflammatory arthritides		
DESIGN:	**Study design:** Database analysis MedWatch **Setting:** N/A **Cases:** 19		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA** NR 4 months NR	**INF** NR 4 months NR	
INCLUSION CRITERIA:	Patients with refractory RA who developed confusion and difficulty walking		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	MTX, prednisone, amlodipine, estradiol, zolpidem, dexamethasone, a;prasolam, hydrocodone, naproxen sodium, acyclovir, metronidazole, ceftriaxone, ranitidine, atenolol, fluoxetine, piroxicam		

Authors: Mohan et al **Year: 2001**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR **Disease severity:** NR		
	ETA	**INF**	
Mean age (years):	NR	NR	
Sex (% female):	NR	NR	
Ethnicity:	NR	NR	
Other germane population qualities:			
• TJC	NR	NR	
• SJC	NR	NR	
• DMARD use (%)	NR	NR	
• MTX use (%)	NR	NR	
• Corticosteroids use (%)	NR	NR	
• DAS score	NR	NR	
• HAQ score	NR	NR	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** N/A **Secondary Outcome Measures:** N/A **Timing of assessments:** patients were identified from FDA database after ETA and INF therapy		
RESULTS:	**Health Outcome Measures:** • 17 cases of demyelination after ETA and 2 cases after INF treatment were detected in MedWatch, with patial to complete resolution upon discontinuation.		

Authors: Mohan et al **Year: 2001**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Fever • Confusion • Gait disturbance • Parasthesias • Optic neuritis • Bladder problems • Visual	**ETA/INF** 1 2 4 8 4 2 4		
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:**	N/A N/A		
QUALITY RATING:	**N/A**		

Evidence Table 8 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Mohan et al.**[162] **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		

<table>
<tr><td colspan="4">Authors: Mohan et al.
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: N/A</td></tr>
<tr><td></td><td><u>Patients with TB (n=25)</u></td><td></td><td></td></tr>
<tr><td>Mean age at diagnosis (years):</td><td>59</td><td></td><td></td></tr>
<tr><td>Sex (% female):</td><td>72</td><td></td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td></td><td></td></tr>
<tr><td>Other germane population qualities:</td><td>NR</td><td></td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: NR

Secondary Outcome Measures: NR

Timing of assessments: NR</td></tr>
<tr><td>RESULTS:</td><td colspan="3">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</td></tr>
</table>

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**		

*primary outcome measures

Evidence Table 8 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Nuki et al**.[152] **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: Salliot et al.**[161] **Year: 2006** **Country:** France		
FUNDING:	NR but authors report no conflict of interest		
RESEARCH OBJECTIVE:	To evaluate the rate of infections in rheumatic patients treated with TNF-alpha blockers in daily practice and to determine potential risk factors of infections.		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Tertiary care **Sample size:** 709 w/ follow-up and 623 w/ follow-up and before		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** NR NR 276	**ETA** NR NR 455	**ADA** NR NR 182
INCLUSION CRITERIA:	Patients receiving a TNF-alpha blocker and with a follow-up and also those with a control period before treatment initiation		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A		

Authors: Salliot et al. **Year: 2006**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe		
	Follow-up (n=709)	**Follow-up and control (n=623)**	
Mean age (years):	45.9	46.5	
Sex (% female):	60.4	60.4	
Ethnicity:	NR	NR	
Other germane population qualities:			
• RA (%)	57.7	58.2	
• Spondylarthopathies (%)	37.2	37.1	
• Other conditions (%)	5.1	4.6	
• Mean disease duration	11.8	12.1	
• Previous DMARDs used (#)	3.0	3.1	
• MTX use (%)	43.7	43.6	
• Corticosteroids use (%)	58.5	58.3	
• Follow-up (years)	1.7	1.7	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Infections, any and serious		
RESULTS:	**Health Outcome Measures:** • 34.5% experienced an infection during the course of treatment; Incidence rate: 48.2 per 100 patient-yrs • 6.2 percent experienced a serious infection; incidence rate : 10.4 per 100 patient-yrs • The rates of serious infections in daily practice were higher than ones reported in efficacy trials • Infections by treatment: Any: INF 69.8, ETA 44.1, ADA 37.3 per 100 patient-yrs Serious: INF 10.2, ETA 12.3 and ADA 5.3 per 100 patient-yrs		

Authors: Salliot et al. **Year: 2006**			
ADVERSE EVENTS: **Overall adverse effects reported:** • infections • Y	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 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: Schaible**[148] **Year: 2000** **Country:** NR		
FUNDING:	NR but author is employee of Centocor		
RESEARCH OBJECTIVE:	Long term safety of infliximab		
DESIGN:	**Study design:** Retrospective analysis of clinical trials data **Setting:** NR **Sample size:** 913		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** Various 12 weeks-3 years 771	**Control** N/A 12 weeks-3 years 192	
INCLUSION CRITERIA:	Patients with CD or RA		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concurrent immunomodulatory therapy		

<table>
<tr><td colspan="4">Authors: Schaible
Year: 2000</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>INF</u></td><td><u>Control</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Sex (% female):</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Long term safety</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
N/A</td></tr>
</table>

Authors: Schaible **Year: 2000**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Infections • Pneumonia • Cellulites • Sepsis • Skin ulceration • UTI • Abscess • New malignancies • Recurrent malignancies	**INF** NR 26% 1.2% 0.5% 0.5% 0.1% 0% 0.1% 0.6% 0.25%	**Control** NR 16% 0.5% 0% 1.0% 0.5% 1.0% 0.5% NR NR	
Significant differences in adverse events:	Incidence of infections is significantly higher for INF than for placebo-treated patients (26% vs. 16%; *P* = 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*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:**	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A NR		
QUALITY RATING:	**N/A**		

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Schiff et al.,[146] Tesser et al.,[145] and Fleischmann et al.,[144]** **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: Schiff et al., Tesser et al., and Fleischman 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: Schiff et al., Tesser et al., and Fleischman 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: Schiff et al., Tesser et al., and Fleischman 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 8 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Schiff et al.**[150] **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="4">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 colspan="3">Groups similar at baseline: N/A
Disease severity: Mild-moderate-severe</td></tr>
<tr><td>NR</td><td></td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Serious adverse events including TB, and malignacies</td></tr>
<tr><td>RESULTS:</td><td colspan="3">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 • Y	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**		

*primary outcome measures

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Slifman et al.**[137] **Year: 2003** **Country:** Multinational
FUNDING:	NR
RESEARCH OBJECTIVE:	To evaluate postlicensure cases of opportunistic infection, including *Listeria monocytogenes*, in patients treated with TNFs
DESIGN:	**Study design:** Database analysis (MedWatch)/ case series **Setting:** Multicenter **Sample size:** 15
INTERVENTION: **Dose:** **Duration:** **Sample size:**	INF or ETA Various Varied 15 cases
INCLUSION CRITERIA:	Patients with Listeria monocytogenes that were treated with Eta or Inf for RA or Crohn's disease
EXCLUSION CRITERIA:	N/A
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concurrent use of immunosuppressant drugs

Authors: Slifman et al. **Year: 2003**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** N/A
	INF or ETA
Median age (years):	69.5
Sex (% female):	53
Ethnicity:	NR
Other germane population qualities:	
• INF (%)	93.3
• ETA (%)	6.7
• Median # of doses	2.5
• RA (%)	64
• Crohn's disease (%)	36
• MTX use (%)	47
• Death (%)	40
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** All adverse event reports of listeriosis or *Listeria* infection associated with the use of inf or eta that were entered into AERS from 1998 (the time of initial licensure of inf) through December 2001. Cases were included only if there was a culture that was reported positive for *L monocytogenes*. **Timing of assessments:** N/A
RESULTS:	**Health Outcome Measures:** • For all ages and indications, the estimated rate of cases (reporting rates) of listeriosis reported to the FDA within the first year of starting treatment with inf was ~43 cases per 1,000,000 persons (8/186,500). • RA patients treated with inf (US cases only), the estimated rate of cases of listeriosis reported to the FDA was ~61 cases per 1,000,000 persons (5/82,000). • In 2000, the annual incidence of listeriosis in the US for all ages was estimated to be 3 cases per 1,000,000. • Patients on INF had a higher rate of infection than patients on ETA

Authors: Slifman et al. **Year: 2003**	
ADVERSE EVENTS: **Overall adverse effects reported:** •	<u>INF or ETA</u> N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** No **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:**	<u>INF or ETA</u> N/A N/A
QUALITY RATING:	**N/A**

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Tesser et al.,[145] Schiff et al.,[146] and Fleischmann et al.,[144]** **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: Tesser et al., Schiff et al., and Fleischmann 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: Tesser et al., Schiff et al., and Fleischmann 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: Tesser et al., Schiff et al., and Fleischmann 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 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Vermeire et al.**[186] **Year: 2003** **Country:** Belgium
FUNDING:	NR
RESEARCH OBJECTIVE:	The investigation of antinuclear antibodies in Crohn's disease patients.
DESIGN:	**Study design:** Case series **Setting:** University hospital **Sample size:** 125
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 5 mg/kg 12 months 125
INCLUSION CRITERIA:	Presence of single or multiple perianal or other enterocutaneous draining fistula(e) resistant to treatment with antibiotics or immunosuppressives for at least 3 months; moderately to severely active Crohn's disease of at least 6 months' duration, with colitis, ileitis, or ileocolitis, confirmed by radiography or endoscopy, and refractory to or dependent on oral corticosteroid therapy (>8 mg/day prednisone equivalent); dependent on corticosteroids had failed all attempts to wean steroids completely; luminal disease and refractory or intolerant to MTX, azathioprine, 6-mercaptopurine, or cyclosporine.
EXCLUSION CRITERIA:	NR
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR

Authors: Vermeire et al. **Year: 2003**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Moderate-severe
	INF
Median age (years):	34
Sex (% female):	65.6
Ethnicity:	NR
Other germane population qualities:	
• Mean disease duration	NR
• DMARD use (%)	NR
• MTX use (%)	NR
• Corticosteroids use (%)	42.4
• DAS score	NR
• HAQ score	NR
• Median CDAI	257
• Immunosuppressive use (%)	44
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Detection of antinuclear antibodies **Timing of assessments:** Baseline, 4, 8 and 12 weeks for refractory luminal and baseline, 2,6,10,14 weeks for those with fistulizing disease and all at 6 and 12 months
RESULTS:	**Health Outcome Measures:** • N/A **Intermediate Outcome Measures:** • The cumulative ANA prevalence was 71 in 125 (56.8%) after a maximal follow-up of 24 months, almost half developed after 1st infusion and almost 80% after fewer than 3 infusions • Associated with the presence of ANA was being of female sex and the presence of skin manifestations • 2 patients (1.6%) developed lupus-like syndromes

Authors: Vermeire et al. **Year:2003**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Lupus-like syndrome • Autoimmune hemolytic anemia • Papulosquamous rash	**INF** NR 2(1.6%) 1(0.8%) 14 (11.2%)		
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 ANALYSISADEQUATE:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** None **Loss to follow-up differential high:** N/A		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**INF** NR NR		
QUALITY RATING:	**N/A**		

Adverse Events ***Targeted Immune Modulators***

STUDY:	**Authors: Wallis et al.**[138] **Year: 2004** **Country:** Multinational	
FUNDING:	Amgen	
RESEARCH OBJECTIVE:	The relationship between the use of TNF antagonists and onset of granulomatous infection was examined	
DESIGN:	**Study design:** Database analysis (MedWatch)/case series **Setting:** Multicenter **Sample size:** >346,000; 649 cases	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	INF Various Various 566 cases (>233,000 treated)	ETA Various Various 83 cases (>113,000 treated)
INCLUSION CRITERIA:	All patients treated with inf or eta	
EXCLUSION CRITERIA:	N/A	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Concurrent use of immunosuppressant drugs	

Authors: Wallis et al. **Year: 2004**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** N/A	
	INF	ETA
Median age (years):	60	58
Sex (% female):	66	59
Ethnicity:	NR	NR
Other germane population qualities:		
• Corticosteroid use (%)	41	66
• MTX use (%)	43	41
• Crohn's disease (%)	14	0
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Granulomatous infections **Timing of assessments:** N/A	
RESULTS:	**Health Outcome Measures:** ▪ Granulomatous infections were reported at rates of ~239 per 100,000 patients who received inf and ~74 per 100,000 patients who received eta ($P < .001$). ▪ TB was the most frequently reported disease, occurring in ~144 and ~35 per 100,000 inf-treated and eta-treated patients, respectively ($P < .001$). ▪ A risk of granulomatous infection that was 3.25-fold greater among patients who received inf than among those who received eta.	

Authors: Wallis et al. **Year: 2004**	
ADVERSE EVENTS: **Overall adverse effects reported:** •	INF or ETA 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 or ETA N/A N/A
QUALITY RATING:	**N/A**

Evidence Table 8 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Wasserman et al.**[155] **Year: 2004** **Country:** Canada
FUNDING:	Schering-Plough
RESEARCH OBJECTIVE:	Description of infusion-related reactions to infliximab (during or within 1 hour of infusion) in patients with active RA.
DESIGN:	**Study design:** Prospective cohort study **Setting:** Quaternary care center **Sample size:** 113 patients, 1183 infusions
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** 3 mg/kg wks 0,2,6 then every 8, dose could be increased to 5 mg/kg at week 14 based on clinical grounds Mean 60.6 weeks 113
INCLUSION CRITERIA:	18–75 years old; diagnosis of RA according to the 1987 ACR criteria; active disease (6 tender and 6 swollen joints in addition to at least 2 of the following: morning stiffness 45 min, ESR > 28 mm/h, and CRP > 2 mg/dl., despite MTX treatment; failed at least 3 DMARDs.
EXCLUSION CRITERIA:	Previous exposure to biologically-based therapies; current signs and symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease; history of lymphoproliferative disease, including lymphoma, or signs suggestive of such a disease; any known malignant disease and were screened for TB prior to study initiation
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Stable doses of corticosteroids (10 mg/day) and/or NSAIDs

Authors: Wasserman et al. **Year: 2004**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe
Mean age (years): **Sex (% female):** **Ethnicity:** **Other germane population qualities:** • TJC • SJC • Mean disease duration • MTX use (%) • Corticosteroids use (%)	45.7 years 87 NR 21.3 10.8 13.6 years 100 59- prednisone
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Infusion reactions categorized as (a) allergic, including pruritis, urticaria, and/or facial or generalized swelling, (b) cardiopulmonary, comprising hypotension (decrease in systolic pressure > 20 mm Hg), hypertension (increase in systolic pressure > 20 mm Hg, tachycardia (increase in heart rate > 20 beats/min), and/or shortness of breath, and (c) miscellaneous, including headache, nausea, and/or vomiting. **Timing of assessments:** During treatment and 1-2 hours after
RESULTS:	**Health Outcome Measures:** • 104 infusion-related reactions out of 1183 infusions performed (8.8%) and 60 of 113 patients (53%) experienced at least one reaction during the course of their treatment. • Infusion related reactions; Allergic- 45 (3.8%); Cardiopulmonary- 35 (3.0%); Misc.- 24 (2.0%) • Reactions following pretreatment or not with diphenhydramine at infusions 3 and 4 – Pretreated 14.7% vs. Not pretreated 14.3%

Authors: Wasserman et al. **Year:2004**	
ADVERSE EVENTS: **Overall adverse effects reported:** • Urticaria • Headache • Hypotension • Pruritis • Hypertension	**INF** 104 infusion related reactions (8.8%) the most common were the following 13% 9% 9% 7% 6%
Significant differences in adverse events:	There were no dose related differences between the 3 mg/kg and 5 mg/kg
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:** No
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**INF** N/A 3 (2.7%) due to infusion reactions
QUALITY RATING:	**Fair**

*primary outcome measures

Evidence Table 8 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Westhovens et al.**[57] **Year: 2006** **Country:** Multinational		
FUNDING:	Centocor Research and Development, Inc		
RESEARCH OBJECTIVE:	To assess the risk of serious infections following 22 weeks of infliximab therapy		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 1084		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo + MTX** N/A 22 weeks 363	**INF 3 + MTX** 3 mg/kg wks 0,2,6,14 22 weeks 360	**INF 10 + MTX** 10 mg/kg wks 0,2,6,14 2 weeks 361
INCLUSION CRITERIA:	Diagnosis of RA according to the ACR: had active disease despite receiving MTX; patients may or may not have been treated with other concomitant DMARDs.		
EXCLUSION CRITERIA:	opportunistic infections; serious infections during the 2 months prior to screening; known HIV, active, latent or history of TB with inadequate documentation of treatment; an inability to receive prophylaxis with isoniazid; history of lymphoproliferative disease or malignancy; CHF.		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Chloroquine, azathioprine, penicillamine, oral or intramuscular gold, hydroxychloroquine, sulfasalazine, leflunomide, cyclosporine, oral corticosteroids, or NSAIDs		

<table>
<tr><td colspan="4">Authors: Westhovens et al.
Year: 2006</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes - except for median disease duration but not statistically significant (P = 0.083)
Disease severity: Moderate-severe</td></tr>
<tr><td></td><td><u>Placebo + MTX</u></td><td><u>INF 3 + MTX</u></td><td><u>INF 10 + MTX</u></td></tr>
<tr><td>Mean age (years):</td><td>52.0</td><td>53.0</td><td>52.0</td></tr>
<tr><td>Sex (% female):</td><td>83.2</td><td>80.0</td><td>77.8</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:
• TJC
• SJC
• Median disease duration
• DMARD use (%)
• MTX use (%)
• Corticosteroids use (%)
• DAS score
• HAQ score
• Concomitant conditions predisposing to infection, no. (%)</td><td>

22
15
8.4
100
100
59.2

1.5

29 (8.0)</td><td>

22
15
7.8
100
100
59.2

1.5

29 (8.1)</td><td>

22
15
6.3
100
100
59.0

1.5

20 (5.5)</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Rate of serious infections

Secondary Outcome Measures: ACR 20/50/70; DAS28

Timing of assessments: Weeks 0,2,6,14,22</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
Week 22
• ACR20 INF3 58% INF10 61% MTX 26%
• ACR50 INF3 32.1% INF10 35.4% MTX 9.7%
• ACR70 INF3 14.0% INF10 16.1% MTX 4.7%
• DAS28 response (mean) INF3 3.5 INF10 3.3 MTX 4.4
• All INF 3 or INF 10 vs. MTX had a statistical significance of P < 0.001</td></tr>
</table>

Authors: Westhovens **Year: 2006**			
ADVERSE EVENTS (%): **Overall adverse effects reported:** • Serious infections • Pneumonia • Serious AEs • Rash	**Placebo + MTX** 66.2 1.7 0 7.5 1.7	**INF 3 + MTX** 69.7 1.7 0.8 7.8 4.7	**INF 10 + MTX** 72.3 5.0 1.1 7.5 4.4
Significant differences in adverse events:	Rate of serious infections was significantly higher in the 10mg/kg group compared to placebo: RR: 3.1 95% CI 1.2 – 7.9 No significant differences in serious infections in the 3 mg/kg group: RR 1.0 95% CI 0.3 – 3.1		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** 18 from efficacy analysis		
ADEQUATE RANDOMIZATION:	**Yes**		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 7.6 % **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Placebo + MTX** 6.3 2.2	**INF 3 + MTX** 7.2 5.0	**INF 10 + MTX** 8.9 5.5
QUALITY RATING:	**Good**		

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Wolfe and Michaud**[173] **Year: 2004** **Country:** US			
FUNDING:	National Data Bank for Rheumatic Diseases (US) funded by Amgen, Aventis, Bristol-Myers, Centocor, Merck, Novartis, Pharmacia, Pfizer, Squibb, Wyeth-Australia			
RESEARCH OBJECTIVE:	To determine the rate of and standardized incidence ratio for lymphoma in patients with RA and in RA patient subsets by treatment group			
DESIGN:	**Study design:** Observational – prospective cohort study **Setting:** Multicenter (908 practices) **Sample size:** 18,572			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** N/A N/A 6433	**ETA** N/A N/A 2729	**MTX** N/A N/A 5593	**No MTX/ No biologics** N/A N/A 4474
INCLUSION CRITERIA:	Participants in the National Data Bank for Rheumatic Diseases (NDB) long-term study of the outcomes of RA; cases were identified from this group as those who developed lymphoma during the 2 ½ year observational period			
EXCLUSION CRITERIA:	Cases were rejected if not enough information could be obtained to verify the patient's lymphoma			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	**GOOD**			

<table>
<tr><td colspan="5">Authors: Wolfe et al.
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="4">Groups similar at baseline: Yes
Disease severity: N/A</td></tr>
<tr><td></td><td><u>INF</u></td><td><u>ETA</u></td><td><u>MTX</u></td><td><u>No MTX/ No biologics</u></td></tr>
<tr><td>Mean age (years):</td><td>60.7</td><td>56.4</td><td>61.2</td><td>60.4</td></tr>
<tr><td>Sex (% female):</td><td>77.3</td><td>79.3</td><td>75.7</td><td>75.7</td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>• TJC</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• SJC</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Mean disease duration</td><td>13.7</td><td>14.1</td><td>13.5</td><td>13.5</td></tr>
<tr><td>• DMARD use (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• MTX use (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• DAS score</td><td>1.2</td><td>1.2</td><td>1.1</td><td>1.0</td></tr>
<tr><td>• HAQ score</td><td></td><td></td><td></td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="4">Primary Outcome Measures: Standardized incidence ratio (SIR)
Secondary Outcome Measures: N/A
Timing of assessments: Patients in database questioned every 6 months whether they have developed lymphoma</td></tr>
<tr><td>RESULTS:</td><td colspan="4">Health Outcome Measures:
• For the whole study population, lymphoma patients were more likely to be older (P = 0.005), male (P = 0.001), have more education (P = 0.027), and be non-Hispanic white (P = 0.066).
• The SIR for the whole population was 1.9 (C.I.: 1.3-2.7); indicating a greater risk for lymphoma in patients with RA.
• The SIR for patients taking biologics (INF or ETA) was 2.9 (C.I.: 1.7- 4.9). This CI falls within that for the whole population, so there is not a statistical difference between patients taking biologics and the rest of the RA population. (The authors suggest the increased SIR observed for patients taking biologics may be attributed to patients with the greatest risk of lymphoma being prescribed these drugs.)
• No significant differences were observed between treatment groups.</td></tr>
</table>

Authors: Wolfe et al. **Year: 2004**	
ADVERSE EVENTS: **Overall adverse effects reported:** • NR	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 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:**	NR
QUALITY RATING:	**Fair**

Evidence Table 8 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Wolfe et al.**[168] **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	

<table>
<tr><td colspan="3">Authors: Wolfe et al.
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: Yes with slight exceptions in age and sex
Disease severity: N/A</td></tr>
<tr><td></td><td><u>Pre-INF</u></td><td><u>INF</u></td></tr>
<tr><td>Mean age (years):</td><td>59.8</td><td>61.4</td></tr>
<tr><td>Sex (% female):</td><td>76.9</td><td>73.5</td></tr>
<tr><td>Ethnicity (% white):</td><td>NR</td><td>NR</td></tr>
<tr><td></td><td>90.9</td><td>94.4</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td></tr>
<tr><td>• Corticosteroid use (%)</td><td>54.6</td><td>50.4</td></tr>
<tr><td>• MTX use (%)</td><td>47.9</td><td>74.6</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: TB
Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="2">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.</td></tr>
</table>

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.**[179] **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**			

*primary outcome measures

Evidence Table 8 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Wolfe et al.**[189] **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 • Y	**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**

*primary outcome measures

Evidence Table 8 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Zink et al.**[149] **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:** • infections • Y	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**.[182] **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		

Authors: Chung et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe		
	Placebo	**INF5**	**INF10**
Mean age (years):	60 ± 12	62 ± 15	62 ± 13
Sex (% female):	24	14	16
Ethnicity (% white):	88	88	84
Current or prior angina (%):	29	18	24
Myocardial infarction (%):	63	50	67
Diabetes mellitus (%):	41	28	37
NYHA Class III/IV (%):	96/4	96/4	92/8
LVEF (%):	0.25 ± 0.07	0.23 ± 0.07	0.24 ± 0.06
OUTCOME ASSESSMENT:	**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		
RESULTS:	**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		

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 seperately	**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: Fleischmann et al.**[194] **Year: 2003** **Country:** US		
FUNDING:	Immunex Corporation		
RESEARCH OBJECTIVE:	Safety and efficacy of etanercept in elderly patients with RA.		
DESIGN:	**Study design: Retrospective analysis** **Setting:** 4 double-blind RCTs and 5 open label studies **Sample size:** 1128		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Less than 65 years** Twice week NR 931	**65 years or more** Twice a week NR 197	
INCLUSION CRITERIA:	Participant in one of 9 trials, 8 which evaluated patients with long-standing disease who had failed previous DMARD therapy and one that evaluated patients with RA ≤ 3 years and never used MTX.		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Fleischmann et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Mild-moderate-severe		
	Less than 65 years	**65 years or more**	
Mean age (years):	48	70	
Sex (% female):	78	74	
Ethnicity (%): White			
White/black/other	87/4/9	94/0/6	
Early RA (%)	37	34	
Advanced RA (%)	63	66	
Disease duration (Mean)	1.0	0.9	
Early RA	12	14	
Advanced RA	NR	NR	
Other germane population qualities:			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR 20/50/70 in patients receiving therapy for one year and safety in all patients that received ETA was calculated per patient year **Secondary Outcome Measures:** NR **Timing of assessments:** N/A		
RESULTS:	**Health Outcome Measures at one year for under 65 and 65 or more, respectively:** • ACR 50 44% vs. 40% (*P* = NR) • ACR 70 20% and 17% (*P* = NR) **Intermediate Outcome Measures at One Year:** • ACR 20 69% and 66%		

Authors: Fleischmann et al. **Year: 2003**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Medically important infections • Cancer	**Less than 65 years** NR 3% 1%	**65 years or more** NR 7% 2.5%	**drug 3**
Significant differences in adverse events:	Yes- for medically important infection $P = 0.003$. Report also says that the less than 65 group had ISR, headaches and rhinitis "statistically more significantly" than the older group but did not report the numbers.		
ANALYSIS:	**ITT: No** **Post randomization exclusions:** Yes		
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:**	**Less than 65 years** NR NR	**65 years or more** NR NR	
QUALITY RATING:	**N/A**		

Evidence Table 9 ***Targeted Immune Modulators - Subgroups***

STUDY:	**Authors: Fleischmann et al.**[193] **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

<table>
<tr><td colspan="7">Authors: Fleischmann et al.
Year: 2005</td></tr>
<tr><td rowspan="8">POPULATION CHARACTERISTICS:</td><td colspan="6">Groups similar at baseline:
Disease severity: Mild-moderate-severe</td></tr>
<tr><td colspan="2">RA</td><td colspan="2">PsA</td><td colspan="2">AS</td></tr>
<tr><td><u>Less than 65 years</u></td><td><u>65 years and more</u></td><td><u>Less than 65 years</u></td><td><u>65 years and more</u></td><td><u>Less than 65 years</u></td><td><u>65 years and more</u></td></tr>
<tr><td>Sample size:</td><td>2772</td><td>579</td><td>251</td><td>14</td><td>273</td><td>4</td></tr>
<tr><td>Median age (years):</td><td>47</td><td>70</td><td>46</td><td>70</td><td>42</td><td>65</td></tr>
<tr><td>Sex (% female):</td><td>77</td><td>73</td><td>46</td><td>71.4</td><td>24.5</td><td>0</td></tr>
<tr><td>Ethnicity (%white):</td><td>78.6</td><td>89.5</td><td>89.2</td><td>100</td><td>92.7</td><td>100</td></tr>
<tr><td>Other germane population qualities:</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="6">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</td></tr>
<tr><td>RESULTS:</td><td colspan="6">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.</td></tr>
</table>

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:	**N/A**			

Evidence Table 9 ***Targeted Immune Modulators - Subgroups***

STUDY:	**Authors: Fleischmann et al.,**[144] **Schiff et al.,**[146] **Tesser et al.**[145] **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: Gottlieb et al.**[195] **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:	**Elderly (n=99)**	**Obese (n=652)**	**Diabetic (n=122)**
Overall adverse effects reported:	NR	NR	NR
• Accidental injury	15.2%	16.7%	18.9%
• Headache	14.1%	16.6%	13.9%
• Pharyngitis	13.1%	16.4%	12.3%
• Rhinitis	12.1%	12.3%	12.3%
• Infection	11.1%	12.1%	NR
• Any malignancy	6.1%	1.2%	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**		

*primary outcome measures

Evidence Table 9 ***Targeted Immune Modulators—Subgroups***

STUDY:	**Authors: Katz et al.**[196] **Year: 2004** **Country:** US		
FUNDING:	NR- but data came from manufacturer		
RESEARCH OBJECTIVE:	To report the first large evaluation of infliximab exposure during pregnancy		
DESIGN:	**Study design:** case series **Setting:** Safety database **Sample size:** 131 direct and 15 indirect exposure		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** NR From 1 to 9 infusions 131 and 15		
INCLUSION CRITERIA:	Patients that either were treated with INF or their partners		
EXCLUSION CRITERIA:	N/A		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	5-aminosalicylate; 6-mercaptopurine/azathioprine; corticosteroids; metronidazole; MTX; ciprofloxacin; NSAIDs; proton pump inhibitors; H2 antagonists; narcotics; cyclosporine		

Authors: Katz et al. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe		
	INF- direct	**INF-indirect**	
Mean age (years):	33	33	
Sex (% female):	100	100	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Crohn's Disease	82	6	
• Fistulizing Crohn's	24/82	2/6	
• Rheumatoid Arthritis	8	2	
• Juvenile Rheumatoid	2	0	
• Ulcerative Colitis	1	0	
• Spondyloarthropathies	0	2	
• Unknown	3	0	
• MTX use (%)	8	20	
• Corticosteroids use (%)	31	40	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Pregnancy results		
RESULTS:	**Health Outcome Measures:** • Live births occurred in 67% (64/96), miscarriages in 15% (14/96), and therapeutic termination in 19% (18/96) of the pregnancies directly exposed to INF. • Indirect exposure resulted in 9 live births and 1 miscarriage. • General population rates live births occurred in 67%, miscarriages in 17% , and therapeutic termination in 16% • Comparing the general population with the INF treated there is no statistical difference live births (95% CI: 56.3, 76.0), miscarriages (95% CI: 8.2, 23.2), and therapeutic terminations (95% CI: 11.5, 28.0) among the 96 women		

<table>
<tr><td colspan="4">Authors: Katz et al.
Year: 2004</td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
• infections
• Y</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>ARE GROUPS COMPARABLE AT BASELINE:</td><td colspan="3">N/A</td></tr>
<tr><td>ASCERTAINMENT METHODS ADEQUATE AND EQUALLY APPLIED:</td><td colspan="3">N/A</td></tr>
<tr><td>STATISTICAL ANALYIS ADEQUATE:</td><td colspan="3">Yes</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: 27%
Loss to follow-up differential high: N/A</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:</td><td><u>Direct</u>
25%
N/A</td><td><u>Indirect</u>
33%
N/A</td><td><u>drug 3</u></td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">N/A</td></tr>
</table>

*primary outcome measures

Evidence Table 9 ***Targeted Immune Modulators - Subgroups***

STUDY:	**Authors: Kwon et al**.[180] **Year: 2003** **Country:** US
FUNDING:	FDA
RESEARCH OBJECTIVE:	To describe adverse event reports of heart failure after TNF antagonist therapy.
DESIGN:	**Study design:** Database review **Setting:** Multicenter (FDA's MedWatch program) **Sample size:** 47
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**ETA or INF** Any Long term therapy 47
INCLUSION CRITERIA:	Patients who reported heart failure as an adverse event while taking ETA or INF therapy in the US since licensure of the drugs until February 2002; new onset failure and exacerbation of preexisting heart failure included
EXCLUSION CRITERIA:	Heart failure reports temporally associated with other heart failure-inciting events (such as myocardial infarction) were excluded
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	N/A

Authors: Kwon et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** **Disease severity:** Mild-moderate-severe		
	New Onset Heart Failure without risk factors	**New Onset Heart Failure with risk factors**	**Heart failure exacerbation**
Median age (years):	59	67	70
Sex (% female):	74%	42%	44%
Ethnicity:	NR	NR	NR
Any:			
• RA	15	14	9
• CD	3	3	0
• Psoriatic arthritis	0	1	0
• Juvenile RA	1	0	0
• Unknown	0	1	0
Therapy:			
• ETA	12	14	3
• INF	7	5	6
Concomitant therapy:			
• Corticosteroids use	8	10	5
• NSAIDs	3	5	1
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Number of patients with new heart failure; number of patients with heart failure exacerbation **Secondary Outcome Measures:** Number of patients under 50 years of age; number of patients under 50 with heart failure resolution of discontinuation of TNF antagonist therapy		
RESULTS:	**Health Outcome Measures:** • Thirty eight patients (81%) developed new-onset heart failure; while 9 (19%) experienced heart failure exacerbation of which: 19 patients had no documented risk factors. 10 patients were under age 50. • Of the patients under 50, after cessation of TNF antagonist therapy 3 patients experienced complete resolution of heart failure, 6 patients showed improvement, and 1 patient died • Young age was associated with greater short term response		

Authors: Kwon et al. **Year: 2003**			
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:	Yes		
STATISTICAL ANALYSISADEQUATE:	No		
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 9 ***Targeted Immune Modulators - Subgroups***

STUDY:	**Authors: Rudwaleit et al.**[192] **Year: 2004** **Country:** Germany		
FUNDING:	BMBF (Kompetenznetz Rheuma), FKZ 01GI9946		
RESEARCH OBJECTIVE:	To identify parameters predicting clinical response to TNF blockers in AS		
DESIGN:	**Study design:** post-hoc data analysis of 2 RCTs **Setting:** Clinic **Sample size:** 99		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**INF** NR 12 weeks 69	**ETA** NR 12 weeks 30	
INCLUSION CRITERIA:	AS according to the modified New York criteria and had to have active axial disease, defined as a BASDAI score of ≥4 (scale 0–10, 0 meaning no activity and 10 high disease activity)[15] and a spinal pain score of ≥4 (numerical rating scale 0–10) despite concurrent treatment with NSAIDs.		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Rudwaleit et al.
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>INF</u></td><td><u>ETA</u></td><td><u>All</u></td></tr>
<tr><td>Mean age (years):</td><td>39.6</td><td>35.6</td><td>38.4</td></tr>
<tr><td>Sex (% female):</td><td>35</td><td>27</td><td>33</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>• Disease duration mean (yrs)</td><td>15.6</td><td>13.03</td><td>14.8</td></tr>
<tr><td>• MTX use (%)</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• BASDAI score (mean)</td><td>6.4</td><td>6.6</td><td>6.4</td></tr>
<tr><td>• BASFI score (mean)</td><td>5.3</td><td>5.7</td><td>5.4</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Logistic regression likelihood ratio tests

Timing of assessments: 12 weeks</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Predictors of major response (BASDAI50) are shorter disease duration (P = 0.003), younger age (P = 0.009), and lower BASFI (P = 0.007). Raised CRP and a higher BASDAI may also have predictive capabilities.
• After adjustment for disease duration, age was not statistically significantly associated with major response anymore.</td></tr>
</table>

Authors: Rudwaleit 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		
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:	**N/A**		

Evidence Table 9 ***Targeted Immune Modulators – Subgroups***

STUDY:	**Authors: Vermeire et al.**[191] **Year: 2002** **Country:** Belgium		
FUNDING:	Centocor; Schering- Plough; Funds for Scientific Research Belgium		
RESEARCH OBJECTIVE:	To assess whether demographic or clinical parameters influence short-term response to infliximab in patients with Crohn's diesease		
DESIGN:	**Study design:** case series **Setting:** University clinic **Sample size: 240** consecutive patients		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Refractory** 5mg/kg week 0 4 weeks 137	**Fistulizing** 5mg/kg weeks 0,2,6 10 weeks 103	
INCLUSION CRITERIA:	Refractory CD or dependent on corticosteroids for at least 6 months with colitis, iletis or ileocolitis; or at least one entereocutaneous draining fistula(s) resistant to conventional treatment for at least 3 months		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes- not specified		

Authors: Vermeire et al. **Year: 2002**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Moderate - severe		
	Refractory	**Fistulizing**	
Median age (years):	34	37	
Sex (% female):	61.3	67	
Ethnicity:	NR	NR	
Other germane population qualities:			
• Mean disease duration	10.7	13.0	
• Previous surgery for CD (%)	NR	NR	
• Patients with fistulae (%)	0	100	
• Mean baseline CDAI	N/A	N/A	
• Mercaptopurine/Azathioprine use (%)	55.5	62.1	
• Corticosteroids use (%)	54.7	32.0	
• HAQ score	N/A	N/A	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Interaction of demographic or clinical variables with disease response **Timing of assessments:** Refractory- 4 weeks; Fistulizing- 10 weeks		
RESULTS:	**Health Outcome Measures:** • Response rates Fistulizing: 74.3%; Refractory: 72.9%; Overall: 73.5% (172/234) • Young age, Crohn's colitis and concomitant immunosuppressive therapy were associated with a greater short term-response to INF therapy.		

Authors: Vermeire et al. **Year: 2002**	
ADVERSE EVENTS: **Overall adverse effects reported:** • Acute infusion reactions • Lupus-like syndrome • Hematological problems • Malignancy	**Overall** NR 7 (3%) 2 (< 1%) 3 (1%) 3 (1%)
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:** 6/240 (2.5%) **Loss to follow-up differential high:** No
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**Overall** 2.5% NR
QUALITY RATING:	**N/A**