Drug Class Review
on
Targeted Immune Modulators

Final Report

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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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List of Abbreviations

ACR20/50/70	American College of Rheumatology, numbers refer to percentage improvement
ADA	adalimumab
AKA	anakinra
ANA	anti-nuclear antibodies
anti-ds DNA	antibodies to double-stranded DNA
anti-TNF	antibodies against tumor necrosis factor
AS	ankylosing spondylitis
ASA	Assessment in Ankylosing Spondylitis
ASAS20	ASA 20% improvement
ASAS50	ASA 50% improvement
ASAS70	ASA 70% improvement
ASHI	arthritis-specific health index
BASDAI	Bath AS Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
CAHP	Childhood Arthritis Health Profile
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopy Index of Severity
CDER	Center for Drug Evaluation Research
CHAQ	Childhood Health Assessment Questionnaire
CHF	congestive heart failure
CHQ	Childhood Health Questionnaire
CI	confidence interval
CRP	C-reactive protein
DAS	disease activity score
DMARD	disease-modifying antirheumatic drug
ESR	eyrthrocyte sedimentation rate
ETA	etanercept
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
HAQ	Health Assessment Questionnaire
HAQ-DI	Disability Index of the Health Assessment Questionnaire
HQL	health-related quality of life
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
INF	infliximab
ISR	injection site reaction
ITT	intention to treat
JIA	juvenile idiopathic arthritis
JRA	juvenile rheumatoid arthritis
JCA	juvenile chronic arthritis
LFT	liver function test
LOCF	last observation carried forward
MTX	methotrexate
N/A	not applicable
NICE	National Institute for Clinical Excellence

NNT	number needed to treat
NR	not reported
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PASI	Psoriasis Area and Severity Index
PsA	psoriatic arthritis
QALY	quality-adjusted life-year
QoL	quality of life
RA	rheumatoid arthritis
RF	rheumatoid factor
RR	relative risk
s.c.	subcutaneous
SF-36	Medical Outcomes Study Short Form 36 Health Survey
TB	tuberculosis
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor alpha
TNFβ	tumor necrosis factor beta
URTI	upper respiratory tract infection
UTI	urinary tract infection
WBC	white blood cell

INTRODUCTION

A. Targeted Immune Modulators (TIMs)

Targeted immune modulators (TIMs) – commonly referred to as biological response modifiers or simply *biologics* – are a relatively new category of medication used in the treatment of certain types of immunologic and inflammatory diseases, including rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), plaque psoriasis, and Crohn's disease. The US Food and Drug Administration (FDA) approved the first of the biologics (infliximab) in 1998 and approved five additional agents since that time for treating various rheumatic conditions and psoriasis: etanercept (1998), anakinra (2001), adalimumab (2002), alefacept (2003), and efalizumab (2003). Table 1 summarizes currently approved biologics in the US, including trade name, manufacturer, route of administration, therapeutic mechanism of action, and approved (labeled) uses.

Table 1: Targeted Immune Modulators

Generic Name	US Trade Name	Manufacturer	Route	Half-life	Onset of Action	Mechanism of Action	Labeled Uses
Infliximab	Remicade®	Centocor	Intravenous	9.8 days	2-14 days	TNF inhibitor	- RA - Crohn's Disease - PsA - AS - Ulcerative colitis
Etanercept	Enbrel®	Amgen Wyeth Immunex	Subcutaneous	4.8 days	1-28 days	TNF inhibitor	- RA - JRA - PsA - AS - Plaque Psoriasis
Adalimumab	Humira®	Abbott	Subcutaneous	10-18 days	1-14 days	TNF inhibitor	- RA - PsA
Anakinra	Kineret®	Amgen	Subcutaneous	7-8 hours	7-21 days	IL-1 receptor antagonist	- RA
Efalizumab	Raptiva®	Genentech	Subcutaneous	6.2 days	14 days	CD11a inhibitor	- Plaque Psoriasis
Alefacept	Amevive®	Biogen	Intramuscular	11-12 days	30-60 days	CD2 antagonist	- Plaque Psoriasis

TIMs work by selectively blocking mechanisms involved in the inflammatory and immune response. Tumor necrosis factor (TNF) inhibitors block specific proinflammatory mediators known as cytokines. Adalimumab, etanercept, and infliximab produce their primary effect by blocking TNF-α from interacting with cell surface TNF receptors. Adalimumab is a fully human monoclonal antibody that binds specifically to TNF-α, blocking its interaction with both the p55 and p75 cell surface TNF receptor. Etanercept is a soluble dimeric form of the p75 TNF-α receptor linked to the Fc portion of human immunoglobulin G1 (IgG1). It exerts its action by binding circulating TNF and preventing it from interacting with a cell surface receptor. Infliximab is a chimeric (mouse/human) anti-TNF-α antibody that binds both the circulating and transmembrane forms of TNF-α, thereby preventing binding with the receptor. Interleukin-1 (IL-1), another naturally occurring cytokine, has both immune and pro-inflammatory actions. Anakinra is a human recombinant protein that competitively blocks the IL-1 receptor, thus blocking various inflammatory and immunological responses.

The immunosuppressant agents alefacept and efalizumab produce their immune response by interfering with T lymphocyte activation. Alefacept is a dimeric fusion protein that consists of the extracellular CD2-binding portion of the human leukocyte function antigen (LFA-3) and the Fc portion of human IgG1. Efalizumab is a recombinant humanized IgG1 monoclonal antibody that binds to human CD11a and inhibits the binding of LFA-1 to intercellular adhesion molecule-1 (ICAM-1).

Of the six agents, only adalimumab, anakinra, etanercept, and infliximab currently are approved by the FDA for treating a condition under review in this report. Because they have a similar mechanism of action, adalimumab, etanercept, and infliximab are used interchangeably in the treatment of RA, although the clinical response to the different agents can vary widely in an individual patient. Alefacept, anakinra, and efalizumab each produces its effect by affecting a different point in the inflammatory and immune response cascade. Table 2 summarizes dosages and administration for different indications.

Table 2: Recommended Dosage and Administration

Generic Name	Indication	Dosage and Administration
Infliximab	RA	3 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to maximum of 10 mg/kg every 4 weeks
	Crohn's Disease	5 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to 10 mg/kg
	PsA	5 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter
	AS	5 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 6 weeks thereafter
	Active ulcerative colitis	5 mg/kg induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter
Etanercept	RA PsA AS	25 mg twice weekly as subcutaneous injections or 50 once weekly as subcutaneous injection
	JRA (patients 4-17 years)	0.8 mg/kg per week (maximum 50 mg per week) given as one or two subcutaneous injections
	Plaque Psoriasis	50 mg given twice weekly (administered 3 or 4 days apart) as a subcutaneous injection for 3 months, followed by 50 mg weekly
Adalimumab	RA	40 mg every other week as subcutaneous injection; may increase to 40 mg per week
	PsA	40 mg every other week as subcutaneous injection
Anakinra	RA	100 mg daily as subcutaneous injection; dose should be decreased to 100 mg every other day in renal insufficiency
Efalizumab	Plaque Psoriasis	Initial 0.7 mg/kg subcutaneous injection followed by weekly doses of 1 mg/kg (not to exceed total of 200 mg)
Alefacept	Plaque Psoriasis	15 mg given once weekly as an intramuscular injection. Treatment should be continued for 12 weeks; re-treatment with an additional 12 week course may be initiated provided that CD4+ T lymphocytes counts are < 250 cells/μL and a 12-week interval has passed since the end of the initial treatment cycle

In this report, we review the comparative effectiveness, safety, and tolerability of TIMs. Our review covers the use of these drugs in adult patients with RA, AS, PsA, or Crohn's disease and pediatric patients with JRA. The next section briefly describes the epidemiology and pathophysiology of these conditions, as well as clinical features, assessment methods, management goals, and treatment strategies. Furthermore, we review the role of the targeted immune modulators in treating patients with these diseases.

B. Rheumatoid Arthritis (RA)

RA is an autoimmune disease that affects about one percent of the population worldwide. The exact etiology of RA is not completely understood, but genetic susceptibility factors have been described in certain populations. The hallmarks of the disease are inflammation of the synovial tissues with progressive erosion of bone leading to malalignment of the joint and disability in most cases. Studies have shown the importance

of CD4+ T cells, B cells, and cytokines in the pathogenesis of RA. TNF-α plays a central role in the pathobiology of RA. It is an important regulator of other pro-inflammatory molecules and stimulates the secretion of matrix metalloproteinases. It also exerts a direct effect on the multiple tissues inside the joint including chondrocytes, macrophages, synovial fibroblasts, and osteoclasts. Together, its action leads to inflammation and the formation of pannus, a localized mass of tissue that causes localized joint destruction.[1]

The diagnosis of RA is primarily a clinical one. Constitutional symptoms, such as fatigue and low grade fevers, are common before the onset of joint swelling and pain. Joint stiffness is almost always present and is frequently most severe after periods of prolonged rest. The disease tends to affect the small joints of the hands and feet first in a symmetric pattern, but other joint patterns are often seen. In a subset of patients, RA can be a devastating disease with numerous extra-articular manifestations. Severe disease may be complicated by involvement of the eyes, lungs, nerves, and the cardiovascular system.
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The diagnosis of RA is primarily a clinical one. Constitutional symptoms are common before the onset of joint swelling and pain. Joint stiffness is almost always present and is frequently most severe after periods of prolonged rest. The disease tends to affect the small joints of the hands and feet first in a symmetric pattern, but other joint patterns are often seen. A serum rheumatoid factor is present in up to 75 percent of patients with RA but is frequently negative in early disease. A more specific marker, anti-cyclic citrullinated peptide (CCP) antibody, has recently been described and may be a useful marker in patients with early disease.[2] Table 3 presents the classification criteria for RA proposed by the American College of Rheumatology (ACR). These criteria were developed for use in clinical trials, but may be relatively insensitive in early disease.

Table 3: Criteria for the Classification of RA* (revised 1987)

1.	Morning stiffness lasting greater than one hour
2.	Arthritis in 3 or more joint areas
3.	Arthritis of the hand joints (metacarpophalangeal [MCP], proximal interphalangeal [PIP], wrists)
4.	Symmetric arthritis
5.	Rheumatoid nodules
6.	Serum rheumatoid factor
7.	Radiographic changes: erosions or unequivocal periarticular osteopenia

*Patients are said to have RA if they meet 4 of 7 criteria.[3]

Treatment is aimed at controlling pain and inflammation and ultimately, slowing or arresting the progression of joint destruction. The key to successful management of RA is the early identification of the disease and the rapid institution of effective therapies.[4] Methotrexate (MTX) is the cornerstone of most RA treatment regimens as it has demonstrated good disease control and tolerability. However, MTX toxicity may limit the use of MTX, and many patients do not adequately respond to MTX monotherapy. In patients with persistent disease despite aggressive management with oral agents, biologic agents, often in combination with MTX, are now considered the standard of care. Lifelong therapy is usually necessary

C. Juvenile Rheumatoid Arthritis (JRA)

JRA is a form of arthritis that, by definition, lasts at least 6 weeks in a child under the age of 16. It is a systemic disease with a variable presentation and has three established subtypes: pauciarticular (<5 joints involved), polyarticular (>or= 5 joints involved), and systemic (arthritis with fever and a rash).[5]

Joint pain, stiffness, and swelling are the hallmarks of JRA. Children with systemic disease often present with constitutional symptoms such as fever or rash. Similar findings may be seen in polyarticular disease but are rare with pauciarticular presentation. Uveitis, an inflammatory disease of the eye, is common. Children with the most severe forms of JRA may have significant disability from progressive destructive arthritis. Long-term consequences of the disease include growth disturbances, deformity of the joints, and blindness.

Initial therapeutic strategies are aimed at decreasing pain and swelling and improving the child's functional status. Non-steroidal anti-inflammatory drugs (NSAIDs) are first line therapy and are usually fairly well tolerated in children. Systemic steroids are usually avoided, if possible, because of adverse effects on bone growth. However, intra-articular steroid injections can be an effective strategy, particularly if only a few joints are afflicted with active disease. As in RA, oral disease-modifying antirheumatic drugs (DMARDs) are used next, with MTX being the most widely used. When the disease is resistant to oral therapies, biologic agents are indicated.

D. Ankylosing Spondylitis (AS)

AS is a chronic inflammatory arthritis with prominent involvement of the axial skeleton with prominent involvement of the spine and sacroiliac joints. Peripheral joint disease can occur and may be destructive in some cases. The peak age of onset is in the 20s, and men are affected more frequently than women by a ratio of about 3 to 1. The onset is indolent with prominent stiffness in the low back, which is characteristically worse at night and in the early morning. The sacroiliac joints are usually the first joints involved and the

disease is characterized by progressive involvement of the spine. Enthesitis, inflammation of the insertion of ligaments and tendons on bones, is one of the hallmarks of the disease.

Existing diagnostic criteria are relatively insensitive and have limited utility in clinical practice. AS usually presents with inflammatory back pain and stiffness in a young adult, although 20 percent present with peripheral joint involvement and more than 50 percent have joints other than the spine affected at some stage. Radiographs of the sacroiliac joints, when abnormal, can be useful in assessing the presence of AS; however, they are frequently normal in early disease. Over time, patients with AS develop progressive fusion of the spine with resultant deformity and disability.

For years NSAIDs were the standard of care for the treatment of AS, as they are effective in treating pain and stiffness. However, they do not have any effect on disease progression. Traditional DMARDs have been used, mostly because a lack of other more effective therapies, although they are usually ineffective in treating spinal arthritis. As TNF has been implicated in the pathophysiology of AS, biologic agents targeting TNF have become a standard treatment approach.[6] Studies are under way to assess whether treatment with these agents affects the natural history of AS.

E. Psoriatic Arthritis (PsA)

PsA is a chronic inflammatory arthritis associated with the skin disease psoriasis. In most cases, the psoriasis predates the onset of the PsA. The presentation, however, is highly variable. In all cases, symptoms include pain and stiffness in the affected joint as well as joint line tenderness, swelling, and sometimes loss of range of motion. Pitting of the fingernails often correlates with the extent and severity of the disease.[7] Dactylitis, swelling of a whole digit, is a characteristic clinical finding. Enthesitis, spondylitis, sacroiliitis, and inflammatory eye disease (iritis, uveitis) may occur.

The etiology and pathogenesis of psoriasis and PsA are not completely understood, but genetic, immunologic, and environmental factors are all likely to play a role.[8] The first line of treatment is NSAIDs, although in most cases DMARDs are necessary. Corticosteroids may be used but do not have much of a role in chronic disease management in psoriatic disease. If disease continues to be active despite the use of MTX or other oral DMARDS, biologics may be indicated.[9]

F. Crohn's Disease

Crohn's disease is a condition of the bowel causing inflammation involving the full thickness of the bowel wall. This may occur at any point from the mouth to the anus. This chronic inflammation leads to fibrosis

and obstructive symptoms with sinus tracts and fistulae. Fistulizing disease is a serious complication of Crohn's disease; it is basically abnormal communication between the gut and the skin or other internal organs, with small bowel or colonic contents draining to the skin or other organs. Abdominal pain and diarrhea, with or without bleeding, are characteristic of the disease. Constitutional symptoms are very common, predominantly fatigue and weight loss. Nonspecific digestive symptoms may predate the onset of clinically overt disease. Extra-intestinal symptoms may occur and include inflammatory eye disease, arthritis, and sclerosing cholangitis. Clinical diagnosis is made on the basis of history and physical examination and is confirmed on endoscopy and biopsy of the involved segment of the GI tract. Patients with aggressive or poorly controlled disease may suffer numerous complications; these include severe hemorrhage, intestinal obstruction, perforation, development of fistulae and abscess formation, malabsorption with nutritional deficiencies, and rarely, malignancy.

Treatment is aimed at controlling the inflammation and preventing complications. Mild disease may be controlled with 5-aminosalicylate (ASA) drugs or antibiotics. If the disease is resistant to these interventions or is more severe, corticosteroids are frequently used. If symptoms persist despite steroids or if the disease flares on tapering the steroids, immunomodulatory agents (azathioprine, 6- mercaptopurine [6-MP], and MTX) are instituted. Patients with unremitting disease, the presence of fistulous disease, or requiring aggressive management may warrant use of a biologic in an effort to avoid surgery. It is recommended that medical therapy be exhausted before surgical therapy is considered, except in cases of catastrophic complications such as acute colonic obstruction, massive hemorrhage, or bowel perforation.

G. Scope and Key Questions

The purpose of this review is to help policy makers and clinicians make informed choices about the use of targeted immune modulators. We compare the efficacy, effectiveness, and safety (adverse events) of adalimumab, alefacept, anakinra, efalizumab, etanercept, and infliximab in patients with RA, JRA, AS, PsA, and Crohn's disease.

The participating organizations of the Drug Effectiveness Review Project (DERP) are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to their constituencies. The Oregon Evidence-based Practice Center initially prepared preliminary key questions identifying the populations, interventions, and outcomes of interest, and we based the eligibility criteria for studies on these preliminary questions. Representatives of organizations participating in the DERP, in conjunction with experts in the fields of health policy, rheumatology, pharmacotherapy, and research methods

reviewed, revised, and approved the questions and outcome measures. The participating organizations approved the following key questions:

1. How do included drugs compare in their effectiveness for alleviating symptoms and stabilizing the disease in patients with RA, JRA, AS, PsA, and Crohn's disease?

2. What are the comparative incidence and severity of complications of these drugs?

3. Do the included drugs differ in effectiveness or adverse events in different age, sex, or ethnic groups, or in patients taking other commonly prescribed drugs?

The first key question addresses the issue of effectiveness: do the biologics differ in their effects under real-life circumstances? This report addresses both efficacy (i.e., whether biologics differ in their effects under ideal or highly controlled circumstances) and effectiveness. We distinguish between *efficacy* (*explanatory*) studies and *effectiveness (pragmatic)* studies; studies conducted in community-based settings that use less stringent eligibility criteria (i.e., broad range of population characteristics and disease severity), have long follow-up periods (i.e., greater than one year), and assess health outcomes are characterized as *effectiveness* studies. Studies conducted in more highly selected populations over shorter periods of time are characterized as *efficacy* studies. We summarize the results of efficacy and effectiveness studies separately as the results of effectiveness studies are more generalizable than results from highly selected populations (i.e., efficacy studies). However, effectiveness studies may have lower internal validity because of a higher risk of bias.

For assessing efficacy, effectiveness, and safety our review includes methodologically valid controlled clinical trials, placebo-controlled trials, fair- or good-quality systematic reviews, and fair- or good-quality observational studies. Table 4 summarizes outcome measures and study eligibility criteria.

Table 4: Outcome Measures and Study Eligibility Criteria

Outcome	Outcome Measures	Study Eligibility Criteria
Efficacy / Effectiveness	Health outcomes: • Quality of Life • Functional capacity • Pain • Reduction in the number of swollen or tender joints • Response • Remission • Hospitalizations • Mortality If no studies with health outcomes were available, we included intermediate outcomes: • Radiological outcomes	• Outpatient study population • Head-to-head randomized controlled clinical trials or meta-analyses comparing one TIM to another o Good or fair quality o ≥ 3 months study duration o N ≥ 100 • When sufficient evidence was not available for head-to-head comparisons we evaluated placebo-controlled trials o Good or fair quality o ≥ 3 months study duration o N ≥ 100 • Controlled observational studies were reviewed for quality of life, functional capacity, hospitalizations and mortality - outcome measures rarely assessed in controlled trials o Good or fair quality o ≥ 12 months study duration o N ≥ 100
Safety/ Tolerability	• Overall adverse events • Withdrawals because of adverse events • Serious adverse events • Specific adverse events, including: - serious infectious diseases - lymphoma - congestive heart failure (CHF) - autoimmunity	• Head-to-head randomized controlled clinical trials or meta-analyses comparing one TIM drug to another o Good or fair quality o ≥ 3 months study duration o N ≥ 100 • Placebo-controlled trials o Good or fair quality o ≥ 3 months study duration o N ≥ 100 • Observational studies o Good or fair quality o ≥ 6 months study duration o N ≥ 100

As equipotency among the reviewed biologics is not well established, we assume that comparisons made within the recommended dosing range are appropriate (Table 2). Dose comparisons made outside the

recommended daily dosing range are acknowledged in our report, but we do not use them to determine the quality of the evidence.

Under normal circumstances, TIMs are rarely administered in primary care practices. They are used by specialists such as rheumatologists, gastroenterologists, and sometimes dermatologists. Some agents may be patient-administered with proper training, but they are usually given under the supervision of a specialist physician.

METHODS

A. Literature Search

To identify articles relevant to each key question we searched MEDLINE, Embase, The Cochrane Library, and the International Pharmaceutical Abstracts; we used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for selected indications (RA, JRA, AS, PsA, Crohn's disease), drug interactions, and adverse events with a list of six specific TIMs (adalimumab, alefacept, anakinra, efalizumab, etanercept, infliximab). We limited the electronic searches to "human" and "English language"; we searched sources from 1980 to 2005 (March) to delimit literature relevant to the scope of our topic.

We used the National Library of Medicine publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses; we also manually searched reference lists of pertinent review articles and letters to the editor. All citations were imported into an electronic database (EndNote, version 8.0). Additionally, we hand-searched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the FDA.

Further, the Center for Evidence-based Policy at the Oregon Health and Science University (OHSU) contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations, using a protocol available at www.ohsu.edu/drugeffectiveness. We received dossiers from four pharmaceutical companies (Abbott Laboratories, Amgen Pharmaceuticals, Centocor, Genentech, Wyeth/Amgen Pharmaceuticals)

Our searches found 815 citations, unduplicated across databases; we found an additional 103 articles from manually reviewing the reference lists of pertinent review articles. All studies presented in pharmaceutical dossiers had been identified through our searches. The total number of citations included in the database was 918. For further details on the search strategy, see Appendix A.

B. Study Selection

Two people independently reviewed abstracts; if both reviewers agreed that the study did not meet eligibility criteria, it was excluded. We obtained the full text of all remaining articles. Records were considered for exclusion if they did not meet pre-established eligibility criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons to medications outside our scope of interest.

With respect to study design we took a "best evidence" approach for this review. Results from well-conducted, head-to-head trials provide the strongest evidence to compare drugs with respect to effectiveness, efficacy, and adverse events; head-to-head trials were defined as those comparing one TIM with another. RCTs of at least 3 months' duration having an outpatient study population with a total sample size greater than 100 participants were eligible for inclusion.

If we could not find sufficient evidence of efficacy or effectiveness from at least one randomized, double-blinded trial for a certain indication, we reviewed other study designs as needed. Thus, to present the best available evidence, we also reviewed experimental studies with fewer than 100 participants or with an open-label design. In addition, we reviewed large (n > 100), well-conducted, observational studies (cohort studies, case control studies, case series) with a follow-up of at least 1 year to augment findings from experimental studies. Long-term observational studies can provide evidence on outcomes that may be difficult to observe in RCTs due to limitations in sample sizes and study durations. Furthermore, observational data can provide information whether treatment effects observed in RCTs can be translated to less selected populations.[10] Nevertheless, the strength of evidence of these results for comparing different drugs must be rated lower than results from the most preferred type of trial.

If no head-to-head evidence was published, we reviewed placebo-controlled trials for indications of interest. We reviewed all placebo-controlled trials to provide an overview of efficacy without taking drug equivalency into account. We compared results of approved dosing ranges, but no evidence on exact comparative dosing is currently available. Study populations, disease severity, and concomitant treatments can differ considerably across placebo-controlled trials. Comparisons of treatment effects across trials must, therefore, be made with caution.

We included meta-analyses in the evidence report if they were relevant to a key question and of good or fair methodological quality (based on the QUORUM statement[11]). We did not summarize individual studies in evidence tables if they were included in a high-quality meta-analysis. We excluded meta-analyses that were not based on a comprehensive systematic literature search or did not maintain the units of the studies in their statistical analyses. We checked our database to guarantee that our literature search had detected trials included in any meta-analyses that we discarded and obtained any missing articles.

For adverse events we included both experimental and observational studies. For observational studies we included those with large sample sizes (> 100 patients) that lasted at least 6 months and reported an included outcome.

We initially reviewed studies with health outcomes as the primary outcome measures. Outcomes were quality of life, functional capacity, alleviation of symptoms, hospitalizations, and mortality. If no study measuring health outcomes was available for a particular indication or population subgroup, we included intermediate outcomes (e.g., radiological changes). Safety outcomes included overall and specific adverse events (e.g., serious infections, lymphoma, autoimmunity), withdrawals attributable to adverse events or lack of efficacy, and drug interactions.

We included a total of 268 articles on an abstract level and retrieved those as full text articles for background information or to be reviewed for inclusion into the evidence report. We did not review studies that were included in a high-quality meta-analysis (listed in Appendix B).

C. Data Abstraction

We designed and used a structured data abstraction form to ensure consistency in appraisal for each study. Trained reviewers abstracted data from each study and assigned an initial quality rating. A senior reviewer read each abstracted article, evaluated the completeness of the data abstraction, and confirmed the quality rating. We abstracted the following data from included trials: study design, eligibility criteria, intervention (drugs, dose, duration), additional medications allowed, methods of outcome assessment, population characteristics, sample size, loss to follow-up, withdrawals attributed to adverse events, results, and adverse events reported. We recorded intention-to-treat results if available.

D. Quality Assessment

We assessed the internal validity (quality) of trials based on predefined criteria (Appendix C) developed by the US Preventive Services Task Force (ratings: good-fair-poor)[12] and the National Health Service Centre for Reviews and Dissemination.[13] External validity (generalizability) was assessed and reported but did not influence quality ratings. We did not rate the quality of descriptive studies (case series, database reviews).

Two independent reviewers assigned quality ratings; they resolved any disagreements by discussion and consensus or by consulting a third, independent party. Elements of internal validity assessment included, among others, randomization and allocation concealment, similarity of compared groups at baseline, use of intention-to-treat analysis, and overall and differential loss to follow-up.

Loss to follow-up was defined as the number of persons randomized who did not reach the endpoint of the study,[14] independent of the reason and the use of intention-to-treat analysis. We adopted no formal cut-off

point of loss to follow-up since many studies defined withdrawals due to acute worsening of the disease as an outcome measure.

Trials that had a fatal flaw in one or more categories were rated poor quality and not included in the analysis of the evidence report; trials that met all criteria were rated good quality. The majority of trials received a quality rating of fair. This includes studies that presumably fulfilled all quality criteria but did not report their methodologies to an extent that answered all of our questions. Therefore, the "fair quality" category includes trials with quite different strengths and weaknesses and a range of validity.

E. Data Synthesis

Throughout this report we synthesized the literature qualitatively. If data were sufficient, we augmented findings with quantitative analyses. We conducted meta-analyses of data for placebo-controlled trials that were fairly homogenous in study populations and outcome assessments. Our outcome measure of choice for RA was the relative risk (RR) of achieving an ACR 20/50/70 response (American College of Rheumatology [ACR], numbers refer to percentage improvement [see Appendix D for a summary of different scales]). We did not find sufficient data to pool results of the Health Assessment Questionnaire (HAQ) or other measures of health-related quality of life. We chose the ACR 50 outcome measure because response to treatment can be viewed as a close proxy to health outcomes. Therefore, such an outcome measure has more clinical significance than a comparison of mean changes of scores on rating scales. A 50 percent improvement on the ACR scale (i.e., an ACR50 response) is commonly viewed as a clinically significant response.

For each meta-analysis, we conducted a test of heterogeneity (I^2 statistic) and applied both a random and a fixed effects model. We report the random effects model results if moderate or high heterogeneity ($I^2 > 30\%$) was present. In addition, we calculated the number needed to treat (NNT) based on the pooled risk difference.

We assessed publication bias using funnel plots and Kendell's tests. However, given the small number of component studies in our meta-analyses, results of these tests must be viewed cautiously. All statistical analyses were conducted using StatsDirect, version 2.3.8.

Because only limited head-to-head evidence on TIMs was available, we conducted adjusted indirect comparisons when data was sufficient and trials were of similar design, conducted in similar settings with a comparable patient population. We based these analyses on the method proposed by Bucher et al.[15] Evidence suggests that adjusted indirect comparisons agree with head-to-head trials if component studies are similar

and treatment effects are expected to be consistent in patients included in different trials.[16, 17] Nevertheless, findings must be interpreted cautiously.

RESULTS

We identified 922 citations from searches and reviews of reference lists. In total we included 71 studies: 35 RCTs, four observational extensions of RCTs, four meta-analyses, 17 observational studies, and nine studies of other design (e.g., database reviews, case series). Furthermore, we retrieved 112 articles for background information.

Reasons for exclusions were based on eligibility or methodological criteria (Figure 1, QUORUM Tree).

Of the 71 included studies, 74 percent were financially supported by pharmaceutical companies and 9 percent were funded by governmental agencies or independent funds. We could not determine a funding source for 17 percent of the included studies.

KEY QUESTION 1

How do included drugs compare in their effectiveness for alleviating symptoms and stabilizing the disease in patients with rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Crohn's disease?

We included 27 RCTs, two trials of other design, four meta-analyses, and three studies of other design. No RCTs were head-to-head trials. One study was characterized as an effectiveness trial.[18] Most of the included efficacy studies were conducted in narrowly defined populations and/or were limited to less than 1 year of follow-up.

I. Rheumatoid Arthritis (RA)

The following drugs are currently approved by the FDA for the treatment of RA: adalimumab, anakinra, etanercept, and infliximab.

A. Summary of the Evidence

Overall, the evidence on the comparative effectiveness of TIMs for the treatment of RA is fair to poor. We found only one head-to-head study, which was a non-randomized, open-label effectiveness trial comparing etanercept to infliximab.[18] Etanercept had significantly greater response rates at 3 and 6 months than infliximab, however, no differences existed after 1 year. Otherwise, no evidence directly comparing the efficacy and safety of one TIM to another could be found. Adjusted indirect comparisons of randomized placebo-controlled trials suggest that no substantial differences exist among the efficacy of adalimumab,

etanercept, and infliximab. Point estimates favor adalimumab, etanercept, and infliximab over anakinra. However, differences do not reach statistical significance in adjusted indirect comparisons which is likely attributable to a lack of power. Adjusted indirect comparisons of anti-TNF drugs as a class compared to anakinra result in a statistically significantly greater efficacy of anti-TNF drugs on ACR 20 but not on ACR 50. These findings are largely consistent with a meta-analysis and adjusted indirect comparisons conducted by the UK Health Technology Assessment Programme.[19]

Good to fair evidence exists from meta-analyses and large RCTs that adalimumab, anakinra, etanercept, and infliximab are significantly more efficacious than placebo for the treatment of RA. Treatment effects are large and consistent across studies. We did not find any evidence on the efficacy and safety of alefacept and efalizumab for the treatment of RA.

In addition, good to fair evidence exists that combination treatment of adalimumab, anakinra, etanercept, and infliximab with MTX leads to clinically and statistically greater improvements than MTX plus placebo.

Although etanercept monotherapy failed to show a benefit relative to MTX monotherapy with respect to health outcomes (SF-36 [Medical Outcomes Study Short Form 36 Health Survey], HAQ, ASHI [Arthritis-Specific Health Index]) and ACR response rates after 52 weeks of treatment,[20-22] radiographic outcomes were significantly better in etanercept- than in MTX-treated patients.[20, 21] Two of these studies were conducted in patients with early RA.[20, 22] All three trials report a statistically significantly faster onset of efficacy for etanercept than for MTX treatment. This difference remained statistically significant for the first months of treatment.

No synergistic effects of a combination treatment of etanercept, anakinra, and MTX compared to an etanercept-MTX regimen could be detected.[23] Furthermore, the frequency of serious adverse events was substantially higher in the etanercept-anakinra combination groups. However, this finding is based on one trial.

B. Description of Studies

For RA, we did not find any head-to-head RCTs comparing one TIM to another. We found one non-randomized, open-label trial that assessed the long-term effectiveness and safety of etanercept, infliximab, and leflunomide.[18] This study could be characterized as an effectiveness trial. In addition, we included four meta-analyses of placebo-controlled trials, nine RCTs that were not included in any meta-analysis, and one

uncontrolled trial. We did not find any studies on alefacept and efalizumab. Included studies are presented in Table 6.

C. Study Populations

All patients suffered from active RA. However, the definition of active disease varied across studies. The non-randomized study was population-based and enrolled patients who had a diagnosis of RA based on the clinical judgment of the treating physician and who had failed to respond to at least one DMARD.[18] Most RCTs employed the ACR criteria[3, 24] to classify the diagnosis of RA. Some trials, however, used stricter eligibility criteria. Disease duration and concomitant treatments also varied across studies. Most patients used NSAIDS or oral corticosteroids in addition to the study medication. The majority of trials enrolled patients who had failed at least one DMARD treatment or were on a stable dose of MTX with unsatisfactory response. Two studies examined the efficacy of TIMs in patients with early RA and no prior MTX exposure.[22, 25] One RCT evaluated the efficacy and safety of a combination treatment of etanercept and anakinra.[23] Patients with an autoimmune disease other than RA, a history of active listeriosis or mycobacterial infection, or recent antibiotic treatment were generally excluded from studies.

D. Outcome Measures

All trials assessed response rates as defined by the ACR or by the European League Against Rheumatism (EULAR). These scales (ACR20/50/70, DAS28 [Disease Activity Score]) combine measures of global disease activity with counts of tender and swollen joints and acute phase laboratory parameters (see Appendix D). In addition, most studies evaluated health outcomes such as quality of life, functional capacity (e.g., SF-36, HAQ, ASHI), or discontinuation rates due to disease worsening. Some studies used the modified Sharp Method (radiographs of hands, wrists, and feet) to assess disease progression.

E. Methodological Quality

Study quality varied across studies. Some "fair" ratings are probably more attributable to inadequate reporting than to methodological flaws. Randomization methods and blinding were generally adequate; all studies used a double-dummy design (i.e., using an identical container for active treatment and placebo) to guarantee blinding; method of allocation concealment was rarely reported. The non-randomized trial was open-label and did not blind outcome assessors.

F. Sponsorship

All studies, except the non-randomized trial, were funded by the pharmaceutical industry.

G. Comparative Efficacy and Effectiveness

We did not identify any head-to-head RCTs. A fair, non-randomized, open-label trial assessed the efficacy and safety of etanercept (n = 166), infliximab (n = 135), and leflunomide (n = 103).[18] This Swedish study was population-based and had minimal exclusion criteria. Study duration was 12 months. Etanercept had significantly greater ACR20 response rates at 3 months ($P < 0.02$) and 6 months ($P < 0.05$), and greater ACR50 response rates at 6 months ($P < 0.005$) than infliximab. No significant difference could be detected thereafter. Although patient characteristics were similar at baseline, results must be interpreted cautiously because of an increased risk of bias in such a study design. Both, etanercept and infliximab had significantly greater response rates than leflunomide.

Indirect Head-Head Comparisons

In addition, we conducted adjusted indirect comparisons based on our meta-analyses of placebo-controlled trials to compare the treatment effects of individual TIMs. We included data from published studies or from the CDER website on dosages at or around approved dosing regimens. If data was sufficient, we conducted meta-analyses and adjusted indirect comparisons using ACR50 responses as outcome measures. For all analyses we used only data derived from study arms at or near the recommended dosage.

We chose ACR50 because a 50 percent improvement is likely to translate to a clinically significant improvement in health-related quality of life. For example, a patient with 12 swollen and 8 tender joints at baseline would need to have fewer than six swollen and four tender joints at the trial endpoint. This would be accompanied by at least a 50 percent improvement in at least three of the following five measures: the patient's assessment of pain, the patient's assessment of global disease activity, the physician's assessment of global disease activity, the HAQ-Disability Index, and either a C-reactive protein (CRP) or sedimentation rate (Westergren erythrocyte sedimentation rate [WESR]).

The underlying assumption for adjusted indirect comparisons to be valid is that the relative efficacy of an intervention is consistent across included studies.[15] Included TIM-studies primarily differ in study duration, disease duration, and concomitant treatments. Differences in study durations did not appear to be a factor altering the effect size. We included only studies of more than 3 months of study duration. Most RCTs reported the onset of significant responses between 4 and 8 weeks. Treatment responses were sustained up to 2 years in open-label extension studies. Sensitivity analyses based on different study durations did not substantially change the point estimates of the treatment effect. Likewise, sensitivity analyses excluding studies without concomitant MTX treatment, or studies on patients with early RA, did not substantially

change the point estimate. One exception was the sensitivity analysis of infliximab where removing a study on patients with early RA[25] substantially changed the effect size. However, it was unclear if this effect was attributable to true heterogeneity or to a lesser influence of random error in this large trial. Results presented below exclude this study. Overall, diagnostic criteria and eligibility criteria appeared to be sufficiently similar to make adjusted indirect comparisons a reasonable approach. However, given the small number of studies and the subsequent lack of precision, results should still be interpreted cautiously.

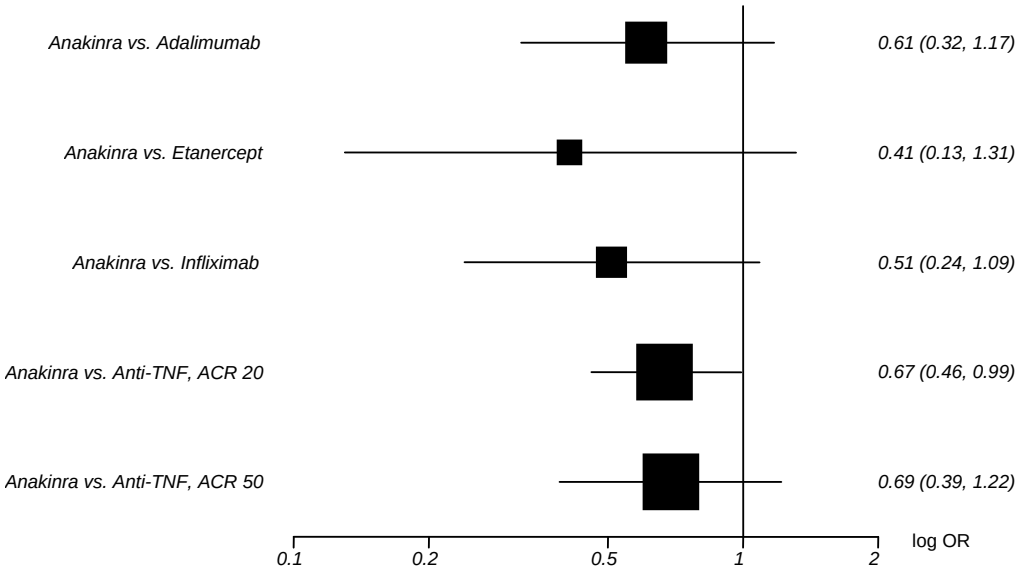
Results of adjusted indirect comparisons are depicted in Table 5 and Figure 1; corresponding forest plots for meta-analyses are presented in Appendix E. Findings suggest that no substantial differences exist among the efficacy of adalimumab, etanercept, and infliximab. However, given the wide confidence intervals, clinically significant differences cannot be excluded with certainty. Confidence intervals encompass differences that would be clinically significant. More data is needed to increase the precision of these estimates.

Point estimates favor adalimumab, etanercept, and infliximab over anakinra. However, differences do not reach statistical significance in adjusted indirect comparisons which is likely attributable to a lack of power. Adjusted indirect comparisons of anti-TNF drugs as a class compared to anakinra result in a statistically significantly greater efficacy of anti-TNF drugs on ACR 20 but not on ACR 50. Figure 1 depicts results of adjusted indirect comparisons of anakinra with adalimumab, etanercept, infliximab, and anti-TNF drugs as a class.

Table 5: Adjusted Indirect Comparisons of TIMs for the Treatment of RA

Comparison	RR (95% CI) for ACR50 response
Adalimumab vs. Etanercept	0.67 (0.21-2.09)
Adalimumab vs. Infliximab	0.87 (0.39-1.93)
Anakinra vs. Adalimumab	0.61 (0.32-1.17)
Anakinra vs. Etanercept	0.41 (0.13-1.31)
Anakinra vs. Infliximab	0.51 (0.24-1.09)
Etanercept vs. Infliximab	1..32 (0.78 - 4.61)

Figure 1: Adjusted Indirect Comparisons of Anakinra with anti-TNF Drugs for the Treatment of RA



H. General Efficacy

Because of the lack of head-to-head trials, we reviewed placebo-controlled trials. We have summarized evidence on the general efficacy of TIMs in the treatment of RA. This, however, does not provide evidence on the comparative efficacy and tolerability of TIMs. If we identified high quality meta-analyses, we report the pooled estimates but do not describe the results of individual component studies, except when outcome measures of interest are reported (e.g., quality of life, functional capacity) that were not quantitatively analyzed in a meta-analysis.

Adalimumab

Five fair-rated studies examined the efficacy of adalimumab in patients with RA.[26-30] Overall, 2,354 patients with active RA, not adequately responding to standard DMARD therapies, were included. In one study, participants remained on their standard antirheumatic therapy regardless of the DMARD therapy.[27] Two trials allowed only MTX as a concomitant DMARD,[26, 28] and in two studies no DMARDS were permitted as concomitant treatments.[29, 30] The longest study lasted 52 weeks;[28] study durations of the other trials were 12 weeks,[30] 24 weeks,[26, 27] and 26 weeks,[29] respectively. The most common dosing regimen was 40 mg adalimumab biweekly; however, doses ranged from 20 mg and 40 mg weekly to 80 mg biweekly. Across all dosing regimens, response rates compared to placebo on ACR20/50/70 were significantly greater for

adalimumab. Likewise, significantly more patients on adalimumab achieved improvements in health outcome measures (HAQ, SF-36, FACIT [Functional Assessment of Chronic Illness Therapy]) than patients on placebo. In the 52-week trial, 41.5 percent of patients on adalimumab 40 mg biweekly achieved an ACR50 response, compared to 9.5 percent on placebo ($P < 0.001$).[28] HAQ scores at 52 weeks also significantly favored the adalimumab 40 mg biweekly group (-59 vs. -0.25; $P < 0.001$). The radiographic progression of disease as assessed on the modified Sharp score was significantly less in adalimumab-treated patients at study endpoint ($P < 0.001$).

We pooled data of the five studies described above to receive summary effect sizes for a treatment regimen of 40mg adalimumab biweekly, which is the recommended dosage for the treatment of RA. Our outcomes of choice were pooled relative risk (benefit) ratios to achieve ACR 20/50/70 responses and the corresponding NNTs. The NNTs (benefit) for ACR20/50/70 are 3 (95%CI 2-4), 4 (95%CI 3-6), and 8 (95%CI 6-11), respectively. In other words, three patients have to be treated with adalimumab to achieve one more ACR20 response than placebo; four patients to achieve an additional ACR50 response and eight patients for an additional ACR70 response. Because of moderate heterogeneity (I^2-statistics), we used random effects models. The small number of component studies did not enable us to reliably assess publication bias. Reported data was not sufficient to calculate pooled estimates for HAQ. Study characteristics, pooled relative risk ratios, and forest plots are presented in Appendix E.

Anakinra

We identified one high quality meta-analysis that pooled one unpublished and three published RCTs.[31] Overall, this Health Technology Assessment from the United Kingdom (UK) included 1,007 patients. Pooled results presented statistically significantly greater improvements of anakinra- than placebo-treated patients on all outcome measures (ACR20/50/70, HAQ, Patient Global Assessment). The NNTs to achieve one additional responder on ACR20/50/70 were 7, 11, and 33, respectively. Adjusted indirect comparisons with two anti-TNF agents (etanercept, infliximab) suggested that anakinra may be significantly less effective at relieving clinical symptoms than anti-TNF drugs (ACR20: RR 0.21; 95%CI 0.10-0.32). We replicated this indirect comparison with a larger number of studies assessing anti-TNF drugs. Although our results also suggest that anakinra is significantly less effective in achieving an ACR20 response than TNF inhibitors as a class, the effect size was smaller in our calculations than in the results of the U.K. report and just reached statistical significance (RR: 0.67; 95%CI 0.45-0.99). Furthermore, indirect comparisons of ACR50 response rates did not present a statistically significant difference (RR: 0.69; 95%CI 0.39-1.22) Corresponding forest plots are presented in Appendix E.

A fair RCT, not included in the meta-analysis described above, reported similar results for patients with active RA who were treated with 100 mg anakinra or placebo for 24 weeks.[32] Anakinra had significantly higher response rates than placebo (ACR50: 17% vs. 8%; P < 0.01) and faired significantly better on all health outcome measures (HAQ: -0.29 vs. -0.18; P < 0.05; patient's assessment of disease activity: -17.7 vs. -8.9; P < 0.001; patient's assessment of pain: -19.0 vs. -11.7; P < 0.01).

We pooled data from three trials that provided sufficient information for critical, methodological appraisal.[32-34] We did not include a study that was published as an abstract only.[35] Our outcomes of choice were pooled relative risk (benefit) ratios to achieve ACR 20/50/70 responses and the corresponding NNTs. Because of moderate heterogeneity (I^2-statistics), we used random effects models. The NNTs (benefit) for ACR20/50/70 are 6 (95%CI 4-9), 10 (95%CI 7-18), and 35 (95%CI 75[harm]-14[benefit]) respectively. In other words, six patients have to be treated with anakinra to achieve one more ACR20 response than placebo; 10 patients to achieve an additional ACR50 response and 35 patients for an additional ACR70 response. The NNT for an ACR70 response did not reach statistical significance and thus the confidence interval includes the possibility of harm. The small number of component studies did not enable us to reliably assess publication bias. Reported data was not sufficient to calculate pooled estimates for HAQ. Study characteristics, pooled relative risk ratios, and forest plots are presented in Appendix E.

Etanercept

Two well conducted meta-analyses examined the efficacy of etanercept in patients with RA.[36, 37] Both studies reported significantly greater improvements for etanercept-treated patients at study endpoint. Pooled results indicated that 39 percent of patients treated with the recommended dose of 50 mg etanercept per week reached an ACR50 response, compared to four percent of patients on placebo (RR: 8.89; 95% CI 3.61 – 21.89).[36] The NNT to achieve one additional ACR50 response was 3.

Two fair trials compared etanercept to MTX over 52 weeks.[20-22] Although both studies failed to show statistically significant differences between etanercept (25 mg twice weekly) and MTX (20 mg/week) in health outcome measures (SF-36, HAQ, ASHI), and ACR response rates at study endpoints (52 weeks), radiographic outcomes were significantly better in patients on ETA than on MTX. Improved radiographic outcomes were maintained during an extension of the ERA (Early Rheumatoid Arthritis) trial to 24 months.[38] Both trials report statistically significantly better efficacy outcomes for etanercept- than for MTX-treated patients during the first months of treatment. One study was conducted in patients with early RA.[20, 22] The TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study, which was conducted in 686 patients with moderate to severe RA, provided similar results on health outcomes.[21] In

addition, this study compared etanercept and MTX mono-therapies to a combination of MTX (20 mg/week) and etanercept (25 mg twice weekly). Overall, the combination treatment achieved significantly better results on most outcome measures than etanercept and MTX alone. A significantly higher proportion of patients on the combination treatment than on MTX and etanercept reached ACR50 response after 52 weeks (69% vs. 43%; 69% vs. 48%; P < 0.0001 for both comparisons) or were on remission (DAS < 1.6; 35% vs. 13%; 35% vs. 16%; P< 0.0001 for both comparisons). Patients on the combination treatment presented a significantly greater retardation of joint damage than patients on MTX or etanercept monotherapy. This study reported no differences in adverse events.

A fair, 12-week trial assessed health-related quality of life as a secondary outcome measure (HAQ, SF-36, feeling thermometer) in patients with longstanding RA who had failed DMARD treatments.[39, 40] Two regimens of etanercept (10 mg and 25 mg twice weekly) were compared to placebo; no DMARDS were allowed. Both etanercept groups achieved statistically significantly greater improvements on all outcome measures compared to placebo.

A fair, 24-week study did not detect any synergistic effects of a combination treatment of etanercept (25 mg or 50 mg/week) and anakinra (100 mg/day) compared to etanercept monotherapy.[23] Overall, 242 patients who were on stable doses of MTX treatment were enrolled. At endpoint, combination treatment did not lead to greater efficacy than etanercept only. Furthermore, the frequency of serious adverse events was substantially higher in the combination groups (14.8% for 50 mg etanercept + anakinra, 4.9% for 25 mg etanercept + anakinra vs. 2.5% for etanercept only; no P-values reported). Likewise, withdrawals due to adverse events were higher in the combination groups than in the etanercept group (8.6% vs. 7.4%; no P-values reported).

We pooled data from five studies[21, 40-43] to receive summary effect sizes for a treatment regimen of 50 mg etanercept per week, which is the recommended dosage for the treatment of RA. Our outcomes of choice were pooled relative risk (benefit) ratios to achieve ACR20/50/70 responses and the corresponding NNTs. Because of high heterogeneity (I^2-statistics), we used random effects models. The high heterogeneity was mainly attributable to the Klareskog et al.[21] study, which was larger and of higher methodological quality than the remaining studies. Effect sizes in this study were smaller than in the other studies. No substantial differences in study populations, concomitant treatments, or study durations could explain the high heterogeneity. The most likely explanation is the small number of component studies and the higher methodological quality of the Klareskog et al. study. The directionality of the treatment effect is consistent for all studies and favors etanercept. The NNTs (benefit) for ACR20/50/70 were 2 (95%CI 1-5), 3 (95%CI 2-4), and 5 (95%CI 4-8), respectively. In other words, two patients have to be treated with etanercept to achieve one more ACR20

response than placebo; three patients to achieve an additional ACR50 response and eight patients for an additional ACR70 response. The small number of component studies did not enable us to reliably assess publication bias. Reported data was not sufficient to calculate pooled estimates for HAQ. Study characteristics, pooled relative risk ratios, and forest plots are presented in Appendix E.

Infliximab

Two well conducted meta-analyses determined the general efficacy of infliximab in RA.[37, 44] Pooled results of both studies report significantly greater improvements on all outcome measures than placebo. For 10 mg infliximab every 8 weeks, the ACR50 response rate was 30 percent compared to 5 percent for placebo. The NNT to achieve one additional response was 4.

A recent, good RCT enrolled 1,049 patients with early RA and compared the benefits of initiating treatment with MTX (20 mg) alone or a combination of MTX and infliximab (3 mg/kg or 6 mg/kg) over 52 weeks.[25] At endpoint, patients in the combination groups had significantly higher ACR-N (ACR composite score) improvements than patients on MTX monotherapy (38.9% [3 mg infliximab] vs. 46.7% [6 mg infliximab] vs. 26.4% [placebo]; $P < 0.001$); the ACR50 response was 45.6% vs. 40.4% vs. 32.1%, respectively. In addition, HAQ and SF-36 scores improved significantly more in the combination groups than in the MTX group. More patients in the combination groups had serious adverse events (14% vs. 11%; P-value not reported) and serious infections (5.6% [3 mg/kg infliximab] vs. 5.0% [6 mg/kg infliximab] vs. 2.1% [MTX]; $P = 0.02$ and $P = 0.04$) than patients on placebo. Response rates in this trial are similar to those reported in a Belgian uncontrolled trial over 62 weeks.[45] Response rates in this study could be raised by increasing the dosage of infliximab by 100 mg in patients not optimally responding. Results of an open-label extension of a 52-week RCT[46] included in one of the meta-analyses reported that response rates on HAQ and SF-36 were maintained for another year.[47] Radiographic progression of disease was significantly lower than in the MTX only group.

We pooled data from four studies[25, 46, 48] to receive summary effect sizes for a treatment regimen of 3-10 mg/kg infliximab every 4 to 8 weeks, which is the recommended dosage for the treatment of RA. Our outcomes of choice were pooled relative risk (benefit) ratios to achieve ACR 20/50/70 responses and the corresponding NNTs. We assumed that Paulus response rates are very similar to ACR response rates. Because of high heterogeneity (I^2-statistics), we used random effects models. The high heterogeneity was mainly attributable to the St. Clair et al. study,[25] which was larger and conducted in MTX naïve patients with early RA. Effect sizes in this study were smaller than in the other studies. In a sensitivity analysis we removed the St. Clair et al. study, which substantially reduced heterogeneity. Because it is unclear if the smaller treatment effect in the St.Clair et al. study is attributable to less random error in this large study or to true heterogeneity,

we present the pooled relative risks with and without St. Clair et al. in Appendix E. Data was not sufficient to pool for ACR70 response rates. The small number of component studies did not enable us to reliably assess publication bias. Reported data was not sufficient to calculate pooled estimates for HAQ. The NNTs (benefit) for ACR20/50 (without St. Clair et al.) was 3 (95%CI 2-4) and 4 (95%CI 3-5). In other words, three patients have to be treated with infliximab to achieve one more ACR20 response than placebo; four patients to achieve an additional ACR50 response. NNTs were identical for estimates including the St. Clair et al. study. Study characteristics, pooled relative risk ratios, and forest plots are presented in Appendix E.

Table 6: Summary of Efficacy Trials in Adult Patients with RA

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ETANERCEPT vs. INFLIXIMAB									
Geborek et al. 2002[18]	Non-randomized trial	404	12 months	ETA/ INF/ Leflunomide	ACR20/50	DAS28	Population-based; active RA; had failed at least one DMARD treatment; mean disease duration: 14.5 yrs.	ACR 20 response rates significantly greater for ETA than for INF at 3 months (P<0.02) and 6 months (P<0.05); no differences at 12 months	Fair
ADALIMUMAB									
Furst et al. 2003[27]	RCT	636	24 weeks	ADA +Standard RA therapy/ Placebo + Standard RA therapy	safety	ACR20/50/70, HAQ	Active RA for at least 3 months; DMARD naïve/or on stable regimen; mean disease duration: 10.5 yrs.	ACR20/50/70 response rates significantly greater with ADA than with placebo	Fair
Keystone et al. 2004[28]	RCT	619	52 weeks	ADA +MTX/ Placebo + MTX	Sharp, ACR 20, HAQ	ACR 50/70	Active RA; on stable MTX regimen; mean disease duration: 11 yrs.	ACR20/50/70 response rates significantly greater with ADA than with placebo	Fair
Van de Putte et al. 2003[30]	RCT	284	12 weeks	ADA/ Placebo	ACR 20	ACR50; ACR70; TJC; SJC; DAS28; HAQ.	Active RA; had failed at least one DMARD treatment; mean disease duration: 10 yrs.	ACR20/50/70 response rates significantly greater with ADA than with placebo	Fair

Table 6: Summary of Efficacy Trials in Adult Patients with RA (continued)

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Van de Putte et al. 2004[29]	RCT	544	26 weeks	ADA / Placebo	ACR20	ACR50/70, HAQ	Active RA; had failed at least one DMARD treatment; mean disease duration: 11 yrs.	ACR20/50/70 response rates significantly greater with ADA than with placebo	Fair
Weinblatt et al. 2003[26]	RCT	271	24 weeks	ADA+MTX / MTX + Placebo	ACR20, HAQ	ACR 50/70, SF-36	Active RA; on stable MTX regimen; had failed at least one other DMARD; mean disease duration: 12 yrs.	ACR20/50/70 response rates significantly greater with ADA than with placebo	Fair
ANAKINRA									
Clark et al. 2004[31]	MA	1007	> 6 mo	MTX +Placebo	ACR20/50/70	HAQ	Adults with RA	ACR20/50/70 response rates significantly greater with ANA than with placebo; adjusted indirect comparisons suggest that ANA is significantly less efficacious than anti-TNF	Good
Cohen et al. 2004[32]	RCT	501	24 weeks	AKA+MTX/ MTX+Placebo	ACR20	ACR50/70, HAQ	> 6 months history of active RA; stable MTX regimen; mean disease duration: 10.5 yrs.	ACR20/50/70 response rates at 24 weeks significantly greater with ANA than with placebo	Fair
ETANERCEPT									
Blumenauer et al. 2003[36]	MA	955	> 6 mo	ETA(+MTX) / (MTX+) placebo	ACR20/50/70		Adults with RA	ACR20/50/70 response rates significantly greater with ETA than with placebo	Good

Table 6: Summary of Efficacy Trials in Adult Patients with RA (continued)

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Jobanputra et al. 2002[37]	MA	1062	4 weeks – 1 year	ETA(+MTX) / (MTX +)placebo	ACR20/50/70	safety	Adults with RA	ACR20/50/70 response rates significantly greater with ETA than with placebo	Good
Bathon et al. 2000[20, 22, 38]	RCT	632	52 weeks	ETA / MTX	ACR20/50/70	SF-36, HAQ, ACR-N, modified Sharp	early, active RA; mean disease duration: 1 yr.	Up to 6 months significantly higher ACR 50/70 response rates for ETA than for MTX; no differences thereafter. At 12 months no differences in ACR20 but less joint erosion for ETA; no significant differences in SF-36, HAQ, and ASHI scores	Fair
Genovese et al. 2004[23]	RCT	242	24 weeks	ETA+MTX / ETA+ANA+ MTX	ACR50	ACR20/70, SF-36	> 6 months history of active RA; stable MTX regimen; mean disease duration: 10 yrs.	No additional benefit from ETA-ANA combination therapy; Adverse events rates significantly higher in combination than in ETA group	Fair
Klareskog et al. 2004[21]	RCT	682	52 weeks	ETA / MTX / MTX + ETA	Sharp	ACR20/50/70, HAQ	> 6 months history of active RA; unsatisfactory response to at least one DMARD other than MTX; mean disease duration: 6.5 yrs.	ETA + MTX regimen achieved better results on most outcome measures than ETA or MTX monotherapies	Good

Table 6: Summary of Efficacy Trials in Adult Patients with RA (continued)

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Moreland et al. 1999[39, 40]	RCT	234	12 weeks	ETA / Placebo	ACR20/50	SF-36, HAQ	Active RA; had failed 1 to 4 DMARD treatments other than MTX; mean disease duration: 12 yrs.	ACR20/50 response rates, HAQ and SF-36 scores significantly greater with ETA than with placebo	Fair
INFLIXIMAB									
Blumenauer et al. 2002[44]	MA	529	> 6mo	MTX+ Placebo	ACR20/50/ 70	Withdrawa ls, safety	Adults with RA	ACR20/50/70 response rates significantly greater with INF than with placebo	Good
Jobanputra et al. 2002[37]	MA	630	4 weeks – 1 year	MTX + Placebo	ACR20/50/ 70	safety	Adults with RA	ACR20/50/70 response rates significantly greater with INF than with placebo	Good
Durez et al.[45]	Uncontroll ed trial	511	62 weeks	INF + standard therapy	ACR20/50/ 70	Remission	Adult outpatients with active RA and insufficient response to standard INF therapy	Dose increase led to remission in 7% of patients after 62 weeks	N/A
St. Clair et al. 2004[25]	RCT	104 9	52 weeks	INF+MTX / MTX	ACR-N	ACR20/50/ 70, Sharp	Early RA, MTX naïve patients; mean disease duration: 0.9 yrs.	ACR20/50/70 response rates and HAQ scores were significantly greater with INF+MTX than with MTX	Fair

ADA: adalimumab MA: meta-analysis
AKA: anakinra MTX: methotrexate
ETA: etanercept
INF: infliximab

II. Juvenile Rheumatoid Arthritis (JRA)

Currently only etanercept is approved by the FDA for the treatment of JRA.

A. Summary of the Evidence

The evidence on the comparative effectiveness of TIMs for the treatment of JRA is poor. One RCT provides fair evidence that etanercept is more efficacious than placebo for the treatment of JRA. However, the highly selected study population is likely to compromise the external validity of this study. One uncontrolled study does not provide convincing evidence on the generally efficacy of infliximab.

B. Description of Studies

For JRA, we did not find any head-to-head trials that compared one TIM to another. We found one placebo-controlled RCT with a 3-month, uncontrolled, open-label run-in phase assessing the efficacy and safety of etanercept.[49] In addition, we included a retrospective analysis of data from a German registry for treatment of JRA[50] and one small, uncontrolled, open-label trial on infliximab.[51] We did not detect any studies on adalimumab, alefacept, anakinra, efalizumab. Included studies are presented in Table 7.

C. Study Population

Patients in the trials suffered from active polyarticular JRA and were between 4 and 17 years of age. Patients had active disease despite treatment with corticosteroids and MTX. Patients with concurrent medical conditions were excluded. The observational study included data of children with juvenile idiopathic arthritis, regardless of the subtype.

D. Outcome Measures

Response based on the Giannini criteria was the primary outcome measure for the open-label trial and the retrospective analysis. The primary outcome measure in the RCT was the number of patients with disease flare. It is unclear if this assessment was based on a validated rating scale. Additional outcome measures were the articluar severity score, duration of morning stiffness, degree of pain, and CRP. The uncontrolled infliximab trial also assessed functional disability (HAQ) and health-related quality of life (SF-36).[51]

E. Methodological Quality

In the etanercept study, only patients who had responded to etanercept treatment during a 3-month open-label run-in period were eligible for randomization (51 out of 69 patients). Therefore, the generalizability

of findings will be low and results are likely to overestimate the true treatment effect and underestimate the incidence of adverse events. The infliximab study had fatal methodological flaws.

F. Sponsorship

Two studies were funded by the pharmaceutical industry.[49, 50] The RCT was also supported by the National Institute of Health. The funding of the infliximab study could not be determined.[51]

G. Comparative Efficacy and Effectiveness

We did not identify any head-to-head trials.

H. General Efficacy

Because of the lack of head-to-head trials, we reviewed placebo-controlled trials. We have summarized evidence on the general efficacy of TIMs in the treatment of JRA.

Etanercept

Fifty-one patients were randomly assigned to etanercept (0.4 mg/kg twice weekly) or placebo.[49] Study duration was 4 months. Significantly more patients on placebo than on etanercept had a disease flare (81% vs. 28%; $P < 0.003$) during the study period. The median time to flare was 116 days for etanercept- and 28 days for placebo- treated patients ($P < 0.001$). As stated above, the highly selected population is likely to have lead to an overestimation of the treatment effects. During the 3 month open-label run-in phase, 64 percent of patients achieved a 50 percent improvement of symptoms based on the Gianinni criteria. This response rate is comparable to that of a retrospective analysis of data of 322 patients treated with etanercept from a German registry.[50] Sixty-one percent had a 50 percent improvement of symptoms at 3 months, 72 percent at 6 months. However, patients in this analysis were not limited to polyarticular JRA. The mean length of treatment in this study was 13.4 months. At one year, 82 percent of the non-systemic patients presented a 50 percent improvement. Subgroup analysis showed markedly lower response rates in patients with systemic arthritis.

Infliximab

One poor, uncontrolled study did not provide convincing evidence on the general efficacy of infliximab for the treatment of JRA.[51] This uncontrolled open-label trial enrolled 24 females with polyarticular JRA. Sixty-two percent of patients dropped out during the first year, 17 percent because of infusion reactions.

Completers-only analysis at one year reports significant improvements on clinical outcomes such as swollen or painful joints. However, neither HAQ nor SF-36 presented a statistically significant improvement at 1 year.

Table 7: Summary of Efficacy Trials in Patients with JRA

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ETANERCEPT									
Horneff et al. 2004[50]	Retrospective data analysis	322	13.4 months	None	Response based on Gianinni criteria;	Tolerability	Active juvenile idiopathic arthritis; had failed at least one DMARD; mean disease duration: NR	Number of tender and swollen joints significantly decreased during 3 months of treatment.	N/A
Lovell et al. 2000[49]	Uncontrolled open-label trial / RCT	51	4 months	ETA / Placebo	Response based on Gianinni criteria; number of patients with disease flare	Articular severity score, pain, CRP	Active polyartricular JRA; had failed corticosteroid and MTX treatment; mean disease duration: 5.8 yrs.	Significantly more patients on ETA than on placebo achieved 50% improvement	Fair

ADA: adalimumab
AKA: anakinra
ETA: etanercept
INF:infliximab
MA: meta-analysis
MTX: methotrexate

III. Ankylosing spondylitis (AS)

The following drugs are currently approved by the FDA for the treatment of AS: etanercept and infliximab.

A. Summary of the Evidence

Overall, the evidence on the comparative effectiveness of TIMs for the treatment of AS is poor. Good to fair evidence from five RCTs exists that etanercept and infliximab are significantly more efficacious than placebo for the treatment of AS. Treatment effects are large and consistent across studies. However, significant differences in study characteristics make this evidence insufficient to identify differences in efficacy among TIMs.

B. Description of Studies

For AS, we did not find any head-to-head trials comparing one TIM to another. We found five placebo-controlled trials; three trials assessed the efficacy of etanercept,[52-54] two the efficacy of infliximab.[55, 56] We did not detect any studies on adalimumab, alefacept, anakinra, and efalizumab. Included studies are presented in Table 8.

C. Study Populations

All patients suffered from active AS and were diagnosed based on the modified New York criteria.[57] Disease duration and concomitant treatments varied across studies. Most patients used NSAIDS in addition to the study medication. The etanercept trials allowed corticosteroids and DMARDs as concomitant treatments.[52-54] Patients in the infliximab trials were permitted to take only NSAIDS in addition to the study drug.[55, 56] One study examined the efficacy of infliximab in patients with severe AS.[55] Patients with an autoimmune disease other than AS, spinal fusion, a history of active listeriosis or mycobacterial infection, or recent antibiotic treatment were generally excluded from studies.

D. Outcome Measures

Most trials assessed response rates as defined by the Assessments in Ankylosing Spondylitis Working Group (ASAS).[58] This scale (ASAS20/50/70 [figures refer to percentage improvement]), combines measures of global disease activity with functional capacity, pain, and acute phase laboratory parameters (see Appendix D). In addition, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was frequently assessed. Two studies evaluated health outcomes.[51, 55]

E. Methodological Quality

Study quality varied; one study was rated good,[54] four were rated fair.[52, 53, 55, 56] These "fair" ratings, however, are probably more attributable to inadequate reporting than to methodological flaws. Randomization methods and blinding were generally adequate; all studies used a double-dummy design (i.e., using an identical container for active treatment and placebo) to guarantee blinding. A high incidence of injection site reactions among users of etanercept de facto often overthrew blinding efforts.

F. Sponsorship

All trials were funded by the pharmaceutical industry.

G. Comparative Efficacy and Effectiveness

We did not identify any head-to-head trials.

H. General Efficacy

Because of the lack of head-to-head trials, we reviewed placebo-controlled trials. We have summarized evidence on the general efficacy of TIMs in the treatment of AS. This, however, does not provide evidence on the comparative efficacy and tolerability of TIMs.

Etanercept

One good[54] and two fair[52, 53] trials evaluated the safety and efficacy of etanercept (25 mg/twice weekly) for the treatment of AS. Studies lasted from 12 to 24 weeks. Overall, these trials included 401 patients. All studies were conducted in patients with moderate to severe AS and allowed concomitant treatment with DMARDs and corticosteroids; one study, however, limited DMARDS to MTX or sulfasalazine.[54] Results of all three trials reported that significantly more patients receiving etanercept than placebo presented clinical improvements on all outcome measures (ASAS20/50/70, BASFI [Bath Ankylosing Spondylitis Functional Index], BASDAI) at study endpoint. Significant differences in efficacy started as early as in week 2. Concomitant DMARD treatment did not influence the magnitude of the treatment effect. In the good-rated trial, 57 percent of patients on etanercept and 22 percent of patients on placebo achieved an ASAS20 response after 24 weeks ($P < 0.001$).[54] Patients receiving etanercept also achieved significantly greater positive responses on the majority of secondary outcomes.

Infliximab

Two fair trials assessed the efficacy and safety of infliximab (5 mg/kg) for the treatment of AS.[55, 56] The larger trial lasted 24 weeks and enrolled 279 patients with moderate to severe AS,[56] and the smaller study

(n = 70) assessed the efficacy and safety of infliximab in patients with severe AS over 12 weeks.[55] Neither trial allowed concomitant DMARD or corticosteroid treatments. Intention-to-treat results of both trials report significantly greater improvements of infliximab- than of placebo-treated patients on all primary outcome measures (ASAS20/40, BASDAI). After 24 weeks 61 percent of infliximab- and 19 percent of placebo-treated patients achieved an ASAS20 response ($P < 0.001$); 51 percent and 11 percent respectively reported a 50 percent improvement on BASDAI.[56] However, in this study the mean disease duration was 5.5 years longer in the placebo group than in the infliximab group (no P-value reported) which might bias the treatment effect. In a 2 year open-label extension hospital admissions for infliximab-treated patients were significantly reduced compared to the 12 months before the start of the trial (10% vs. 41%).[59] This corresponds to a reduction of mean inpatient days from 11.1 days before infliximab treatment to 2.9 days after 2 years of treatment.

Table 8: Summary of Efficacy Trials in Adult Patients with AS

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ETANERCEPT									
Calin et al. 2004[52]	RCT	84	12 weeks	ETA+standard treatment / Placebo+standard treatment	ASAS 20	ASAS50/70, Schober's test	Active, moderate to severe AS; mean disease duration: 12.5 yrs.	Response rates on ASAS20/50/70 were significantly greater for ETA than for placebo	Fair
Davis et al. 2003[54]	RCT	277	24 weeks	ETA+standard treatment / Placebo+standard treatment	ASAS20	ASAS50/70, BASDAI	Active, moderate to severe AS; mean disease duration: 10.3 yrs.	Response rates on ASAS20/50/70 were significantly greater for ETA than for placebo	Good
Gorman et al. 2002[53]	RCT	40	16 weeks	ETA+standard treatment / Placebo+standard treatment	ASAS20	ASAS50/70, BASFI, Schober's test	Active, moderate to severe AS; mean disease duration: 13.5 yrs.	Patients on ETA had significantly greater improvements on BASFI and ASAS20 than patients on placebo	Fair

Table 8: Summary of Efficacy Trials in Adult Patients with AS (continued)

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Braun et al. 2002,[55] 2003,[60] 2005[61, 62]	RCT	70	12 weeks	INF / Placebo	BASDAI	BASFI, BASMI, SF-36	Active, moderate to severe AS; mean disease duration: 15.6 yrs.	Patients on INF had significantly greater improvements on BASDDAI, BASFI, and SF-36 than patients on placebo	Fair
Van der Heijde et al. 2005[56]	RCT	279	24 weeks	INF / Placebo	ASAS20	ASAS40, BASDAI	Active, severe AS; mean disease duration: 10.5 yrs.	Patients on INF had significantly greater improvements on BASDDAI, BASFI, and ASAS40 than patients on placebo	Fair

IV. Psoriatic arthritis (PsA)

The following drugs are currently approved by the FDA for the treatment of PsA: adalimumab, etanercept, and infliximab.

A. Summary of the Evidence

Overall, the evidence on the comparative effectiveness of TIMs for the treatment of PsA is poor. Fair evidence from two RCTs exists that etanercept is significantly more efficacious than placebo for the treatment of PsA. Two RCTs provide fair evidence on the general efficacy of infliximab and one RCT provides fair evidence that adalimumab is more effective than placebo. Treatment effects are large and consistent across studies. However, significant differences in study characteristics make this evidence insufficient to identify differences in efficacy among TIMs.

B. Description of Studies

For PsA, we did not find any head-to-head trials comparing one TIM to another. We found five placebo-controlled trials assessing the efficacy of etanercept.[63, 64] infliximab[65-67] and adalimumab.[68] The studies ranged in duration from 12 to 50 weeks. We did not find any studies on alefacept, anakinra, and efalizumab. Included studies are presented in Table 9.

C. Study Populations

All patients suffered from active PsA. However, the definition of active disease varied across studies. Two trials enrolled patients with at least three swollen and three tender joints at screening;[63, 68] two other studies included patients with at least five swollen and five tender joints,[66, 67, 69] and the third study employed additional criteria which utilized clinical sub-types of PsA to establish the presence of PsA.[64] All five trials consisted of patients who had previously failed DMARD and/or MTX therapies.

D. Outcome Measures

All trials assessed response rates as defined by the ACR. In addition, all five studies used the disease specific Psoriatic Arthritic Response Criteria (PsARC) which is composed of a patient global self-assessment, a physician global assessment, a swollen joint score, and a tender joint score. Further details of this scale are presented in Appendix D. In addition, the Psoriasis Area and Severity Index (PASI) was used in all five studies to measure improvements in both the amount of psoriatic plaque, as well as the severity of the disease. The SF-36 and HAQ were used to assess quality of life. Additionally, one study used a modified Sharp score to assess disease progression.[64]

E. Methodological Quality

All five studies received a fair quality rating. However, the "fair" rating was probably more attributable to poor reporting of methods than to methodological flaws.

F. Sponsorship

All trials were funded by the pharmaceutical industry.

G. Comparative Efficacy and Effectiveness

We did not identify any head-to-head trials.

H. General Efficacy

Because of the lack of head-to-head trials, we reviewed placebo-controlled trials. We have summarized evidence on the general efficacy of TIMs in the treatment of PsA. This, however, does not provide evidence on the comparative efficacy and tolerability of TIMs.

Etanercept

Two fair studies examined the efficacy of etanercept in patients with PsA.[63, 64] Overall, 265 patients with active PsA, not adequately responding to standard DMARD therapies, were included. In both studies patients were allowed to continue MTX therapy as long as it had been stable for four weeks prior. One study lasted 12 weeks;[63] the other trial was double-blinded for 24 weeks.[64] Both studies had the same dosing regimen of 25 mg of etanercept twice-weekly subcutaneous injections. In both studies response rates compared to placebo on ACR20 were significantly greater for etanercept. In the 12 week study, 87 percent of the patients on etanercept achieved a PsARC response compared to 23 percent on placebo ($P < 0.0001$).[63] The longer study had similar results in patients achieving a PsARC response at 12 weeks; 72 percent of the patients on etanercept responded versus 31 percent on placebo.[64] Quality of life was significantly improved as measured by the HAQ in both studies. Mean improvements were 83 percent in etanercept- compared to 3 percent in placebo-treated patients in the 12 week study ($P < 0.0001$). In the longer study, at 24 weeks the mean improvement was 54 percent in the etanercept group and 6 percent in the placebo group ($P < 0.0001$). The longer study assessed the radiographic progression of disease at 24 weeks and found the annualized modified Sharp score was significantly less in etanercept- than in placebo-treated patients ($P = 0.0001$).

Infliximab

We found two fair studies on the use of infliximab in patients with PsA.[65-67] Overall, 304 patients with active PsA, not adequately responding to standard DMARD therapies, were included. In both studies patients were allowed to continue MTX therapy as long as it had been stable for four weeks prior. The earlier study was double-blinded for 16 weeks;[69] the other trial was double-blinded for 24 weeks with cross-over allowed at week 16 for non-responders.[66] Both studies had the same dosing regimen of 5 mg/kg of infliximab at weeks 0, 2, 6, 14 and the longer study had an additional injection at week 22. In both studies response rates compared to placebo on ACR20 were significantly greater for infliximab. In the earlier study, 86 percent of the patients on infliximab achieved a PsARC response compared to 12 percent on placebo ($P < 0.001$).[69] The bigger study had similar results in patients achieving a PsARC response at 14 weeks; 77 percent of the patients on infliximab responded versus 27 percent on placebo.[66] Quality of life was significantly improved as measured by the HAQ in both studies. Mean improvements were 49.8 percent in infliximab compared to -1.6 percent in placebo-treated patients in the smaller study ($P < 0.001$). In the bigger study, at 14 weeks the mean improvement was 48.6 percent in the infliximab group and an 18.4 percent loss in the placebo group ($P < 0.001$).

Adalimumab

At this time only one trial has been reported on in the literature on the use of adalimumab in PsA.[68] The included 313 patients suffering from moderate to severe PsA, which was defined as having at least 3 swollen joints and 3 tender or painful joints, who had an inadequate response or intolerance to NSAID therapy. Patients were allowed to continue current methotrexate therapy as long as the dose had been stable for 4 weeks. The double-blinded phase of the study was 24 weeks, but patients who failed to achieve at least a 20 percent decrease in both swollen and tender joint counts on two consecutive visits could receive rescue therapy with corticosteroids or DMARDs. The dose was 40 mg/kg every other weeks. The adalimumab group saw significantly greater response rates on ACR 20/50/70 than the placebo group (all $P < 0.001$). Sixty percent of the adalimumab group responded according to the PsARC compared to 23 percent on placebo (P = NR).

Table 9: Summary of Efficacy Trials in Adult Patients with PsA

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ADALIMUMAB									
Mease et al. 2005[68]	RCT	313	24 weeks	ADA + MTX / Placebo + MTX	ACR 20, change in modified Sharps score	ACR50/70, HAQ, PsARC, SF-36	Active PsA; failed at least one DMARD; mean disease duration: 9.5 years	ADA had significantly better outcomes than placebo	Fair
ETANERCEPT									
Mease et al. 2000[63]	RCT	60	12 weeks	ETA + MTX / Placebo + MTX	PsARC, PASI	ACR20/50/70, HAQ	Active PsA; failed at least one DMARD; median disease duration: 10 years	ETA had significantly better outcomes than placebo	Fair
Mease et al. 2004[64]	RCT	205	72 weeks (24 blinded, 48 open-label)	ETA + MTX / MTX + Placebo	ACR 20	ACR 50/70, PsARC, PASI, SF-36, HAQ	Active PsA; failed at least one DMARD; mean disease duration 9.1 years	ETA had significantly better outcomes than placebo	Fair

Table 9: Summary of Efficacy Trials in Adult Patients with PsA (continued)

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
INFLIXIMAB									
Antoni et al. IMPACT Study 2005[65]	RCT	104	50 weeks	INF + 1 DMARD / Placebo + 1DMARD	ACR20 and PASI	ACR 50/70 DAS; HAQ; ratings of enthesitis and dactylitis; PSARC.	Active PsA; failed at least one DMARD; mean disease duration 11.4 years	INF had significantly better outcomes than placebo	Fair
Antoni et al.[66] and Kavanaugh et al.[67]	RCT	200	24 weeks	INF + MTX / Placebo + MTX	ACR20; HAQ; SF-36	ACR50/70; PsARC; PASI; dactylitis and enthesopathy	Active PsA; failed at least one DMARD; mean disease duration	INF had significantly better outcomes than placebo	Fair

V. Crohn's Disease

Only infliximab currently is approved by the FDA for the treatment of Crohn's disease.

A. Summary of the evidence

Overall, the evidence on the comparative effectiveness of TIMs for the treatment Crohn's Disease is poor. No evidence directly comparing the efficacy and safety of one TIM to another could be found, and evidence was insufficient to make indirect comparisons.

Fair to good evidence from RCTs exists that infliximab is significantly more efficacious than placebo for initial (i.e., patients with refractory Crohn's disease that had not received a TIM during the previous 12 weeks) and maintenance treatment of Crohn's disease. Treatment effects are large and evident within 1 to 2 weeks. On average, a two to three-fold increase in the number of responders was observed among infliximab-treated patients compared to placebo. Maintenance treatment with infliximab maintains a response significantly longer than placebo, although infections and infusion-related reactions are more common with long-term treatment. Infliximab is also more efficacious than placebo in fistulizing Crohn's disease (a serious complication of Crohn's disease characterized by abnormal communication between the gut and the skin, with small bowel or colonic contents draining to the skin surface). Fair evidence from one small RCT exists that etanercept is no more efficacious than placebo and adverse reactions are more common in etanercept- than placebo-treated patients. We did not find any evidence on the efficacy and safety of adalimumab, alefacept, anakinra, and efalizumab for the treatment of Crohn's disease.

Although some studies allowed stable doses of other immunomodulatory agents, no conclusive evidence exists to determine whether combination treatment of etanercept and infliximab with other agents (azathioprine, 6-MP, MTX) leads to clinically and statistically greater improvements than monotherapy.

B. Description of Studies

For Crohn's disease, we did not find any head-to-head RCTs comparing one TIM to another. We found six placebo-controlled trials and two observational studies that assessed the efficacy and safety of infliximab. We also identified one trial that compared the efficacy and safety of etanercept to placebo. We did not find any studies on adalimumab, alefacept, anakinra, or efalizumab. Included studies are presented in Table 10.

C. Study Populations

All patients suffered from active Crohn's disease of at least 3 months' duration. Some patients also had abdominal or perianal fistulas. Most studies included patients with a Crohn's Disease Activity Index (CDAI) between 220 and 400. However, some trials included patients with CDAI scores as high as 450 (i.e., more severe disease). The non-randomized studies were population-based and followed consecutive patients treated with infliximab.[70, 71] One study included patients with other inflammatory bowel diseases, including ulcerative colitis and indeterminate colitis; however, 88 percent of patients had a diagnosis of Crohn's disease.[70] Disease duration and concomitant treatments varied across studies. On average, disease duration ranged from 8 to 12 years. Many studies allowed concomitant treatment with 5-ASA, antibiotics, corticosteroids, azathioprine, 6-MP, or MTX.

D. Outcome Measures

Most studies utilized the National Cooperative Crohn's Disease Study rating scale, the CDAI, to characterize disease severity. The CDAI assesses eight related variables (e.g., number of liquid or soft stools per day, severity of abdominal pain or cramping, general well-being, the presence or absence of extraintestinal manifestations of disease, the presence or absence of abdominal mass, the use or nonuse of antidiarrheal drugs, the hematocrit, and body weight; see Appendix D) to yield a composite score between 0 and 600; scores below 150 indicate remission while scores above 450 indicate severe illness. Response commonly was characterized by a CDAI reduction greater than or equal to 70 points. Several studies utilized the Inflammatory Bowel Disease Questionnaire (IBDQ). The IBDQ identifies 32 individual items categorized within four major quality of life domains (primary bowel symptoms, systemic symptoms, social impairment, and altered emotional function). Some studies assessed CRP concentrations as an intermediate marker for inflammation. In studies specifically designed to assess fistulizing disease, outcomes included 50 percent reduction in the number of draining fistulas or a complete absence in draining fistulas.

E. Methodological Quality

Although all included trials were given a "fair" quality rating, study quality varied. Several trials did not report the number of patients lost to follow up, and some trials had loss to follow-up exceeding 50%. Smaller trials may not have had sufficient sample size to detect differences in health outcomes (from a patient's perspective). Randomization methods and blinding were generally adequate; all studies used a double-dummy design (i.e., using 0.1% human serum albumin placebo in an identical container to active treatment) to guarantee blinding; method of allocation concealment was rarely reported.

F. Sponsorship

All studies, except the observational studies, were funded by the pharmaceutical industry. Several studies also received funding from the National Institutes of Health or the FDA.

G. Comparative Efficacy and Effectiveness

We did not identify any head-to-head RCTs or observational studies. Additionally, we were unable to make indirect comparisons because there were too few trials and existing trials were too different in design.

H. General Efficacy

Because of the lack of head-to-head trials, we reviewed placebo-controlled trials. We summarized evidence on the general efficacy of TIMs in the treatment of Crohn's disease; however, this does not provide evidence on the comparative efficacy and tolerability of TIMs.

Etanercept

A single fair trial compared etanercept to placebo.[72] Forty-three patients with moderate to severe Crohn's disease (CDAI score 220 to 450) were randomized to receive subcutaneous placebo or etanercept 25 mg twice weekly for 8 weeks. Patients were at least 12 years of age and could not have taken another TIM within 12 weeks. Primary outcome measures were clinical response (CDAI decrease ≥ 70 points) or remission (CDAI score < 150). No statistically significant differences between etanercept and placebo in clinical response or remission were detected at any time. Furthermore, no differences in quality of life or the rate of fistula improvement were observed. Compared to placebo, more etanercept-treated patients reported adverse events (74% vs. 50%; P-value not reported); injection site reactions and headache were the most commonly reported adverse events.

Infliximab

Six fair trials compared infliximab to placebo.[73-78] Two trials assessed the efficacy of a single infliximab infusion,[73, 78] and two trials assessed the efficacy of repeated maintenance infusions.[74, 76] Two additional trials compared infliximab to placebo in patients with Crohn's disease with multiple draining abdominal or perianal fistulas.[75, 77] Two uncontrolled studies reported the efficacy and tolerability of infliximab in consecutively treated patients with inflammatory bowel disease (including Crohn's disease, ulcerative colitis, and indeterminate colitis).[70, 71]

Two trials examined the efficacy of a single infusion of infliximab at doses of 5, 10, and 20 mg/kg in Crohn's disease (CDAI scores between 220 and 400).[73, 78] Randomized patients were refractory to corticosteroids, mesalamine, 6-mercaptopurine, or azathioprine. Both trials demonstrated significantly better efficacy of a single infusion of infliximab compared to placebo. In the smaller European trial, 30 patients with active Crohn's disease were randomized to a single 5, 10, or 20 mg/kg dose of infliximab or placebo.[73] At 4 weeks, all patients underwent a full colonoscopy and ileoscopy and a Crohn's Disease Endoscopy Index of Severity (CDEIS) score was calculated; CDAI scores and CRP concentrations also were assessed. All doses of infliximab were significantly better than placebo at 4 weeks ($P < 0.05$). In the 12 week multinational trial,[78] 108 patients randomized to infliximab 5, 10, or 20 mg/kg or placebo were assessed at 2, 4, and 12 weeks. Responders were characterized as having a CDAI reduction of 70 points or more. Quality of life with respect to bowel function (IBDQ) and CRP concentrations also were assessed. At 4 weeks, compared to placebo, significantly more infliximab-treated patients were characterized as CDAI responders ($P < 0.005$). Quality of life scores and CRP concentrations also were significantly better than placebo in patients treated with infliximab ($P < 0.05$ and $P < 0.01$, respectively).[79]

To assess the ability of infliximab to maintain treatment response, maintenance infusions of infliximab were compared to placebo in a 36 week and a 54 week trial.[74, 76] In both trials, patients with Crohn's disease (CDAI scores between 220 and 400) responding to an initial infliximab infusion were randomized. One trial was a continuation of the 12 week trial described above;[78] in this trial 73 patients responding to the initial 5, 10, or 20 mg/kg infusion of infliximab were randomized to receive infliximab 10 mg/kg repeated at 8-week intervals for four additional doses or placebo.[76] Retreatment with infliximab maintained the initial treatment benefit in 62% of patients compared to 37% of placebo-treated patients ($P = 0.16$). In the ACCENT 1 trial,[74] 335 patients responding (CDAI decrease $\geq$ 70 points) at 2 weeks to an initial infliximab infusion of 5 mg/kg were randomized to repeat infusions of placebo, infliximab 5 mg/kg, or infliximab 10 mg/kg at week 2 and 6 and then every 8 weeks thereafter until week 46. Primary outcome measures included time to loss of response (CDAI $\geq$ 175) and the proportion of week 2 responders in remission (CDAI < 150) at week 30. Compared to placebo, infliximab-treated patients had a significantly longer time to loss of response ($P < 0.001$) and the odds of being in remission at week 30 were nearly three times greater. Infliximab maintenance therapy demonstrated greater mucosal healing compared with the placebo maintenance group at both weeks 10 and 54. Infliximab-treated patients also had fewer hospitalizations, fewer surgeries, decreased corticosteroid use, fewer hours lost from work, and better quality of life scores ($P < 0.05$ for all).[80, 81]

Two trials [75, 77] compared the efficacy and safety of infliximab to placebo in patients with enterocutaneous or perianal fistulas, a serious complication of Crohn's disease characterized by abnormal communication between the gut and the skin with small bowel or colonic contents draining to the skin surface.[75, 77] A 34 week study randomized 94 adult patients who had abdominal or perianal fistulas of at least 3 months' duration as a complication of Crohn's disease to placebo, 5 mg/kg infliximab, or 10 mg/kg infliximab.[75] Doses were administered intravenously at baseline, 2 and 6 weeks. Compared to placebo, significantly more infliximab-treated patients had a reduction of 50% or more from baseline in the number of draining fistulas observed at 2 or more consecutive visits ($P < 0.05$). Likewise, 55 percent of patients on infliximab 5 mg/kg and 38 percent of patients on 10 mg/kg had closure of all fistulas, compared to 13 percent of patients assigned to placebo ($P = 0.001$ and $P = 0.04$, respectively). In the ACCENT II trial,[77] 195 patients with Crohn's disease and one or more draining abdominal or perianal fistulas who responded to 3 open-label 5 mg/kg infusions of infliximab were randomized to maintenance treatment with 8-week infusions of infliximab 5 mg/kg or placebo. Patients that did not respond to open-label treatment (n = 87) also were followed for safety. The primary outcome was defined as time to loss of response. On average, patients randomized to infliximab maintenance therapy maintained their response for more than 26 weeks longer than placebo ($P < 0.001$). At week 54, 36 percent of infliximab-treated patients had a complete absence of draining fistulas compared to 19% of placebo-treated patients ($P = 0.009$). At 6 weeks, infliximab also was more efficacious than placebo in a subgroup of women with rectovaginal fistulas (fistula closure 61% and 45%, respectively).[82] Compared to placebo, infliximab-treated 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 and procedures (65 vs. 126; $P < 0.05$).[83]

Observational evidence of efficacy comes from two case series studies.[70, 71] A Stockholm County, Sweden, population based cohort study supports the general efficacy of infliximab in patients with inflammatory bowel disease.[70] Among 217 consecutive patients treated with infliximab (191 patients had Crohn's disease), 75 percent (n = 163) demonstrated at least some degree of response; 48 percent of patients (n = 104) achieved remission. However, a 2.8 percent mortality rate was observed, emphasizing the need for vigilance in drug surveillance. A second case series analysis in Edmonton, Alberta, reviewed 109 consecutive patients with inflammatory and/or fistulizing Crohn's disease who received infliximab.[71] A clinical response was documented in 73 percent (n = 80) of patients; 55 percent of patients (n = 61) had a partial response and 17 percent (n = 19) had a full response. No deaths were reported.

Table 10: Summary of Efficacy Trials in Adult Patients with Crohn's Disease

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ETANERCEPT									
Sandborn et al., 2001[72]	RCT	43	8 weeks	ETA / placebo	CDAI	Rate of fistula improvement, fistula closure, IBDQ	Patients 12 and older with moderate to severe Crohn's disease	No difference between ETA and placebo in response, remission, quality of life, or fistula improvement	Fair
INFLIXIMAB									
D'Haens et al., 1999[73]	RCT	30	4 weeks	INF / placebo	CDEIS	CDAI, CRP	> 6 month history of moderate to severe active Crohn's disease refractory to corticosteroids, mesalamine, 6-mercaptopurine, or azathioprine	Significantly more improvement in CDEIS, CDAI, and CRP for all doses of INF compared to placebo	Fair

Table 10: Summary of Efficacy Trials in Adult Patients with Crohn's Disease (continued)

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
INFLIXIMAB									
Hanauer et al., 2002[74, 80, 81]	RCT	573	54 weeks	INF / placebo	Proportion of week 2 responders in remission at week 30; time to loss of response	Employment status/work loss, surgeries, SF-36, IBDQ, hospitalizations, corticosteroid discontinuation	> 3 month history of moderate to severe Crohn's disease and CDAI response at 2 weeks to single dose 5mg/kg INF	INF-treated patients were more likely to sustain clinical response, had a shorter time to loss of response, better quality of life, fewer surgeries and hospitalizations, and less work loss than placebo-treated patients	Fair
Ljung et al., 2004[70]	Case series	217	All patients with IBD treated with infliximab between January 1999-April 2001	INF	Adverse events	Clinical response, remission, failure	Consecutive patients with in Stockholm County were included in the study database at the time of first infusion	Overall response rate was 75% with 48% of patients achieving remission	N/A

Table 10: Summary of Efficacy Trials in Adult Patients with Crohn's Disease (continued)

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
INFLIXIMAB									
Present et al., 1999[75]	RCT	94	34 weeks	INF / placebo	Reduction of 50% or more in the number of draining fistulas	Closure of all fistulas, time to beginning of response and duration of response, CDAI, PDAI	Adults with Crohn's disease with multiple draining abdominal or perianal fistulas of at least 3 months' duration	Significantly greater reduction in the number of draining fistulas, shorter time to response, and greater improvement in PDAI for INF compared to placebo; no difference in CDAI at endpoint	Fair
Rutgeerts et al., 1999[76]	RCT	73	36 weeks	INF / placebo	Maintained response (CDAI ≥ 70) or remission (CDAI < 150), discontinuation rate (efficacy)	Mean CDAI, IBDQ, CRP	> 6 months history of moderate to severe active Crohn's disease and previous response to INF	Statistically modest improvements in response, remission, time to loss of response, CDAI, IBDQ and CRP for INF compared placebo	Fair

Table 10: Summary of Efficacy Trials in Adult Patients with Crohn's Disease (continued)

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
INFLIXIMAB									
Sample et al., 2002[71]	Case series	109	≥ 8 weeks from initial treatment	INF	Adverse events	Clinical response, corticosteroid tapering	Consecutive patients with Crohn's disease treated with INF	73% of INF-treated patients had a clinical response and steroids were tapered in 53%; AEs 7%	N/A
Sands et al., 2004[77, 82, 83]	RCT	282	54 weeks	INF / placebo	Time to loss of response after randomization (week 14)	CDAI, IBDQ, hospitalizations, hospitalization days, surgeries	> 3 month history of active Crohn's with multiple draining fistulas and 14 week response (≥ 50% closure) to 3 open label doses of INF 5mg/kg	Significantly longer time to loss of response, fewer draining fistulas, greater improvement in CDAI and IBDQ, fewer hospitalizations ,hospitalization days, and surgeries for INF compared to placebo	Good
Targan et al., 1997[78, 79]	RCT	108	12 weeks	INF / placebo	Response at 4 weeks (≥ 70 point reduction in CDAI)	IBDQ, CRP	> 6 month history of moderate to severe Crohn's disease refractory to corticosteroids, mesalamine, 6-mercaptopurine, or azathioprine	Significantly more responders and greater improvement in IBDQ and CRP for INF compared to placebo	Fair

KEY QUESTION 2

What are the comparative incidence and severity of complications of included drugs?

A. Summary of the Evidence

The overall grade of the evidence on the comparative tolerability is poor. The only direct evidence on the comparative incidence of adverse events comes from one non-randomized, open-label trial comparing etanercept to infliximab in patients with RA.[18] This 12-month study did not report any differences in tolerability. Evidence from placebo-controlled trials and observational studies is insufficient to draw conclusions about the comparative tolerability and safety of TIMs.

In efficacy studies TIMs were generally well tolerated. Injection site reactions (adalimumab, anakinra, etanercept) and infusion reactions (infliximab) were the most commonly and consistently reported adverse events. Some infusion reactions, however, appeared to be more serious than injection site reactions. One percent of patients had severe acute reactions that resembled acute anaphylactic conditions or led to convulsions. Injection site reactions were the most common reason for discontinuation due to adverse events. Incidence rates appear to be significantly higher with anakinra than with anti-TNF drugs.

Long-term, rare but serious adverse events such as malignancies, serious infections, or autoimmunity are a cause of concern for all TIMs and could not be assessed reliably in efficacy trials. Some observational studies indicate that infliximab might have a higher risk of granulomatous infections than etanercept.[84-88] Hepatotoxicity has been reported for infliximab but not for other TIMs. An increased risk of congestive heart failure has been reported for anti-TNF drugs but not for anakinra. The current evidence on rare but severe adverse events is limited to observational evidence such as case reports, database reviews, and open-label extension studies of RCTs which cannot reliably establish a causal relationship. Nevertheless, because of the absence of studies with the methodological strength to account for rare adverse events, even weak evidence may be important.

B. Overall Tolerability

Most studies that examined the general efficacy of TIMs also determined their tolerability. In addition, some RCTs had an open-label extension phase of up to three years.[47, 62, 89] Methods of adverse events assessment, however, differed greatly. Few studies used objective scales such as the UKU-SES (Utvalg for Kliniske Undersogelser Side Effect Scale) or the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often determining whether assessment methods were unbiased and

adequate was difficult. Rarely were adverse events prespecified and defined. Short study durations and small sample sizes additionally limited the validity of adverse events assessment with respect to rare but serious adverse events.

Only two RCTs were designed to assess adverse events as primary outcomes.[27, 90-92] Most published studies assessing adverse events were post hoc analyses or retrospective reviews of databases. We included observational studies if the sample size was larger than 100 and the study duration was at least 1 year (Table 11).

Overall, TIMs appeared to have a good tolerability profile, although some rare but serious adverse events such as serious infections, lymphoma, leucopenia, or demyelinations are of concern.[70, 90-94] Discontinuation rates because of adverse events in patients treated with TIMs ranged from 3 to 16 percent and generally did not differ significantly from those in patients treated with placebo. A 3-year extension study of an RCT assessing infliximab therapy in 70 patients with AS, reports an overall loss to follow-up due to adverse events of 16 percent during 3 years.[62] A two year open-label extension study in children with JRA reports a serious adverse events rate of 16 percent, primarily due to infections.[89]

Injection site reactions, abdominal pain, nausea, headache, diarrhea, upper respiratory tract infections, and urinary tract infections were the most commonly reported adverse events.

The only head-to-head study that we found for efficacy outcomes also assessed differences in tolerability and safety between etanercept and infliximab.[18] This study used the adverse reaction terminology from the WHO to determine adverse events. Overall, no significant differences in adverse events were reported between etanercept and infliximab. The overall discontinuation rates at 20 months were also similar (etanercept 21%; infliximab 25%).

One large, multinational RCT was designed primarily to evaluate the safety of anakinra over 6 months.[90-92] A total of 1,414 patients were randomized to anakinra (100 mg) or placebo. After 6 months the rate of adverse events did not differ significantly between anakinra and placebo, except for injection site reactions (72.6% vs. 32.9%; P-value not reported). Overall discontinuation rates (anakinra 21.6%; placebo 18.7%) and the rate of serious adverse events (anakinra 7.7%; placebo 7.8%) were also similar. However, a trend towards an increased risk of serious infections in anakinra-treated patients was apparent (2.1% vs. 0.4%; P = 0.068). The STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis) study

determined the safety of adalimumab in combination with standard rheumatoid therapy.[27] At 22 weeks, there were no significant differences between adalimumab and placebo with respect to adverse events.

Injection site reactions (adalimumab, anakinra, etanercept) and infusion reactions (infliximab) were the most commonly and consistently reported adverse events. Some infusion reactions, however, appeared to be more serious than injection site reactions. An observational study of 165 consecutive patients with Crohn's disease reported that 8.4 percent of patients had infusion reactions to infliximab.[95] These were mostly non-specific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever. One percent of patients, however, had severe acute reactions that resembled acute anaphylactic conditions or led to convulsions. In clinical trials, 17 percent of patients experienced infusion reactions, 0.5 percent of those were severe.[94] Less than two percent of patients in clinical trials discontinued because of infusion reactions. In contrast, injection site reactions were mainly erythema, pruritus, rash, and pain of mild to moderate severity. However, injection site reactions were the most common reason for discontinuation due to adverse events. The mean, crude incidence of injection site reactions in RCTs and observational studies reviewed for this report was 17.5 percent (95%CI 7.1-27.9) for adalimumab, 22.4 percent (95%CI 8.5-36.3) for etanercept, but 67.2 percent (95% CI 38.7-95.7) for anakinra. The higher incidence of injection site reactions for anakinra over adalimumab and etanercept is consistent with numbers reported in the respective package inserts.[96-98]

C. Specific Adverse Events

Serious Infections

Because of the immunosuppressive nature of TIMs, serious infections including tuberculosis, pneumonia, osteomyelitis, and sepsis are of special concern. The FDA has issued black box warnings about an increased risk of infections for adalimumab and infliximab. The package inserts of anakinra and etanercept also contain warnings in bold letters.

In efficacy trials, the incidence of serious infections was consistently higher in TIM- than in placebo-treated patients. However, although clinically significant, differences rarely reached statistical significance due to lack of power. For example, in the large safety RCT (n = 1,414), a trend towards an increased risk of serious infections in anakinra-treated patients was apparent during the 6 months of treatment (2.1% vs. 0.4%; P = 0.068).[90-92] Long-term observational studies support these findings.[93, 94, 99] The most common serious infections were cases of tuberculosis.[86] In addition, observational studies

reported infections with coccidiomycosis,[100] histoplasmosis,[101] pneumocystis carinii,[102] and listeriosis[84] and candida.[86]

Three retrospective database analyses [85, 86, 103] and a prospective cohort study with a historic control group[104] specifically determined the risk of tuberculosis or granulomatous infections during treatment with infliximab and etanercept. All studies report a significant increase of risk attributable to TIM therapy. Two studies analyzed all reports of tuberculosis[86] or granulomatous infections[85] after infliximab or etanercept therapy through the MedWatch reporting system of the FDA. In general, the MedWatch system relies on voluntary reporting of adverse events and underreporting is likely.[105] Therefore, it lacks an adequate denominator to draw inferences about causation and the comparative risks of any drugs. Among RA patients on infliximab, 24.4 cases of tuberculosis per 100,000 patients treated in the past year.[86] In contrast, the estimated background rate for patients with RA not exposed to TIMs in the US is 6.2 cases per 100,000 patient years. Reported rates are lower than those of a prospective cohort study of patients from the National Data Bank for Rheumatic Diseases (NDP).[104] This study reports 52.5 cases per 100,000 patients years. The median interval from start of infliximab therapy to the diagnosis of tuberculosis was 3 months.[86] By contrast, an analysis of MedWatch data, published in abstract form only, concerning etanercept and tuberculosis reported a median time of 11.5 months from start of etanercept therapy to diagnosis of tuberculosis.[87] The analysis of MedWatch data on granulomatous infections indicated a higher rate among patients treated with infliximab (239 cases per 100,000 patients) than with etanercept (74 cases per 100,000 patients).[85] The rate of tuberculosis in this study was 144 cases per 100,000 patients for infliximab and 35 cases per 100,000 patients for etanercept. However, incidence rates are not comparable across studies because the Wallis et al. study reports cases per treated patients and not per patient years.[85] The third database analysis used the Spanish BIOBADASER (Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologia) which included data on infliximab and etanercept.[103] The reported incidence of tuberculosis was substantially higher than the one derived from MedWatch. In 2001, the estimated incidence was 1,113 per 100,000 patient years; the background incidence for patients with RA not exposed to TIMs in Spain is 95 cases per 100,000 patient years.

Lymphoma

The risk of lymphoma, both Hodgkin and non-Hodgkin lymphoma, is generally increased in patients with RA.[106] Data from controlled trials do not provide sufficient evidence concerning a further increase of risk attributable to TIMs or a combination of TIMs and MTX. A MedWatch report identified 26 reported cases of lymphoproliferative disorders in patients treated with infliximab or etanercept for Crohn's disease or RA as of 2002.[107] The estimated crude incidence rates of lymphoma are 19 per 100,000

patients treated with etanercept and 6.6 per 100,000 patients treated with infliximab. Authors report that in a number of cases, lymphoma developed shortly after starting therapy and regression occurred in two patients after discontinuing therapy. The median time from start of therapy until diagnosis was 8 weeks for etanercept and 6 weeks for infliximab. Given the fact that this study is essentially a case series, a clear causal relationship between TIMs and lymphoma, or differences in risk between drugs cannot be established.

A large prospective cohort study followed 18,572 RA patients registered in the National Data Bank of Rheumatic Diseases (NDB) for up to 3 years.[108] Results indicated that lymphomas are increased in patients on anti-TNF-α therapies. However, confidence intervals for treatment groups overlap and results are insufficient to establish a causal relationship between RA treatments and lymphoma or to delineate differences in risk between treatments. The standardized incidence rate (SIR) in the overall cohort was 1.9 cases per 100,000. The SIR for patients not receiving MTX or any biologic agents was 1.0. The SIR for patients on MTX was 1.7 (95%CI 0.9-3.2), on infliximab was 2.6 (95%CI 1.4-4.5), and on etanercept was 3.8 (95%CI 1.9-7.5).

Existing evidence is insufficient to draw conclusions about an increased risk of malignancies other than lymphoma for patients with TIM therapy. A clinical trial database review did not detect an increased incidence of squamous cell carcinoma in 1,442 RA patients (4,257 patient years) treated with etanercept (crude rate: 2.8 cases/ 1000 patients).[109] However, the median follow-up time was only 3.7 years.

Congestive Heart Failure

A MedWatch analysis reports that half of the patients who developed new onset congestive heart failure (CHF) under etanercept or infliximab treatment did not have any identifiable risk factors.[110] No direct evidence on the comparative risk of CHF exists. Indirect evidences comes from three trials, two on etanercept[111] and one on infliximab,[112] that evaluated the efficacy of these drugs for the treatment of CHF. Study populations did not have any rheumatoid illnesses. The two etanercept trials were terminated early because interim analyses indicated higher mortality rates in patients treated with etanercept. Similarly, the infliximab study presented higher mortality rates in the 10 mg/kg arm than in the placebo and 5 mg/kg arm.[112] The package insert of infliximab issues a contraindication regarding the use in patients with CHF; the package inserts of etanercept and adalimumab emphasize precaution.

Other Adverse Events

Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the risk of rare but serious adverse events such as demyelination, autoimmunity, pancytopenia, and hepatotoxicity. A case series based on data from MedWatch indicated that infliximab and etanercept might be associated with demyelination.[113] Similar cases have been seen in regulatory trials of adalimumab.[97] All neurologic events partially or completely resolved after discontinuation of treatment.

Similarly, reports of autoimmunity have not been confirmed in controlled trials and observational studies. However, case reports suggest an association between infliximab and drug induced lupus and other autoimmune diseases.[93, 94, 114] A prospective cohort study of 125 consecutive Crohn's disease patients treated infliximab reported a cumulative incidence of antinuclear antibodies of 56.8 percent after 24 months.[115] Two patients of this cohort developed drug induced lupus. Development of anti nuclear, anti double-stranded DNA, or anti-histone antibodies have also been reported in regulatory trials of other anti-TNF-α drugs.[96, 97] The infliximab package insert reports that 34 percent of patients treated with infliximab and MTX experienced transient elevations of liver function parameters.[116] Severe liver injury, including acute liver failure has been reported. Owing to a lack of studies with the methodological strength to assess these rare events, conclusions should be drawn on other grounds, such as comorbidities, taking case reports into consideration.

Table 11: Summary of Studies Assessing Adverse Events

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
OVERALL TOLERABILITY							
Braun et al. 2005[60-62]	Open-label extension of RCT	70	3 years	INF	Patients with AS	INF is a well tolerated treatment	Fair
Cheifetz et al. 2003[95]	Case series	165	NR	INF	Patients with CD	Incidence of infusion reactions was 6.1%	N/A
Colombel et al. 2004[93]	Case series	500	Up to 17 months	INF	Patients with CD		N/A
Fleischmann et al. 2003[90-92]	RCT	1,414	6 months	AKA	Patients with RA	AKA is a well tolerated treatment	Fair
Ljung et al. 2005[70]	Case series	217	Up to 3 years	INF	Patients with IBD	19% experienced serious adverse events	N/A
Lovell et al. 2003[89]	Open-label extension of RCT	58	up to 2 years	ETA	Pediatric patients with polyarticular-JRA	16% of patients experienced serious adverse events	Fair
Maini et al. 2004[47]	Open-label extension of RCT	259	2 years	INF	Patients with RA	Rate of severe adverse events was similar in INF and placebo	Fair
Nuki et al.2002[117]	Uncontrolled extension of RCT	309	76 weeks	ANA	Patients with RA	AKA was well tolerated at all dose levels for up to 76 weeks	N/A
Schaible et al. 2000[94]	Retrospective data analysis of clinical trials	913	12 weeks – 3 years	INF	Patients with CD or RA	Incidence of infections was greater in patients treated with INF than placebo	N/A

Table 11: Summary of Studies Assessing Adverse Events (continued)

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
INFECTIOUS DISEASES							
Bergstrom et al. 2004[100]	Retrospective cohort study	985	NR	INF, ETA	Patients with inflammatory arthritis	Patients treated with INF or ETA are more likely to develop symptomatic coccidioidomycosis	N/A
Gomez-Reino et al. 2003[103]	Database analysis BIOBADASER	3118	Any duration	INF, ETA	Patients treated with INF or ETA	TB is more common in patients treated with INF or ETA	N/A
Keane et al. 2001[86]	Database analysis Adverse Event Reporting System	70 cases	N/A	INF	Patients treated with INF	TB may develop soon after treatment with INF	N/A
Lee et al. 2002[88]	Database analysis Adverse Event Reporting System	10 cases	N/A	INF, ETA	Patients treated with INF or ETA	Histioplasmosis infections may be a serious complication of treatment with anti-TNF agents; patients on INF had a higher rate of infections than patients on ETA	N/A

Table 11: Summary of Studies Assessing Adverse Events (continued)

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
Slifman et al. 2003[84]	Database analysis Adverse Event Reporting System	15 cases	N/A	INF, ETA	Patients treated with INF or ETA	Listeria infections may be a serious complication of treatment with anti-TNF agents; patients on INF had a higher rate of infections than patients on ETA	N/A
Wallis et al.[85]	Database analysis Adverse Event Reporting System	622 cases	N/A	INF, ETA	Patients treated with INF or ETA	Patients on INF had a higher rate of granulomatous infections than patients on ETA	N/A
Wolfe et al.[104]	Prospective Cohort study	15,940	3 years	INF	Patients treated with INF	TB is more common in patients treated with INF	Fair

Table 11: Summary of Studies Assessing Adverse Events (continued)

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
LYMPHOMA AND OTHER MALIGNANCIES							
Brown et al. 2002[107]	Database analysis MedWatch	26 cases	N/A	INF, ETA	Patients with RA or CD	Estimated rate of lymphoma per 100,000 treated ETA- 19 INF- 6.6	N/A
Wolfe et al. 2004[108]	Prospective cohort study	18,572	Up to 3 years	INF, ETA	Patients with RA	Patients with RA, treated with INF or ETA are more likely to develop lymphoma than the general population	Good
Lebwohl et al. 2005[109]	Database review	1,442	3.7 years	ETA	Patients with RA	ETA does not seem to be associated with an increase in the incidence of cutaneous squamous cell carcinoma	N/A

Table 11: Summary of Studies Assessing Adverse Events (continued)

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
CONGESTIVE HEART FAILURE							
Chung et al. 2003[112]	RCT	150	28 weeks	INF	Patients with CHF	INF-treated patients were more likely to die or have heart failure than placebo-treated patients	Fair
Kwon et al. 2003[110]	Database review MedWatch	47 cases	N/A	ETA, INF	Patients on ETA or INF therapy	Young age was associated with a greater short term response	N/A
DEMYELINATION							
Mohan et al. 2001[113]	Database analysis MedWatch	19 cases	N/A	Anti-TNF	Patients with inflammatory arthritis	All events temporally related to therapy, with partial or complete resolution on discontinuation.	N/A
AUTOIMMUNITY							
Vermeire et al 2003[115]	Case series	125	Up to 24 months	INF	Patients with CD	ANA developed in 56.8% of treated patients	N/A

Table 11: Summary of Studies Assessing Adverse Events (continued)

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
OTHER ADVERSE EVENTS							
Baeten et al. 2003[99]	Case series	107	13 months	INF	Patients with spondyloarthropathy	Though use of INF is generally safe care must be taken for serious adverse events such as infections and TB.	N/A
Colombel et al. 2004[93]	Case series	500	Up to 17 months	INF	Patients with CD	Short- and long-term INF therapy is generally well tolerated	N/A

AKA: anakinra
CD: Crohn's disease
ETA: etanercept
INF: infliximab
MTX: methotrexate
RA: Rheumatoid arthritis

KEY QUESTION 3

Do the included drugs differ in effectiveness or adverse events in different age, sex, or ethnic groups, or in patients taking other commonly prescribed drugs?

A. Summary of the Evidence

The overall grade of the evidence on efficacy and tolerability in subgroups is poor. We did not identify any study specifically designed to compare the effect of adalimumab, alefacept, anakinra, efalizumab, etanercept, or infliximab in one subgroup of patients compared to another. Subgroup analyses and indirect evidence from placebo-controlled trials provide evidence for some TIM drugs.

Indirect evidence exists from four retrospective analyses[118,119-121] that age is not associated with greater clinical response rates in AS, RA, and PsA. No differences in adverse events between patients older than 65 years and those younger were reported.[120, 121] In one prospective cohort study significantly more females than males developed antinuclear antibodies when treated with infliximab.[115]

Indirect evidence from three RCTs conducted in patients with CHF indicates that treatment with etanercept and infliximab significantly increases the risk of hospitalization and mortality.[111, 112]

B. Age

We did not identify any study specifically designed to compare the effect of adalimumab, alefacept, anakinra, efalizumab, etanercept, or infliximab in a younger versus an older population.

We did not find any age-related information in efficacy trials or observational studies. Indirect evidence exists from four retrospective analyses[118,119-121] that age is not associated with greater clinical response rates in AS, RA, and PsA. A case series in patients with Crohn's Disease reports that young age was associated with an increased short-term response.[118] No differences in adverse events between patients with AS, RA, and PsA older than 65 years and those younger were reported.[120, 121] However, selection bias might have distorted results in these retrospective analyses.

C. Ethnicity

We did not identify any study specifically designed to compare the effect of adalimumab, alefacept, anakinra, efalizumab, etanercept, or infliximab in one racial group compared to another. In general, trials were conducted predominantly in white populations. No indirect evidence suggests that effectiveness or adverse events differ among races.

D. Sex

We did not identify any study specifically designed to compare the effect of adalimumab, alefacept, anakinra, efalizumab, etanercept, or infliximab in females compared to males. On average, study populations comprised more females than males; this fact reflects population and disease demographics and does not provide insight into treatment differences. One prospective cohort study reported that significantly more women than men developed antinuclear antibodies under infliximab (OR 2.5; 95%CI 1.2-5.4).[115] No other indirect evidence suggests that effectiveness or adverse events differ between females and males.

E. Comorbidities

We did not identify any study specifically designed to assess the efficacy of adalimumab, alefacept, anakinra, efalizumab, etanercept, or infliximab in patients with comorbidities.

A posthoc subgroup analysis of a large safety trial determined the safety profile of anakinra in patients with comorbidities (cardiovascular events, pulmonary events, diabetes, infections, malignancies, renal impairment, central nervous system-related events).[92] Overall, the incidence rates of adverse events were similar regardless of comorbidity status.

Indirect evidence exists regarding an increased risk of worsening heart failure and mortality during anti-TNF-α therapy. Three trials, two on etanercept[111] and one on infliximab[112] evaluated the efficacy of these drugs for the treatment of CHF. None of the patients had any rheumatoid illnesses. The two etanercept trials were terminated early because interim analyses indicated higher mortality rates in patients treated with etanercept. Similarly, the infliximab study presented higher mortality rates in the 10 mg/kg arm than in the placebo and 5 mg/kg arm.[112] A MedWatch analysis reported that half of the patients who developed new onset CHF while treated with etanercept or infliximab for RA or other rheumatoid illnesses did not have any identifiable risk factors.[110] The package insert of infliximab issues a contraindication regarding its use in patients with CHF; the package inserts of etanercept and adalimumab express precaution.

F. Other Commonly Prescribed Medications

No formal drug interaction studies have been performed with adalimumab, alefacept, anakinra, efalizumab, etanercept, or infliximab. Concurrent administration of anakinra with TNF-blocking agents (i.e., adalimumab, etanercept, infliximab) may be associated with an increased risk of serious infections, an increased risk of neutropenia, and no additional benefit compared to monotherapy. This evidence comes from a 24 week trial comparing concurrent treatment with anakinra and etanercept to etanercept monotherapy in patients with RA.[23] Patients treated with both anakinra and etanercept had a 7 percent rate of serious infections, compared to no infections observed in patients treated with etanercept alone. Two percent of patients treated concurrently with anakinra and etanercept developed neutropenia. Because adalimumab and infliximab have a similar mechanism of action to etanercept, similar risks are believed to be associated with concurrent treatment with anakinra, although no formal evidence exists.

Because the majority of patients included in clinical studies received one or more concomitant medications (e.g., ASAs, antibiotics, antivirals, azathioprine, corticosteroids, folic acid, narcotics, nonsteroidal anti-inflammatory agents, and 6-MP) with no identifiable differences in safety or tolerability, concomitant treatment with such agents is believed to be safe. One analysis of data from the first 6 months of a large, blinded, placebo-controlled safety trial of anakinra provides evidence for the risk of infections or other serious adverse events for some concomitant medications.[91] In this trial, no statistically significant differences were noted in the risk of infection or other serious adverse events between placebo- and anakinra-treated patients concurrently taking MTX or other DMARDs. Two patients taking anakinra and azathioprine developed serious infections compared to no patients taking azathioprine and placebo, although the number of patients taking azathioprine was deemed to be too small to draw any definitive conclusions. The adverse event profiles were similar for anakinra and placebo for patients who were or were not taking concomitant antihypertensive, antidiabetic, or statin drugs.

Concomitant administration of adalimumab and MTX has demonstrated a 29 to 44 percent reduction in the clearance of adalimumab. However, data do not suggest the need for dose adjustment of either MTX or adalimumab. Studies evaluating concomitant administration of MTX with anakinra or etanercept have not demonstrated changes in the clearance either drug. Although no formal studies have evaluated drug interactions between MTX and alefacept, efalizumab, or infliximab, concomitant administration of these agents is believed to be safe.

Table 12: Summary of Studies Assessing Subgroups

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
AGE							
Fleischman et al. 2005[120]	Retrospective data analysis	4322	NR	ETA	Patients with RA, AS, PsA	No differences in adverse events between patients older and younger than 65 years	N/A
Fleischman et al. 2003[121]	Retrospective data analysis	1128	NR	ETA	Patients with RA	No differences in efficacy and adverse events between patients older and younger than 65 years	N/A
Rudwaleit et al. 2004[119]	Retrospective data analysis	99	12 weeks	ETA, INF	Patients with AS	Age not statistically significantly associated with treatment respponse	N/A
Vermiere et al. 2002[118]	Case series	240	4-10 weeks	INF	Patients with CD	Young age favored short term response to INF therapy	N/A

Table 12: Summary of Studies Assessing Subgroups (continued)

Author, year	Study design	N	Duration	Drug	Population	Results	Quality rating
COMORBIDITIES							
Chung et al. 2003[112]	RCT	150	28 weeks	INF	Patients with CHF	INF-treated patients were more likely to die or have heart failure than placebo-treated patients	Fair
Kwon et al. 2003[110]	Database review MedWatch	47 cases	N/A	ETA, INF	Patients on ETA or INF therapy	Young age was associated with a greater short term response	N/A
Schiff et al. 2004[92]	Subgroup analyses of RCT	1,414	6 months	ANA	Patients with RA		Fair

CONCLUSIONS

Insufficient evidence exists to draw firm conclusions about the comparative efficacy, effectiveness, or tolerability of adalimumab, alefacept, anakinra, efalizumab, etanercept, and infliximab for the treatment of RA, JRA, AS, PsA, and Crohn's disease. No double-blind randomized trial compared one TIM to another. The only direct comparative evidence comes from one open-label effectiveness trial comparing the effectiveness of etanercept to infliximab for the treatment of RA. Although this trial did not detect any differences in effectiveness after one year, the study design cannot completely rule out bias and confounding. Adjusted indirect comparisons suggest that anakinra is less efficacious than anti-TNF drugs for the treatment of RA.

The general efficacy of adalimumab, anakinra, etanercept, and infliximab for the treatment of RA is well established by multiple good to fair RCTs. Effect sizes are large and consistent across studies. Combination therapy with MTX achieved the best results. Monotherapy of etanercept did not reveal a relative benefit to MTX monotherapy. Other TIMs have not been directly compared to MTX. A combination of two TIMs (i.e., etanercept and anakinra) did not raise response or remission rates but significantly increased adverse events.

Evidence on the general efficacy of TIMs for other reviewed indications is limited. Fair evidence exists that etanercept and infliximab are more efficacious than placebo for the treatment of AS and PsA. Multiple good to fair RCTs confirm the efficacy of infliximab for the treatment of Crohn's disease. Etanercept did not significantly improve symptoms of Crohn's disease compared to placebo; however, this finding is limited to one study. JRA is the indication with the sparsest evidence on the efficacy and tolerability of TIMs. Only one RCT provides evidence on the efficacy of etanercept, the only drug approved for the treatment of JRA; however, methodological issues limit the internal validity of this study. Results of an uncontrolled trial of infliximab for JRA are fatally flawed.

Overall, no substantial differences in short-term tolerability and safety appear to exist among TIMs. The existing evidence suggests that differences in short-term tolerability exist primarily with respect to adverse events caused by the route of administration. Anakinra appears to have a substantially higher rate of injection site reactions than anti-TNF drugs. Infliximab carries the risk of severe infusion reactions that cannot occur in drugs administered subcutaneously.

Rare but severe adverse events such as serious infections, lymphoma, autoimmunity, or congestive heart failure are of equal concern for all drugs. Existing evidence is insufficient to draw firm conclusions about the comparative safety among TIMs. Because TIMs are relatively new medications, solid long-term data on safety is generally still missing.

The most obvious differences that might be clinically decisive for choosing a TIM involve dosing and administration. Infliximab requires intravenous administration every 8 to 12 weeks and presents the danger of rare but severe infusion reactions. Adalimumab, anakinra, and etanercept can be administered subcutaneously by the patient. Administration intervals, however, differ substantially: adalimumab requires an injection once a week or once every other week, anakinra has to be administered daily, and etanercept once or twice per week.

Overall, TIMs are highly effective medications for the treatment of RA, JRA, AS, PsA, and Crohn's disease that substantially improve the burden of disease. However, the risk benefit ratio cannot be reliably assessed without sound long-term data on safety.

Gaps in the Evidence

No well-conducted double-blind randomized head-to-head trials exist comparing one TIM with another. Evidence from systematic reviews, placebo-controlled trials, and observational studies is insufficient to draw firm conclusions about one TIM compared to another.

In addition, the lack of sound evidence for the treatment of JRA with TIMs is apparent. Currently, published studies do not have the methodological rigor required to assess the risk benefit ratio of TIM-therapy in a pediatric population.

Given the danger of severe, potentially fatal adverse events, large, long-term, well-conducted, observational studies are paramount to reliably assessing the risk benefit ratio of TIM-therapy. Future research should focus on prospectively evaluating the risk of rare but severe adverse events employing adequate study designs.

Table 13: Summary of the Evidence

Key Question 1: Comparative Efficacy	Rating of the Body of Evidence	Conclusion
RA	Fair-Poor	Only one non-randomized, open-label trial provides direct evidence on the comparative efficacy of etanercept and infliximab; etanercept had significantly greater ACR20/50 response rates after 3 and 6 months but no differences were apparent after 1 year. Indirect comparisons of placebo controlled trials did not find statistically significant differences in efficacy among individual drugs. However, point estimates favor adalimumab, etanercept, and infliximab over anakinra. Adjusted indirect comparisons of anakinra with anti-TNF drugs as a class present a statistically significantly greater efficacy for anti-TNF drugs on ACR 20 but not on ACR 50. Multiple placebo-controlled trials provide good to fair evidence on the general efficacy of adalimumab, anakinra, etanercept, and infliximab for the treatment of RA.
JRA	Poor	We identified no head-to-head trials. The evidence for JRA is limited to one fair placebo-controlled trial establishing the efficacy of etanercept for the treatment of JRA.
AS	Poor	We identified no head-to-head trials. Five placebo-controlled trials provide good to fair evidence on the general efficacy of etanercept and infliximab for the treatment of AS. Significant differences in study characteristics make this evidence insufficient to identify differences among treatments. No studies on adalimumab, alefacept, anakinra, and efalizumab could be detected.
PsA	Poor	We identified no head-to-head trials. Three placebo-controlled trials provide fair evidence on the general efficacy of etanercept and infliximab for the treatment of PsA. Significant differences in study characteristics make this evidence insufficient to identify differences among treatments. No studies on adalimumab, alefacept, anakinra, and efalizumab could be detected.
Crohn's Disease	Poor	We identified no head-to-head trials. Six placebo-controlled trials provide fair evidence on the general efficacy of infliximab for the treatment of Crohn's disease. One fair trial could not detect any significant differences in efficacy between etanercept and placebo. Data was insufficient to conduct statistical indirect comparisons. No studies on adalimumab, alefacept, anakinra, and efalizumab could be detected.

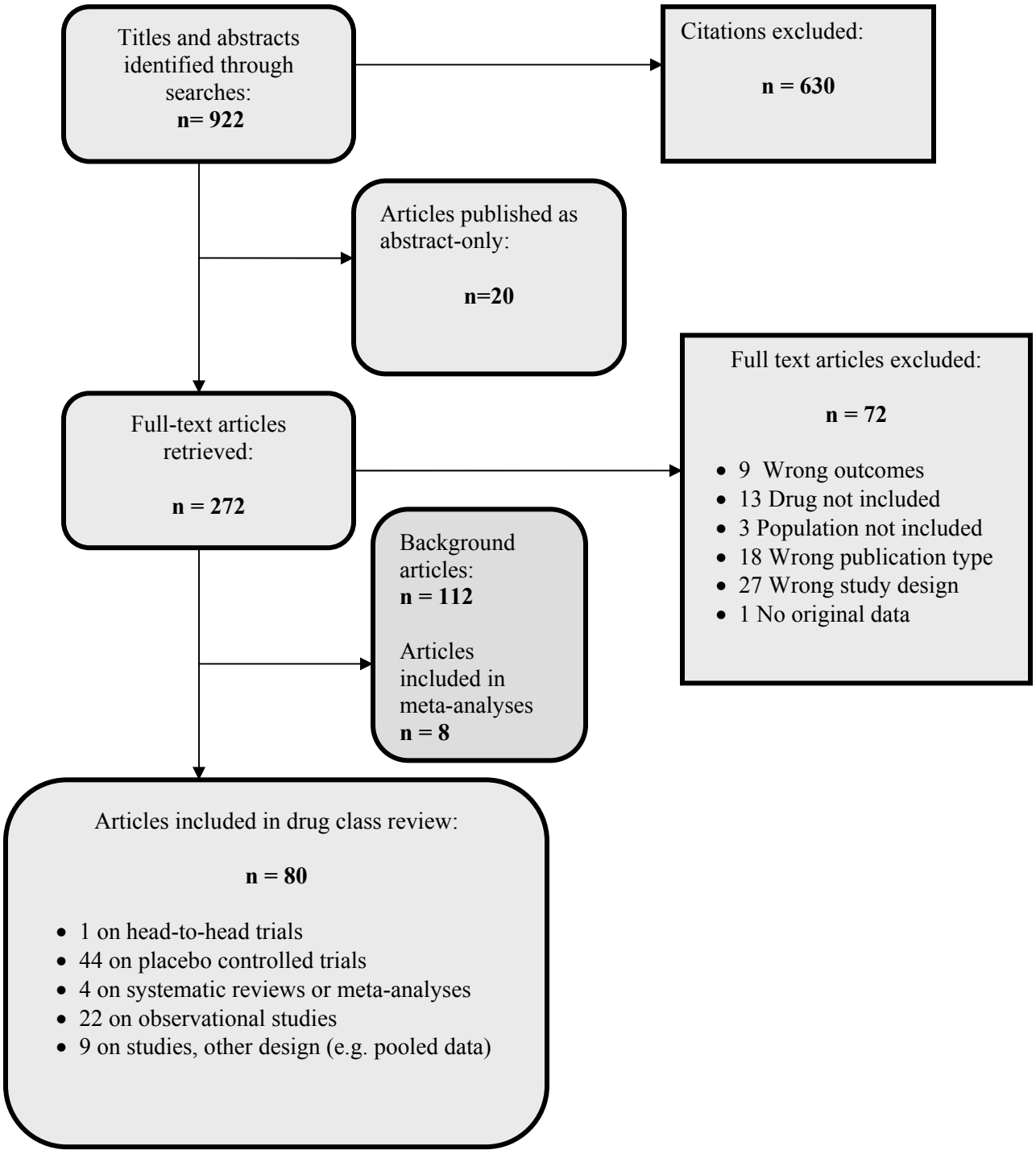
Table 13: Summary of the Evidence

Key Question 2: Comparative Adverse Events	Rating of the Body of Evidence	Conclusion
Tolerability and discontinuation	Fair to Poor	Only one non-randomized, open-label trial provides direct evidence on the comparative tolerability of etanercept and infliximab; no differences were apparent. Overall, the incidence rates of adverse events appear to be similar among reviewed TIMs. Anakinra appears to have a higher rate of injection site reactions than adalimumab and etanercept. Infliximab can cause severe infusion reactions and has a potential for hepatotoxicity that has not been reported for other TIMs. Discontinuation rates because of adverse events did not differ significantly compared to placebo, taking the whole body of evidence into consideration.
Serious infections	Poor	Fair evidence from controlled trials and observational studies suggests that the rate of serious infections is higher for TIMs than for placebo. In particular, a higher risk of tuberculosis is well documented. Observational studies report increased infections with histioplasmosis, pneumocystis carinii, listeriosis or candida. Evidence from controlled trials and observational studies is insufficient to draw conclusions about the comparative risk of serious infections.
Lymphoma	Poor	Observational evidence indicates a higher risk of lymphoma for patients treated with infliximab or etanercept. Evidence from controlled trials and observational studies is insufficient to draw conclusions about the comparative risk of lymphoma.
CHF	Poor	Three RCTs provide fair, indirect evidence about a higher rate of mortality for patients with CHF treated with etanercept or infliximab than with placebo. Evidence from controlled trials and observational studies is insufficient to draw conclusions about the comparative risk of CHF.
Demyelination	Poor	Case reports indicate that etanercept and infliximab might be associated with demyelination. Evidence, however, is insufficient to draw conclusions about differences in the risk of demyelination.
Autoimmunity	Poor	Case reports indicate that TIMs might be associated drug induced lupus and other forms of autoimmunity. Evidence from controlled trials and observational studies is insufficient to draw conclusions about differences in the risk of autoimmunity.
Neutropenia	Poor	One trial indicates that a combination of anakinra and etanercept is associated with an increased risk of panzytopenia. Evidence from controlled trials and observational studies is insufficient to draw conclusions about differences in the risk for panzytopenia
Hepatotoxicity	Poor	Evidence from controlled trials and observational studies is insufficient to draw conclusions about differences in the risk of liver toxicity.

Table 13: Summary of the Evidence

Key Question 3: Subgroups	Rating of the Body of Evidence	Conclusion
Age	Poor	Indirect evidence suggests that young age is associated with increased clinical response rates for patients with Crohn's disease or AS. Evidence is insufficient to draw conclusions about age and differences in treatment effects among TIMs.
Ethnicity	Poor	Evidence is insufficient to draw conclusions about ethnicity and differences in treatment effects among TIMs.
Sex	Poor	Evidence is insufficient to draw conclusions about sex and differences in treatment effects among TIMs.
Comorbidities	Poor	We could not find any studies comparing the efficacy and tolerability of TIMs between a population with a comorbidity and one without the same comorbidity. Indirect evidence suggests that infliximab and etanercept lead to a higher mortality in patients with CHF. Evidence is insufficient to draw conclusions about comorbidities and differences in treatment effects among TIMs.

Figure 2: Results of literature search



APPENDIX A. Search Strategy

#9 Search ("Arthritis"[MeSH] OR "Arthritis, Juvenile Rheumatoid"[MeSH] OR "Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH] OR "Spondylarthritis"[MeSH]) OR "Spondylitis, Ankylosing"[MeSH] OR "Crohn Disease"[MeSH] 146255

#20 Search "infliximab"[Substance Name] OR "TNFR-Fc fusion protein"[Substance Name] OR "adalimumab"[Substance Name] OR "interleukin-1 receptor type I"[Substance Name] OR "efalizumab"[Substance Name] OR "alefacept"[Substance Name] 2074

#22 Search remicade OR enbrel OR humira OR anakinra OR kineret OR raptiva OR aconosine 3922

#30 Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials"[MeSH]) OR "Single-Blind Method"[MeSH] OR "Random Allocation"[MeSH] 264437

#35 Search ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Longitudinal Studies"[MeSH])OR observational studies 775808

#36 Search #20 OR #22 4097

#37 Search #36 AND #9 1474

#38 Search #37 AND #30 200

#39 Search #36 AND #9 Field: All Fields, Limits: Review 403

#37 Search #36 AND #9 1660

#40 Search #37 AND #35 202

#41 Search adverse events OR harms OR drug reactions OR toxicity 346595

#42 Search #41 AND #37 198

#43 Search #42 OR #40 391

EMBASE = 224

Cochrane = 3

Combined, duplicates removed, limited to English = 565 unique records

APPENDIX B. Studies Already Included in Meta-analyses

1. Bresnihan B, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998;41(12):2196-204.

2. Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46(3):614-24.

3. Cohen SB, Moreland L, Cush JJ, Greenwald MW, Block JA, Shergy WJ. Anakinra (recombinant interleukin-1 receptor antagonist): a large, placebo controlled efficacy trial of anakinra in patients with erosive rheumatoid arthritis disease. Arthritis Rheum 2001;44:LB1.

4. Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 1994;344(8930):1105-10.

5. Kavanaugh A, St Clair EW, McCune WJ, Braakman T, Lipsky P. Chimeric anti-tumor necrosis factor-alpha monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. J Rheumatol 2000;27(4):841-50.

6. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343(22):1594-602.

7. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354(9194):1932-9.

8. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41(9):1552-63.

9. Mathias SD, Colwell HH, Miller DP, Moreland LW, Buatti M, Wanke L. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. Clin Ther 2000;22(1):128-39.

10. Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med 1997;337(3):141-7.

11. Moreland LW, Margolies G, Heck LW, Jr., Saway A, Blosch C, Hanna R, et al. Recombinant soluble tumor necrosis factor receptor (p80) fusion protein: toxicity and dose finding trial in refractory rheumatoid arthritis. J Rheumatol 1996;23(11):1849-55.

12. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130(6):478-86.

13. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340(4):253-9.

APPENDIX C. Quality Criteria

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alteration, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alteration, case record numbers, birth dates or week days
        - Open random numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?
2. How many patients were recruited?
3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)
4. What was the funding source and role of funder in the study?
5. Did the control group receive the standard of care?
6. What was the length of follow-up? (Give numbers at each stage of attrition.)

APPENDIX D. Clinical Assessment Scales Commonly Used in Targeted Immune Modulators Trials

General Health Measures

HAQ - Health Assessment Questionnaire
- HAQ Disability Index (HAQ-DI)
- HAQ visual analog (VAS) pain scale
- VAS patient global health scale;
- http://www.hqlo.com/content/1/1/20

SF-36 - Medical Outcomes Study Short Form 36 Health Survey
- 36 items
- Eight health profiles are derived from summarised scores. All dimensions are independent of each other.
- Scale of 0-100, where higher scores indicate better health and well-being.

EQ-5D - EuroQol EQ-5D Quality of Life Questionnaire
- Descriptive system of health-related quality of life states consisting of five dimensions;
  - Mobility
  - Self-care
  - Usual activities
  - Pain/discomfort
  - Anxiety/depression
- Each of which can take one of three responses.
  - No problems
  - Some moderate problems
  - Extreme problems

http://www.euroqol.org/web/

Rheumatoid Arthritis Measures

ACR20/50/70 - American College of Rheumatology 20/50/70% improvement[63]
- 20% reductions in tender and swollen joint counts and in at least three of the following: patient's assessment of pain, patient's global assessment, physician's global assessment, patient's assessment of disability, and acute phase reactant (CRP).
- ACR50 and ACR70 were also assessed (defined in a similar manner as ACR20, but with improvement of at least 50% and 70% in the individual measures, respectively).

Example: ACR 50 response

	Baseline	Endpoint
Tender joints *	12	6
Swollen joints*	8	3
Pain score*	60	20
Patient's global activity score	80	60
Physician's global activity score*	50	20
HAQ-DI	2.0	1.2
CRP`*	3.6	1.4

* at least 50 % improvement

DAS - Disease activity score[122]

- Swollen joint count [SJC] and tender joint count [TJC]), employing the 28 joint count; evaluator's and/or patient's global assessment of disease activity (EGA, PGA); and CRP or ESR
- DAS28 = $(0.56 \times TJC^{1/2}) + (0.28 \times SJC^{1/2}) + (0.7 \times \ln [ESR]) + (0.014 \times PGA [in\ mm])$

Psoriatic Arthritis Measures

PsARC - Psoriatic Arthritis Response Criteria[63]

- Composite measure requires improvement in two factors (with at least one being a joint score), with worsening in none, of the following four factors: patient and physician global assessments (improvement defined as decrease by ≥1 unit; worsening defined as increase by ≥1 unit); and tender and swollen joint scores
- Improvement defined as decrease by ≥30%; worsening defined as increase by ≥30%).

PASI - Psoriasis area and severity index[64]

Composite index of disease severity incorporating measures of;

- Scaling,
    - Erythema, and
    - Induration,

Weighted by severity and affected body surface area

Ankylosing Spondylitis Measures

- **BASDAI** - Bath Ankylosing Spondylitis Disease Activity Index[56]
- Combined assessment of;
    - Fatigue,
    - Spinal pain,
    - Joint pain,
    - Enthesitis, and
    - Morning stiffness

- **BASFI -** Bath Ankylosing Spondylitis Functional Index[56]
- Score ranging from 0 to 10
- Includes 8 questions relating to the patient's function and 2 questions relating to a patient's ability to cope with everyday life.[56]

- **BASMI -** Bath Ankylosing Spondylitis Metrology Index.[56]
- Aggregate score (ranging from 0 to 10) of patient mobility assessments, including tragus-to-wall, lumbar flexion (Schober test), cervical rotation, lumbar side flexion, and intermalleolar distance.

- **ASAS20/50/70 -** Assessment in Ankylosing Spondylitis 20% improvement.[56]
- ASAS20 responder was defined as a patient who showed at least 20% improvement from baseline and had an absolute improvement from baseline of at least 1 unit (on a scale of 0-10) in at least 3 of the following 4 assessment domains:
    - Patient's global assessment,
    - Spinal pain,
    - Function according to the Bath Ankylosing Spondylitis Functional Index (BASFI), and
    - Morning stiffness (the average of the last 2 questions of the BASDAI).

- In addition, ASAS20 responders must not have had deterioration from baseline (defined as a worsening of ≥20% and an absolute worsening of at least 1 unit [on a scale of 0-10]) in the potential remaining assessment domain.
- 40% improvement from baseline and an absolute improvement of at least 2 units [on a scale of 0-10] in at least 3 of the 4 assessment domains defined in the ASAS20 response criteria, with no deterioration from baseline in the potential remaining assessment domain), .

Crohn's Disease Measures

CDAI - Crohn's Disease Activity Index[123]

- This index incorporates eight items:
  - Number of liquid or very soft stools
  - Abdominal pain
  - General well-being
  - Extraintestinal manifestations of Crohn's disease
  - Use of opiates to treat diarrhea
  - Abdominal mass
  - Hematocrit
  - Body weight

These yield a composite score ranging from 0 to approximately 600.
Higher scores indicate more disease activity; patients with scores of 150 or less are considered to have inactive disease, whereas those with scores above 450 are critically ill

CDEIS -Crohn's Disease Endoscopy Index of Severity

- Based on the presence of;
  - Deep or superficial ulceration
  - Proportion of ulcerated surface
  - Presence of ulcerated or nonulcerated stenosis in the terminal ileum and four different segments of the colon

IBDQ – Inflammatory Bowel Disease Questionnaire[77]

- Scores can range from 32 to 224, and higher scores indicate a better quality of life. It examines the following types of symptoms:
  - Bowel
  - Systemic
  - Emotional
  - Social function

Juvenile Rheumatoid Arthritis

Gianinni's criteria of improvement[124]

- 30% improvement from baseline in 3 of any 6 variables in the core set, with no more than 1 of the remaining variables worsening by >30%.
  - Physician global assessment of disease activity;
  - Parent/patient assessment of overall well-being;
  - Functional ability;
  - Number of joints with active arthritis;
  - Number of joints with limited range of motion;
  - Erythrocyte sedimentation rate

APPENDIX E: Study Characteristics, Pooled Relative Risks, and Forest Plots of Meta-analyses

ADALIMUMAB

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Population
Furst et al. 2003[27]	RCT	636	24 weeks	ADA +Standard RA therapy / Placebo + Standard RA therapy	safety	Active RA for at least 3 months; DMARD naïve/or on stable regimen; mean disease duration: 10.5 yrs.
Keystone et al. 2004[28]	RCT	619	52 weeks	ADA +MTX / Placebo + MTX	Sharp, ACR 20, HAQ	Active RA; on stable MTX regimen; mean disease duration: 11 yrs.
Van de Putte et al. 2003[30]	RCT	284	12 weeks	ADA / Placebo	ACR 20	Active RA; had failed at least one DMARD treatment; mean disease duration: 10 yrs.
Van de Putte et al. 2004[29]	RCT	544	26 weeks	ADA / Placebo	ACR20	Active RA; had failed at least one DMARD treatment; mean disease duration: 11 yrs.
Weinblatt et al. 2003[26]	RCT	271	24 weeks	ADA+MTX / MTX + Placebo	ACR20, HAQ	Active RA;stable MTX regimen; had failed at least one other DMARD; mean disease duration: 12 yrs.

Relative risk meta-analysis: ACR-20

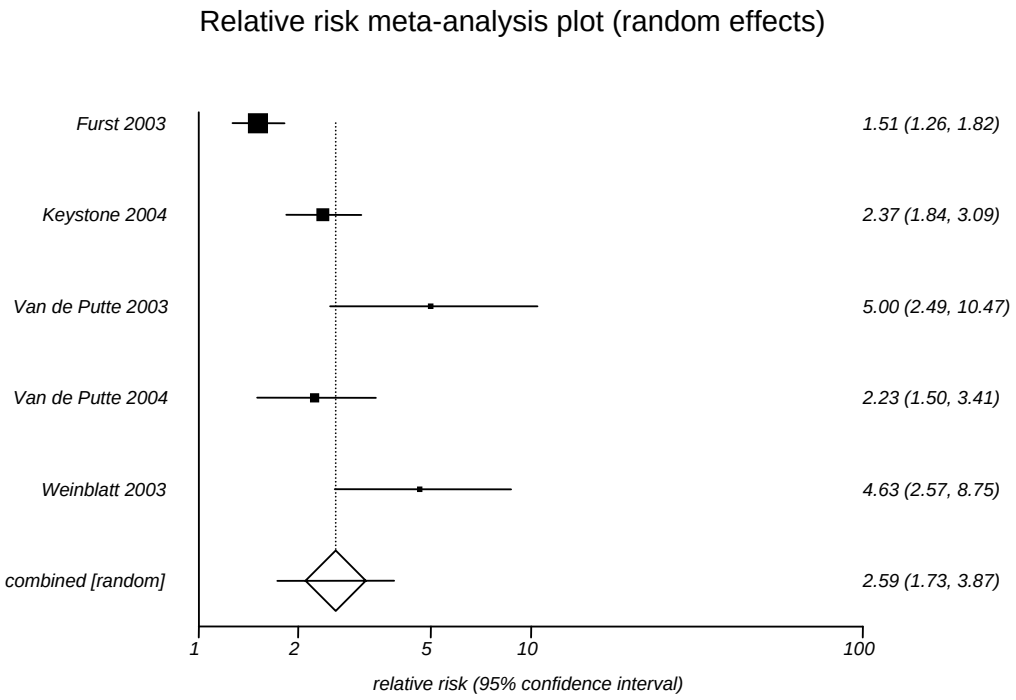
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	1.512649	1.262808	1.819429	55.5	Furst 2003
2	2.366746	1.84119	3.091321	32.491115	Keystone 2004
3	5	2.48527	10.473312	3.549296	Van de Putte 2003
4	2.234921	1.504395	3.410148	14.104478	Van de Putte 2004
5	4.626866	2.572227	8.746322	4.674419	Weinblatt 2003

M-H pooled estimate (Rothman-Boice) of relative risk = 2.100693
Robins-Greenland approximate 95% CI = 1.83305 to 2.407414

Chi-square (for pooled relative risk) = 113.950022 (df = 1) P < 0.0001

Q ("non-combinability" for relative risk) = 24.698049 (df = 4) P < 0.0001

I2: 83.8%



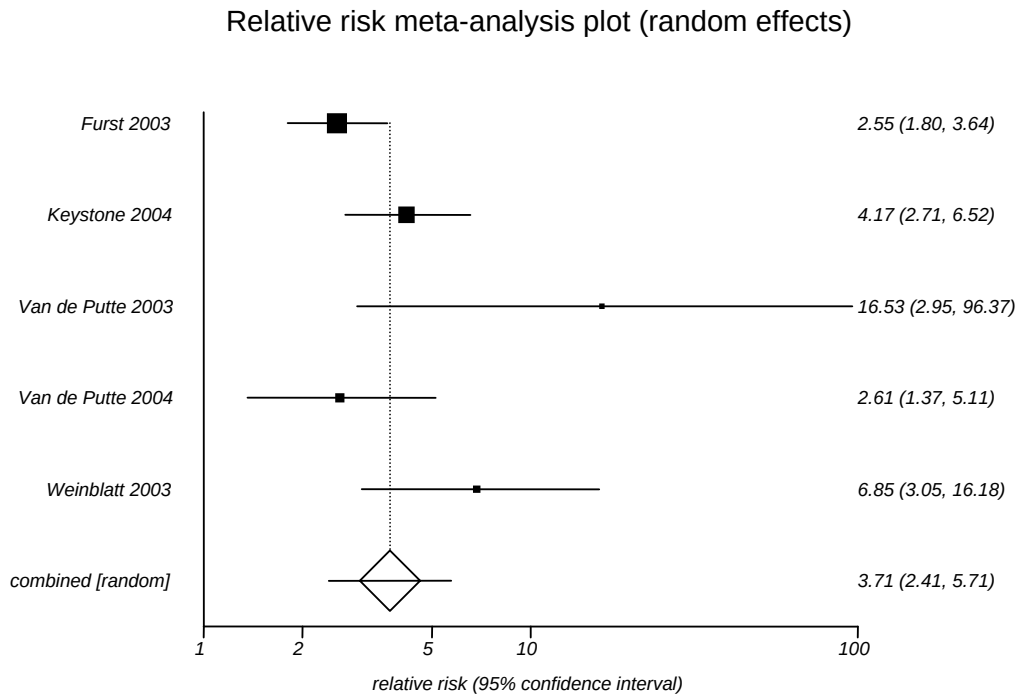
Relative risk meta-analysis: ACR-50

Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	2.552833	1.80314	3.63624	18	Furst 2003
2	4.17033	2.711696	6.522056	12.861066	Keystone 2004
3	16.527778	2.954667	96.371191	0.507042	Van de Putte 2003
4	2.607407	1.365527	5.10824	6.044776	Van de Putte 2004
5	6.847761	3.047254	16.177401	2.596899	Weinblatt 2003

M-H pooled estimate (Rothman-Boice) of relative risk = 3.536893
Robins-Greenland approximate 95% CI = 2.774584 to 4.508643

Chi-square (for pooled relative risk) = 104.031248 (df = 1) P < 0.0001

Q ("non-combinability" for relative risk) = 9.132299 (df = 4) P = 0.0579
I^2 : 56.2%



Relative risk meta-analysis: ACR-70

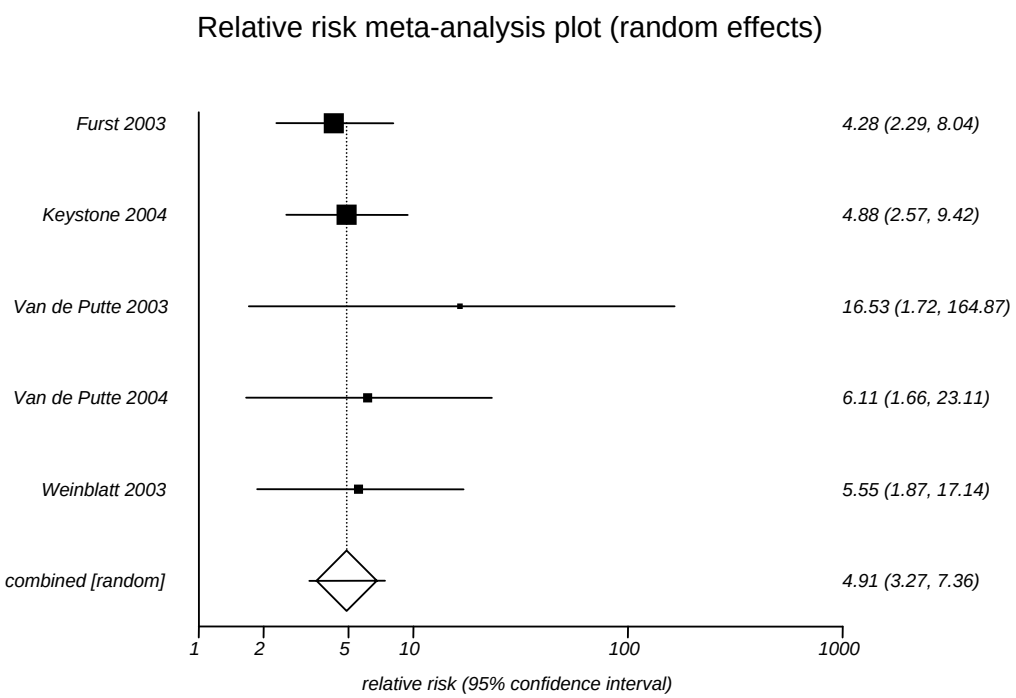
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	4.278545	2.294726	8.036822	5.5	Furst 2003
2	4.879342	2.568811	9.421447	6.092084	Keystone 2004
3	16.531034	1.715513	164.871224	0.253497	Van de Putte 2003
4	6.111111	1.66042	23.11434	1.343284	Van de Putte 2004
5	5.552239	1.873092	17.136578	1.55814	Weinblatt 2003

M-H pooled estimate (Rothman-Boice) of relative risk = 5.038857
Robins-Greenland approximate 95% CI = 3.353377 to 7.571496

Chi-square (for pooled relative risk) = 60.586043 (df = 1) P < 0.0001

Q ("non-combinability" for relative risk) = 1.034209 (df = 4) P = 0.9046

I^2 : 0%


Relative risk meta-analysis plot (random effects)
Furst 2003
Keystone 2004
Van de Putte 2003
Van de Putte 2004
Weinblatt 2003
combined [random]
4.28 (2.29, 8.04)
4.88 (2.57, 9.42)
16.53 (1.72, 164.87)
6.11 (1.66, 23.11)
5.55 (1.87, 17.14)
4.91 (3.27, 7.36)
1
2
5
10
100
1000
relative risk (95% confidence interval)

ANAKINRA

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Population
Bresnihan et al. 1998[33]	RCT	472	24 weeks	AKA / Placebo	ACR-N	> 6 months active RA <8 years; mean disease duration: 3.7-4.3 years
Cohen et al. 2002[34]	RCT	419	24 weeks	AKA+MTX / MTX+ Placebo	ACR 20	> 6 months active RA < 12 years; stable MTX regimen; mean disease duration: 6.3-8.8 years
Cohen et al. 2004[32]	RCT	501	24 weeks	AKA+MTX / MTX+ Placebo	ACR20	> 6 months active RA; stable MTX regimen; mean disease duration: 10.5 yrs.

Relative risk meta-analysis: ACR-20

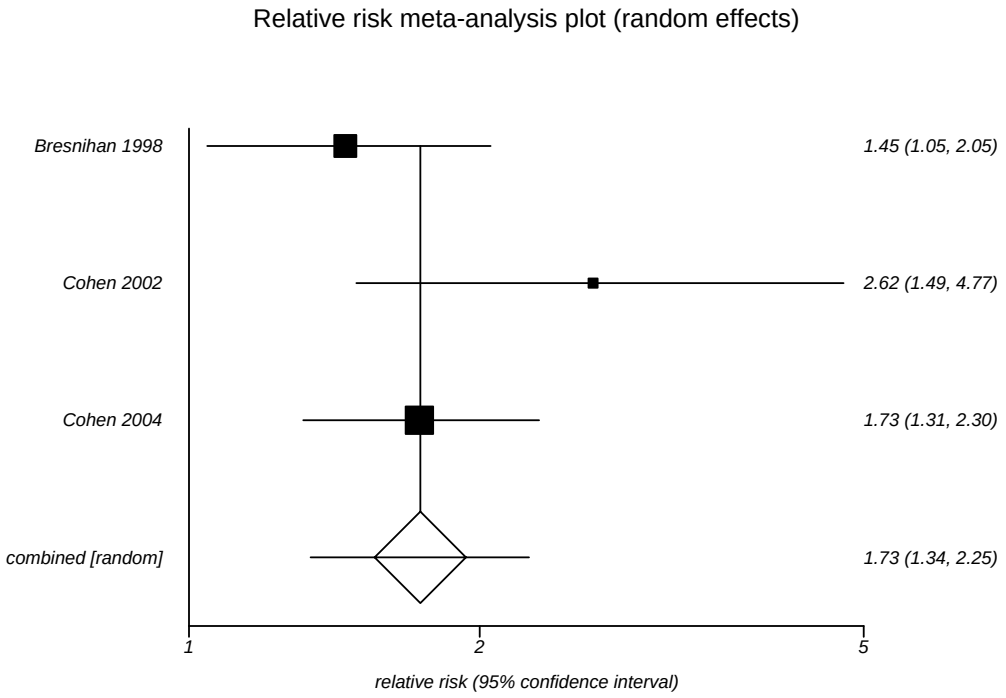
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	1.450566	1.045564	2.052383	21.031161	Bresnihan 1998
2	2.619469	1.491026	4.769021	6.647059	Cohen 2002
3	1.734182	1.312326	2.30411	27.44511	Cohen 2004

M-H pooled estimate (Rothman-Boice) of relative risk = 1.732727
Robins-Greenland approximate 95% CI = 1.413511 to 2.12403

Chi-square (for pooled relative risk) = 27.996519 (df = 1) P < 0.0001

Q ("non-combinability" for relative risk) = 2.927509 (df = 2) P = 0.2314

I^2 : 31.68%



Relative risk meta-analysis: ACR-50

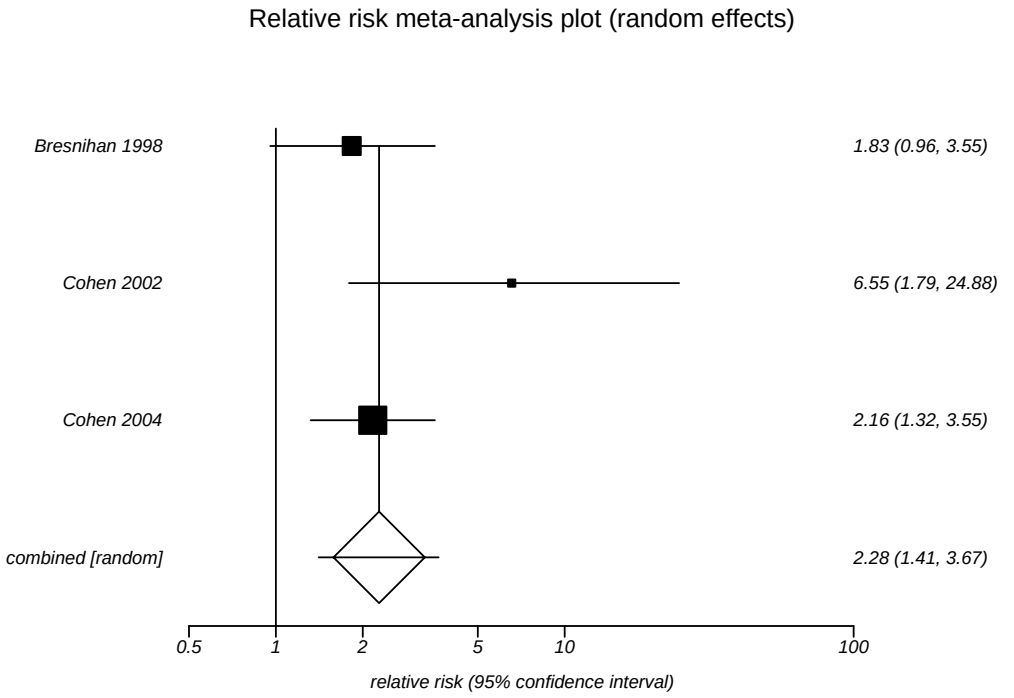
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	1.825431	0.958312	3.546318	6.572238	Bresnihan 1998
2	6.548673	1.790818	24.879122	1.208556	Cohen 2002
3	2.1586	1.318936	3.55346	9.98004	Cohen 2004

M-H pooled estimate (Rothman-Boice) of relative risk = 2.334041
Robins-Greenland approximate 95% CI = 1.590173 to 3.425885

Chi-square (for pooled relative risk) = 18.739732 (df = 1) P < 0.0001

Q ("non-combinability" for relative risk) = 2.631496 (df = 2) P = 0.2683

I^2 : 23.99%



Relative risk meta-analysis: ACR-70

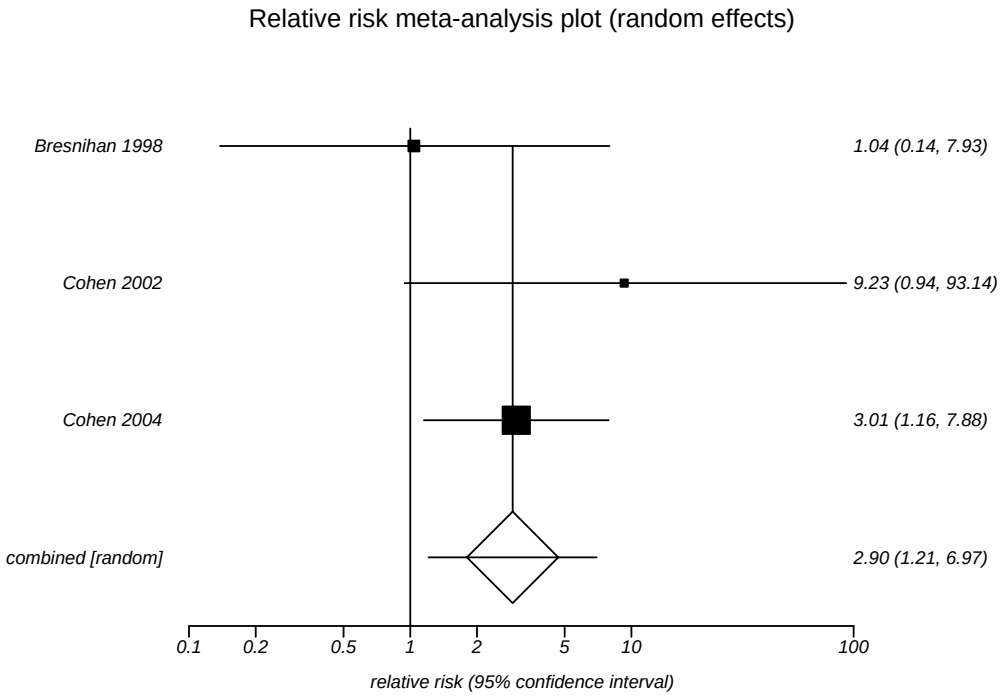
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	1.043103	0.138162	7.92919	0.657224	Bresnihan 1998
2	9.230088	0.942796	93.142286	0.301333	Cohen 2002
3	3.012	1.158293	7.883807	2.49501	Cohen 2004

M-H pooled estimate (Rothman-Boice) of relative risk = 3.179859
Robins-Greenland approximate 95% CI = 1.345937 to 7.512612

Chi-square (for pooled relative risk) = 6.955041 (df = 1) P = 0.0084

Q ("non-combinability" for relative risk) = 1.382147 (df = 2) P = 0.501

I^2 : 0%


Relative risk meta-analysis plot (random effects)
Bresnihan 1998
1.04 (0.14, 7.93)
Cohen 2002
9.23 (0.94, 93.14)
Cohen 2004
3.01 (1.16, 7.88)
combined [random]
2.90 (1.21, 6.97)
0.1
0.2
0.5
1
2
5
10
100
relative risk (95% confidence interval)

ETANERCEPT

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Population
Klareskog et al. 2004[21]	RCT	682	52 weeks	ETA / MTX / MTX + ETA	Sharp	> 6 months active RA; ACR functional class I-III; unsatisfactory response to at least one DMARD other than MTX; mean disease duration: 6.5 yrs.
Lan et al. 2004[41]	RCT	58	12 weeks	ETA+ MTX / Placebo + MTX	Number of swollen/ tender joints	Active RA > one year; stable MTX for 4 weeks; mean disease duration: NR
Moreland et al. 1997[43]	RCT	180	12 weeks	ETA / Placebo	Number of swollen/ tender joints	Active RA; failed 1 to 4 DMARD treatments; mean disease duration: NR
Moreland et al. 1999[39, 40]	RCT	234	12 weeks	ETA / Placebo	ACR20/50	Active RA; failed 1 to 4 DMARD treatments other than MTX; mean disease duration: 12 yrs.
Weinblatt et al. 1999[42]	RCT	89	24 weeks	ETA+ MTX / Placebo + MTX	ACR 20	Active RA; > 6 months MTX, stable >1 month; mean disease duration: 13 years

Relative risk meta-analysis: ACR-20

Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	1.264839	1.111763	1.447291	67.941176	Klareskog 2004
2	2.6	1.649044	4.544377	5	Lan 2004

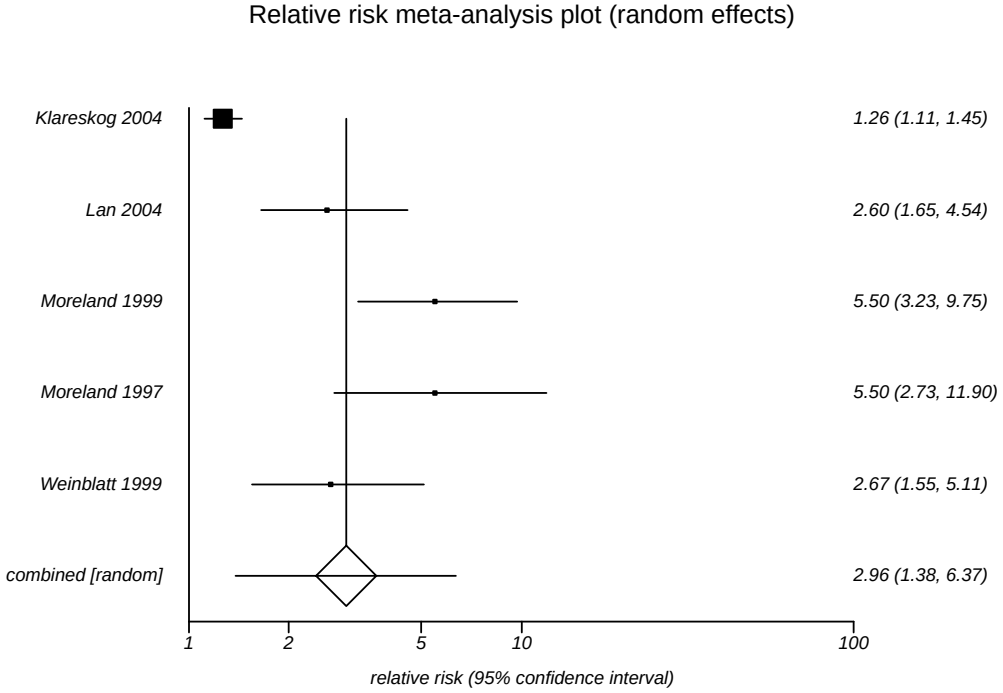
3	5.501166	3.234162	9.749303	5.43038	Moreland 1999
4	5.5	2.730932	11.900985	3	Moreland 1997
5	2.669492	1.547005	5.107559	5.303371	Weinblatt 1999

M-H pooled estimate (Rothman-Boice) of relative risk = 1.83981
Robins-Greenland approximate 95% CI = 1.618818 to 2.09097

Chi-square (for pooled relative risk) = 87.193615 (df = 1) P < 0.0001

Q ("non-combinability" for relative risk) = 56.969838 (df = 4) P < 0.0001

I^2: 92%



Relative risk meta-analysis: ACR-50

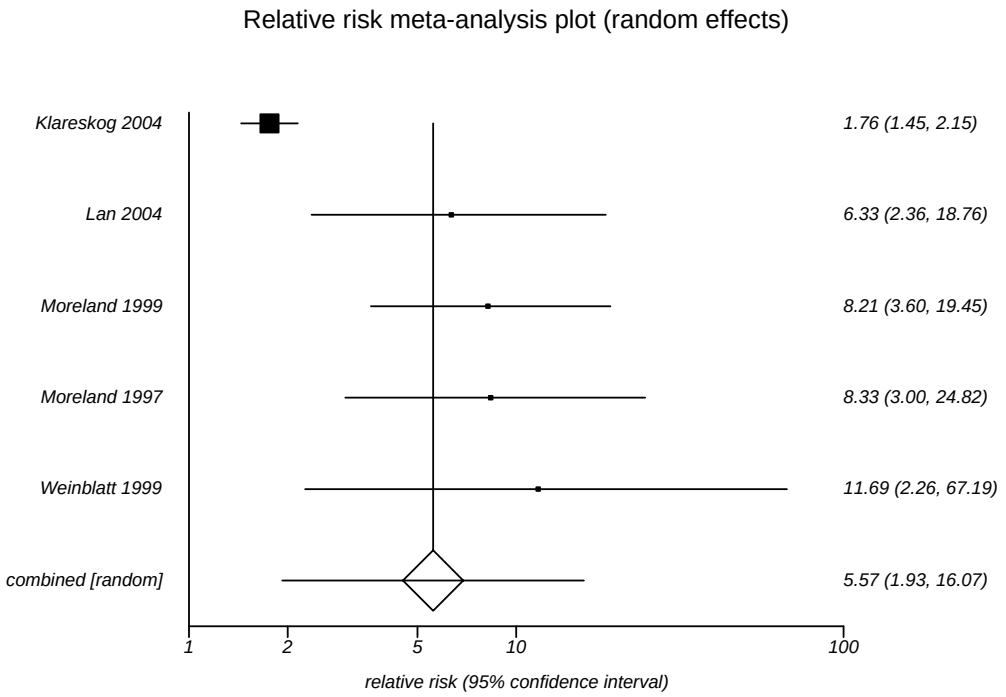
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	1.757365	1.446	2.153791	41.267974	Klareskog 2004
2	6.333333	2.362599	18.757771	1.5	Lan 2004
3	8.205128	3.598388	19.451313	2.468354	Moreland 1999
4	8.333333	2.998444	24.815338	1.5	Moreland 1997
5	11.694915	2.26005	67.188802	0.662921	Weinblatt 1999

M-H pooled estimate (Rothman-Boice) of relative risk = 2.585038
Robins-Greenland approximate 95% CI = 2.130037 to 3.137232

Chi-square (for pooled relative risk) = 92.446788 (df = 1) P < 0.0001

Q ("non-combinability" for relative risk) = 30.10553 (df = 4) P < 0.0001

I^2: 87%



Relative risk meta-analysis: ACR-70

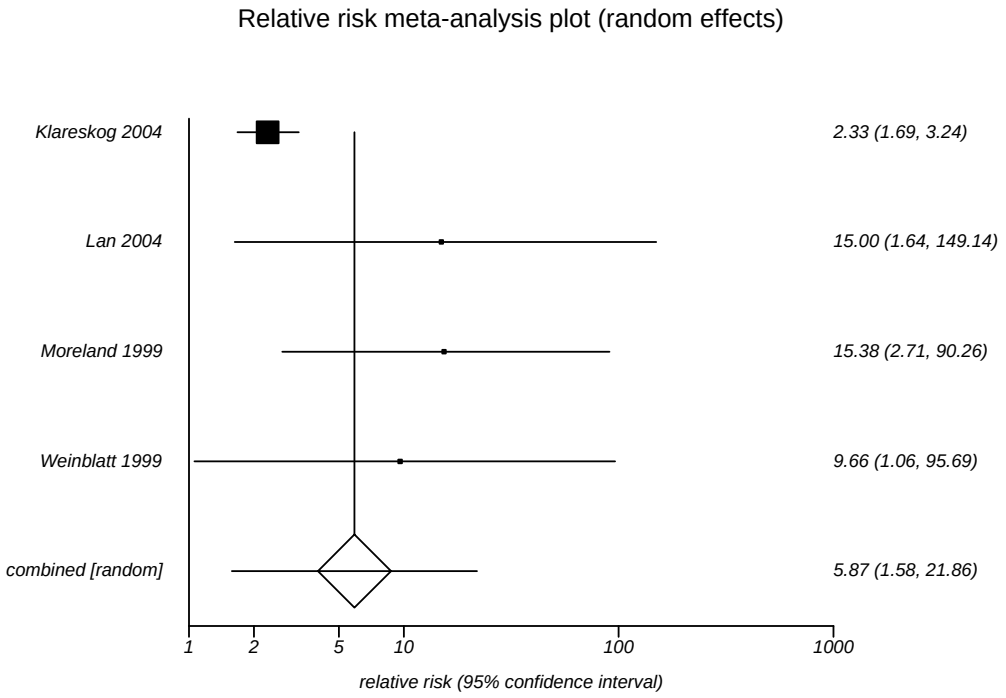
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	2.328338	1.689058	3.237337	19.627451	Klareskog 2004
2	15	1.635418	149.135742	0.25	Lan 2004
3	15.384615	2.714878	90.264012	0.493671	Moreland 1999
4	9.661017	1.061662	95.694514	0.331461	Weinblatt 1999

M-H pooled estimate (Rothman-Boice) of relative risk = 2.910097
Robins-Greenland approximate 95% CI = 2.116173 to 4.001877

Chi-square (for pooled relative risk) = 43.187838 (df = 1) P < 0.0001

Q ("non-combinability" for relative risk) = 6.455625 (df = 3) P = 0.0914

I^2: 53%



INFLIXIMAB

Author, year	Study design	N	Duration	Comparisons	Primary outcome	Population
Kavanaugh et al. 2000[125]	RCT	28	12 weeks	INF+ MTX / Placebo + MTX	ACR 20	RA < 15 years; MTX > 3 months; mean disease duration 4.9 – 7.5 years
Maini et al. 1998[48]	RCT		26 weeks	INF+ MTX / Placebo + MTX	Paulus 20	MTX > 6 months; mean disease duration 7.6 – 114.3 years
Maini et al. 1999[46]	RCT		30 weeks	INF+MTX / Placebo + MTX	ACR 20	MTX stable > 4 weeks; mean disease duration 7.2 – 9.0 years
St. Clair et al. 2004[25]	RCT	1049	52 weeks	INF+MTX / Placebo + MTX	ACR-N	Early RA, MTX naïve patients; mean disease duration: 0.9 yrs.

Relative risk meta-analysis: ACR-20

Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	5.5	1.427618	30.996512	0.666667	Kavanough 2000
2	3.036863	1.947037	4.928533	11.915888	Maini 1999
3	5.75	1.235809	32.88213	0.8	Maini 1998
4	1.179069	1.056888	1.328158	115.059761	St. Clair 2004

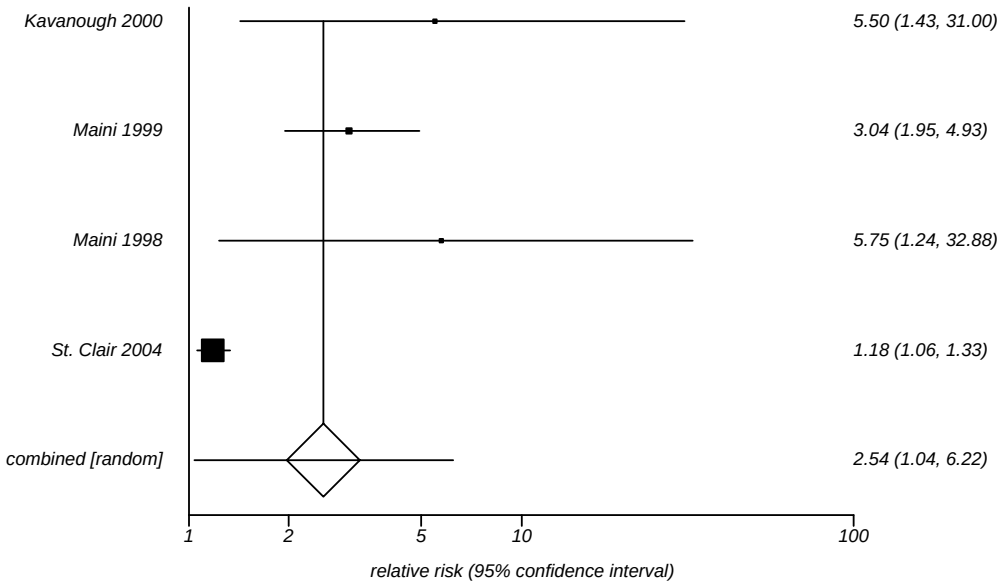
M-H pooled estimate (Rothman-Boice) of relative risk = 1.402318
Robins-Greenland approximate 95% CI = 1.24646 to 1.577664

Chi-square (for pooled relative risk) = 31.639084 (df = 1) P < 0.0001

Q ("non-combinability" for relative risk) = 23.368566 (df = 3) P < 0.0001

I^2 : 87.16%

Relative risk meta-analysis plot (random effects)



Relative risk meta-analysis: ACR-20, St. Clair et al. removed

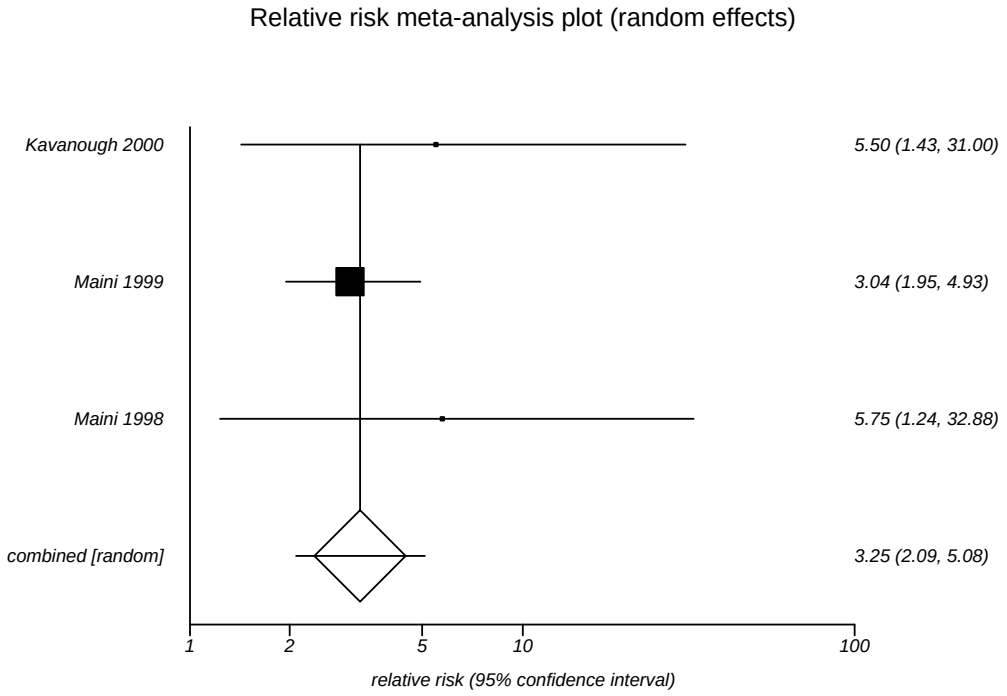
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	5.5	1.427618	30.996512	0.666667	Kavanough 2000
2	3.036863	1.947037	4.928533	11.915888	Maini 1999
3	5.75	1.235809	32.88213	0.8	Maini 1998

M-H pooled estimate (Rothman-Boice) of relative risk = 3.321756
Robins-Greenland approximate 95% CI = 2.128243 to 5.184588

Chi-square (for pooled relative risk) = 27.932639 (df = 1) P < 0.0001

Q ("non-combinability" for relative risk) = 0.743101 (df = 2) P = 0.6897

I^2 : 0%



Relative risk meta-analysis: ACR-50

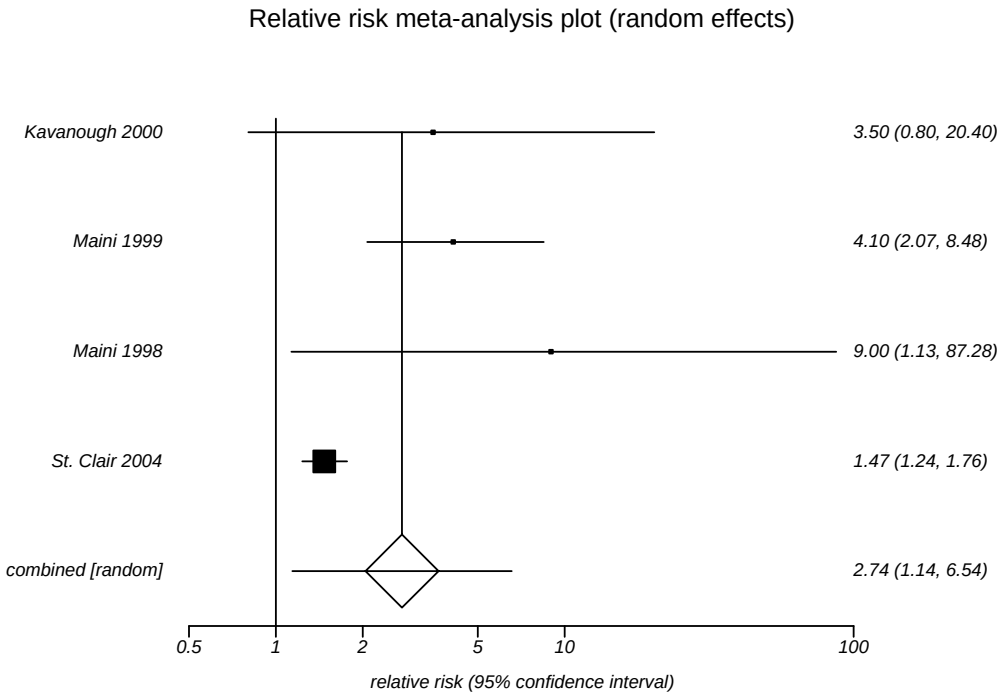
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	3.5	0.804588	20.402506	0.666667	Kavanough 2000
2	4.104202	2.066097	8.480455	5.560748	Maini 1999
3	9	1.134499	87.282643	0.4	Maini 1998
4	1.46875	1.235903	1.763536	69.035857	St. Clair 2004

M-H pooled estimate (Rothman-Boice) of relative risk = 1.72015
Robins-Greenland approximate 95% CI = 1.442358 to 2.051443

Chi-square (for pooled relative risk) = 36.431565 (df = 1) P < 0.0001

Q ("non-combinability" for relative risk) = 10.455016 (df = 3) P = 0.0151

I^2 : 71.3%



Relative risk meta-analysis: ACR-50, St. Clair et al. removed

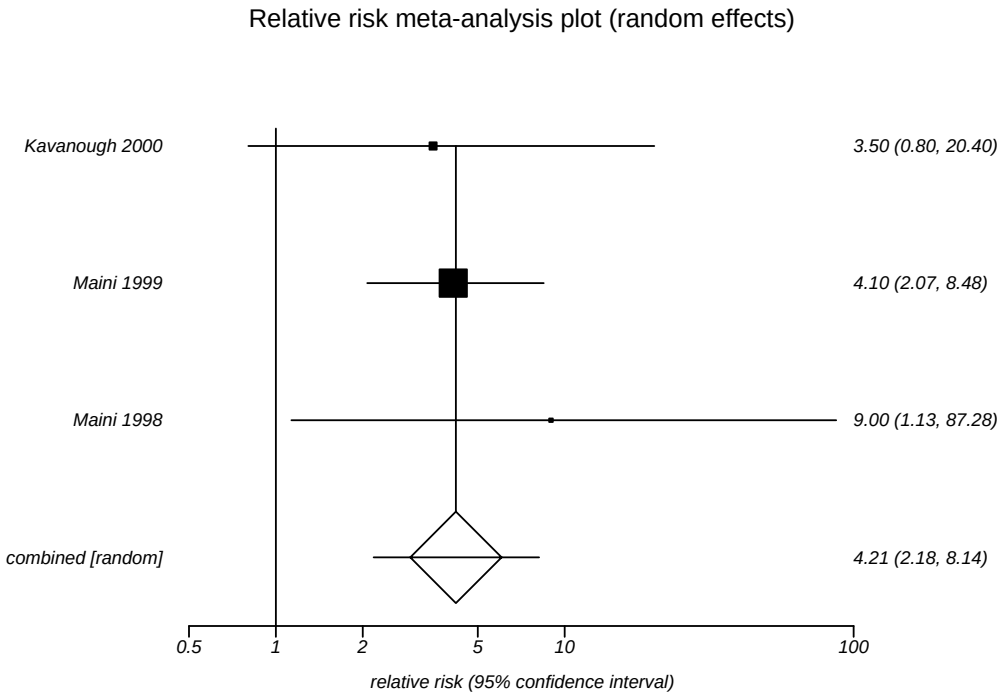
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	3.5	0.804588	20.402506	0.666667	Kavanough 2000
2	4.104202	2.066097	8.480455	5.560748	Maini 1999
3	9	1.134499	87.282643	0.4	Maini 1998

M-H pooled estimate (Rothman-Boice) of relative risk = 4.338911
Robins-Greenland approximate 95% CI = 2.238203 to 8.411279

Chi-square (for pooled relative risk) = 18.883176 (df = 1) P < 0.0001

Q ("non-combinability" for relative risk) = 0.3425 (df = 2) P = 0.8426

I^2 : 0%


Relative risk meta-analysis plot (random effects)
Kavanough 2000
3.50 (0.80, 20.40)
Maini 1999
4.10 (2.07, 8.48)
Maini 1998
9.00 (1.13, 87.28)
combined [random]
4.21 (2.18, 8.14)
0.5
1
2
5
10
100
relative risk (95% confidence interval)

ANTI-TNF-combined

Relative risk meta-analysis: ACR-20

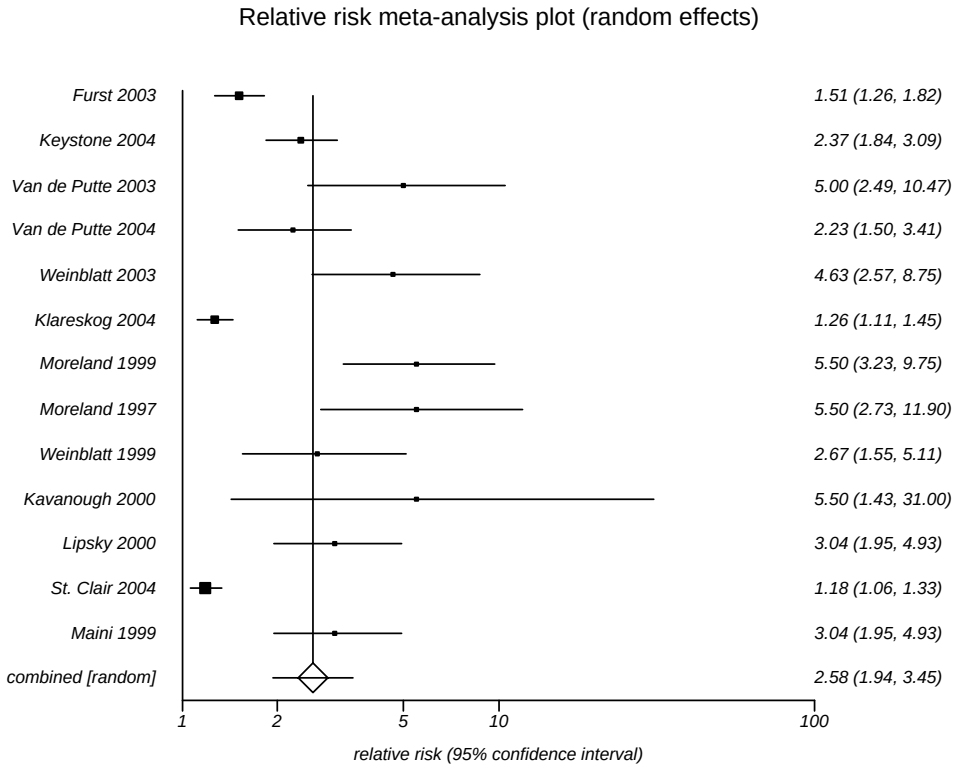
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	1.512649	1.262808	1.819429	55.5	Furst 2003
2	2.366746	1.84119	3.091321	32.491115	Keystone 2004
3	5	2.48527	10.473312	3.549296	Van de Putte 2003
4	2.234921	1.504395	3.410148	14.104478	Van de Putte 2004
5	4.626866	2.572227	8.746322	4.674419	Weinblatt 2003
6	1.264839	1.111763	1.447291	67.941176	Klareskog 2004
7	5.501166	3.234162	9.749303	5.43038	Moreland 1999
8	5.5	2.730932	11.900985	3	Moreland 1997
9	2.669492	1.547005	5.107559	5.303371	Weinblatt 1999
10	5.5	1.427618	30.996512	0.666667	Kavanough 2000
11	3.036863	1.947037	4.928533	11.915888	Lipsky 2000
12	1.179069	1.056888	1.328158	115.059761	St. Clair 2004
13	3.036863	1.947037	4.928533	11.915888	Maini 1999

M-H pooled estimate (Rothman-Boice) of relative risk = 1.779255
Robins-Greenland approximate 95% CI = 1.651402 to 1.917005

Chi-square (for pooled relative risk) = 229.355659 (df = 1) $P < 0.0001$

Q ("non-combinability" for relative risk) = 138.046956 (df = 12) $P < 0.0001$

I^2 : 91.3%



Relative risk meta-analysis: ACR-50

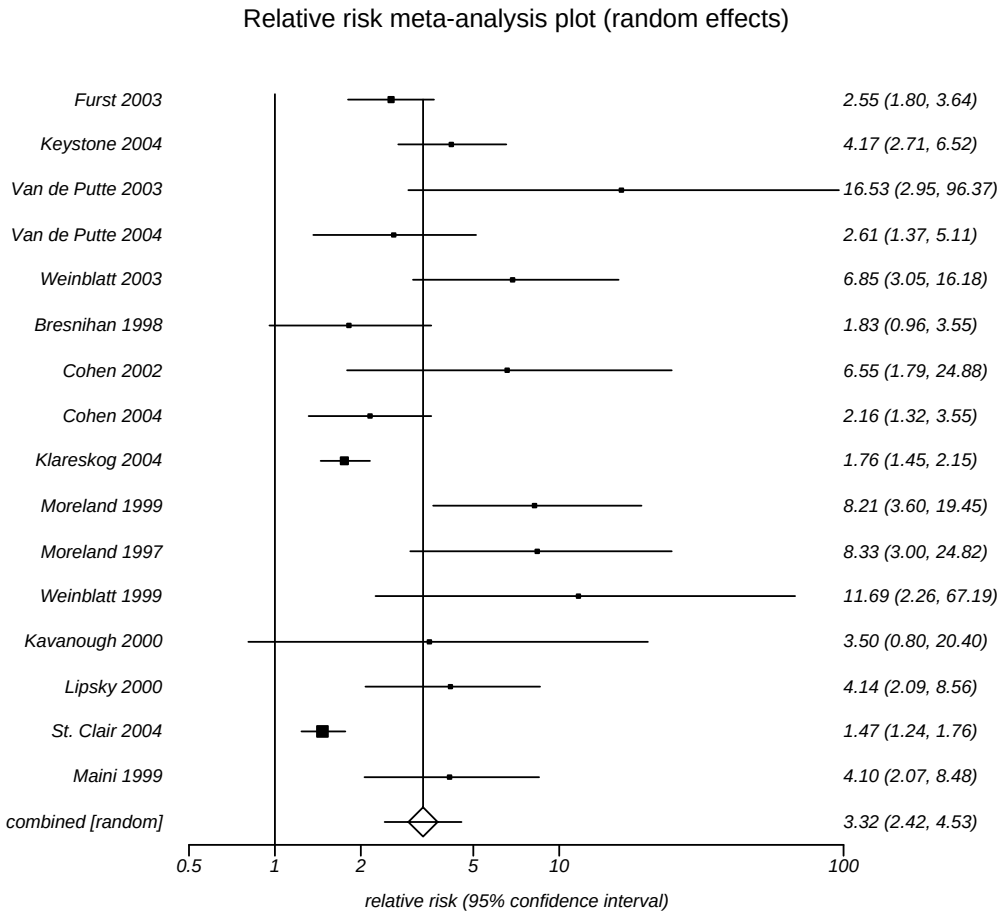
Stratum	Relative risk	95% CI (Koopman)		M-H weight	
1	2.552833	1.80314	3.63624	18	Furst 2003
2	4.17033	2.711696	6.522056	12.861066	Keystone 2004
3	16.527778	2.954667	96.371191	0.507042	Van de Putte 2003
4	2.607407	1.365527	5.10824	6.044776	Van de Putte 2004
5	6.847761	3.047254	16.177401	2.596899	Weinblatt 2003
6	1.825431	0.958312	3.546318	6.572238	Bresnihan 1998
7	6.548673	1.790818	24.879122	1.208556	Cohen 2002
8	2.1586	1.318936	3.55346	9.98004	Cohen 2004
9	1.757365	1.446	2.153791	41.267974	Klareskog 2004
10	8.205128	3.598388	19.451313	2.468354	Moreland 1999
11	8.333333	2.998444	24.815338	1.5	Moreland 1997
12	11.694915	2.26005	67.188802	0.662921	Weinblatt 1999
13	3.5	0.804588	20.402506	0.666667	Kavanough 2000
14	4.141176	2.085196	8.555213	5.560748	Lipsky 2000
15	1.46875	1.235903	1.763536	69.035857	St. Clair 2004
16	4.104202	2.066097	8.480455	5.560748	Maini 1999

M-H pooled estimate (Rothman-Boice) of relative risk = 2.415115
Robins-Greenland approximate 95% CI = 2.162357 to 2.697418

Chi-square (for pooled relative risk) = 244.388978 (df = 1) $P < 0.0001$

Q ("non-combinability" for relative risk) = 76.578282 (df = 15) $P < 0.0001$

I^2 : 80.41%


Relative risk meta-analysis plot (random effects)
Furst 2003
Keystone 2004
Van de Putte 2003
Van de Putte 2004
Weinblatt 2003
Bresnihan 1998
Cohen 2002
Cohen 2004
Klareskog 2004
Moreland 1999
Moreland 1997
Weinblatt 1999
Kavanough 2000
Lipsky 2000
St. Clair 2004
Maini 1999
combined [random]
2.55 (1.80, 3.64)
4.17 (2.71, 6.52)
16.53 (2.95, 96.37)
2.61 (1.37, 5.11)
6.85 (3.05, 16.18)
1.83 (0.96, 3.55)
6.55 (1.79, 24.88)
2.16 (1.32, 3.55)
1.76 (1.45, 2.15)
8.21 (3.60, 19.45)
8.33 (3.00, 24.82)
11.69 (2.26, 67.19)
3.50 (0.80, 20.40)
4.14 (2.09, 8.56)
1.47 (1.24, 1.76)
4.10 (2.07, 8.48)
3.32 (2.42, 4.53)
0.5
1
2
5
10
100
relative risk (95% confidence interval)

APPENDIX F. Abstract-only Studies (Not Included)

1. Antoni C, Kavanaugh A, Manger B, Kalden J, Keenan GF, Schaible T. Responses to infliximab therapy in the ATTRACT trial assessed with disease activity score (DAS); clinical response measured by DAS correlated with arrest of radiologic progression and shows higher response rates than ACR20 criteria. Arthritis Rheum 2000;43 Suppl:S147.

2. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005.

3. Antoni CE, Furst D, Manger B, Lichtenstein GR, Keenan GF, Healy DE, et al. Outcome of pregnancy in women receiving Remicade (infliximab) for the treatment of Crohn's Disease or rheumatoid arthritis. American College of Rheumatology, 65th Annual Scientific Meeting 2001.

4. Breedveld F. Multiple faces of rheumatoid arthritis: diagnostic and therapeutic algorithms. Autoimmun Rev 2004;3 Suppl 1:S22.

5. Cohen SB, Moreland L, Cush JJ, Greenwald MW, Block JA, Shergy WJ. Anakinra (recombinant interleukin-1 receptor antagonist): a large, placebo controlled efficacy trial of anakinra in patients with erosive rheumatoid arthritis disease. Arthritis Rheum 2001;44:LB1.

6. Ericson M, Wajdula J. A double-blind, placebo controlled study of the efficacy and safety of four different doses of etanercept in patients with rheumatoid arthritis. Arthritis Rheum 1999;42:S82.

7. Furst D, Keystone E, Weinblatt M, Kavanaugh A, Weisman M, Fischkoff S, et al. TNF blockade by the fully human monoclonal antibody adalimumab (D2E7) in the Armada trial results in decreases in serum matrix metalloproteinase (MMP) levels along with impressive clinical improvement in refractory RA patients.S215.

8. Gottlieb A, Goffe B, Tsuji W, Zitnik R, Burge D. Etanercept (ENBREL(R)) inhibits radiographic progression in patients with psoriatic arthritis. Abstract 0402 International Investigative Dermatology. The 4th Joint Meeting of the ESDR, Japanese SID & SID, 30th April4thMay 2003, Florida, USA. Journal of Investigative Dermatology 2003;121(1):Abstract #0402.

9. Kavanaugh A, Lipsky P, Furst D, Weisman M, St Clair EW, Smolen J. Infliximab improves long-term quality of life and functional status in patients with rheumatoid arthritis. Arthritis Rheum 2000;43 Suppl:S147.

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11. Manadan AM, Mohan AK. Tuberculosis and etanercept treatment. Arthritis Rheum 2002;46:S166.

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13. Ruderman EM, Markenson J. Granulomatous infections and tumor necrosis factor antagonists therapy: update through June 2002. Arthritis Rheum 2003;48(9):S241.

14. Smolen JS PE, J Bathon, E Keystone, RN Maini, J Kalden, D Baker, B Wang, K De Woody, D van der Heijde, E St Clair. Treatment of early rheumatoid arthritis with infliximab plus methotrexate or methotrexate alone: preliminary results of the ASPIRE Trial. EULAR 2003:OP001.

15. Stichweh DS, Punaro M, V. P. Infliximab-induced double-stranded DNA antibodies in children with rheumatological diseases. Arthritis Rheum 2003;48(9):S100.

16. Wajdula J. A double-blind, placebo-controlled study of the efficacy and safety of four different doses of etanercept in patients with rheumatoid arthritis. Ann Rheum Dis 2000;59 Suppl 1:163.

APPENDIX G. Acknowledgements

Acknowledgements

Reviewers

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Stanley Cohen, MD
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EVIDENCE TABLES

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

STUDY:	**Authors: Bathon et al.,[20] Genovese et al.[38]** **Year: 2000 and 2002** **Country:** US		
FUNDING:	Immunex Corporation		
RESEARCH OBJECTIVE:	To compare ETA and MTX in patients with early rheumatoid arthritis		
DESIGN:	**Study design:** RCT **Setting:** Clinics **Sample size:** 632		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Methotrexate** 20mg/week 12 months 217	**Etanercept10** 10 mg 2x week 12 months 208	**Etanercept25** 25 mg 2x week 12 months 207
INCLUSION CRITERIA:	At least 18 years of age; RA <3 years; positive serum test for rheumatoid factor 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. and Genovese et al. **Year: 2000 and 2002**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Early RA		
	Methotrexate	**Etanercept 10mg**	**Etanercept 25mg**
Mean age (years):	49	50	51
Sex (% female):	75	75	74
Ethnicity (% white):	88	84	86
Other germane population qualities:			
• Tender joint count	30	31	31
• Swollen joint count	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. and Genovese 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 rheumatoid arthritis. 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. and Genovese et al. **Year: 2000 and 2002**			
ADVERSE EVENTS (%): **Overall adverse effects reported:**	**Methotrexate**	**Etanercept10**	**Etanercept25**
• ISR	7	30	37*
• Nausea	29	14*	17*
• Bleeding at injection site	10	14	14
• Skin infection	10	11	14
• Rash	23	16	12*
• Dizziness	11	5	12
• Back pain	6	6	11
• Sinusitis	17	13	10
• Alopecia	12	7	6*
• Mouth ulcer	14	6*	5*
* = P < 0.05 for comparison to MTX			
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		
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*):	**Methotrexate**	**Etanercept10**	**Etanercept25**
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.**[44] **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 INF 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: tender joint count, swollen joint count, 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.**[36] **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 ETA 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: tender joint count, swollen joint count, 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 injection site reaction was increased in patients taking 10 mg ETA versus controls RR 3.86; 95% CI 2.59-5.77 • The risk of injection site reaction 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: Clark, et al.**[31] **Year:** 2004 **Country:** International: Europe, U.S., Canada, Australia
FUNDING:	Health Technology Assessment Programme (U.K.)
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 1007
AIMS OF REVIEW:	To review the evidence on the clinical benefits and hazards of using AKA 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, U.S., 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) ▪ Swollen Joint Count: -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% ▪ Injection Site Reactions: 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.**[126] **Year: 2004** **Country:** Multinational		
FUNDING:	Amgen, Thousand Oaks, CA, USA		
RESEARCH OBJECTIVE:	To evaluate effects of AKA 100mg injection daily versus placebo injection in combination with MTX in patients with persistent RA activity after treatment with MTX alone.		
DESIGN:	**Study design**: RCT **Setting:** Multicenter, university clinic **Sample size:** 501		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Anakinra** 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		
	Anakinra	**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	
• Swollen joint count (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) • Swollen joint count: -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:	**Anakinra**	**Placebo**	
Overall adverse events reported:	90	81	
• Injection site reactions, %	65	24	
o withdrawals	8.4	0.8	
• Serious adverse events, %	4	3	
o withdrawals	0.8	1	
• Infectious events, %	33	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*):	**Anakinra**	**Placebo**	
Loss to follow-up:	NR	NR	
Withdrawals due to adverse events:	9.2%	1.8%	
QUALITY RATING:	**Fair**		

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

STUDY:	**Authors: Durez et al.**[45] **Year: 2005** **Country:** Belgium		
FUNDING:	Schering-Plough (Belgium)		
RESEARCH OBJECTIVE:	To assess the effect of a dose increase of INF in patients with severe RA with insufficient clinical response		
DESIGN:	**Study design:** Uncontrolled trial **Setting:** NR **Sample size:** 511		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Stable dose** 3 mg/kg 62 weeks 405	**Dose increase** 3 mg/kg +100 mg 62 weeks 106	
INCLUSION CRITERIA:	Age between 18 and 80 yr; fulfilling ACR criteria for RA; suffering from active disease despite treatment with MTX at a weekly dose of 15 mg (at least 10 mg in the case of poor tolerance) were studied.		
EXCLUSION CRITERIA:	None reported		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes		

<table>
<tr><td colspan="4">Authors: Durez et al.
Year: 2005</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No
Disease severity: Moderate-severe</td></tr>
<tr><td></td><td><u>Stable dose</u></td><td><u>Dose increase</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>53</td><td>52</td><td></td></tr>
<tr><td>Sex (% female):</td><td>79</td><td>74</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>• Tender joint count</td><td>19.3*</td><td>24.4</td><td></td></tr>
<tr><td>• Swollen joint count</td><td>14.5*</td><td>18.2</td><td></td></tr>
<tr><td>• Mean disease duration</td><td>13</td><td>11</td><td></td></tr>
<tr><td>• DMARD use (%)</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>• MTX use (%)</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>• Corticosteroids use (%)</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>• DAS score</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>• HAQ score</td><td>1.6*</td><td>1.7</td><td></td></tr>
<tr><td></td><td>*P < 0.001</td><td></td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ACR20/50/70; subgroup analysis of patients with dose increase

Timing of assessments: at weeks 6, 22, 30, 54 and 62</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• At 62 weeks: ACR20 66.1%; ACR50 43.2%; ACR70 22.8%
• Remission achieved by 7% of patients at 62 weeks
• At week 62 the dose increase group reached nearly the same rate of ACR20 as the stable dose group.</td></tr>
</table>

Authors: Durez et al. **Year: 2005**			
ADVERSE EVENTS: **Overall serious adverse effects reported: 164 (32% if one per n)** • Serious infections • Malignancies • Cardiovascular events • Hypersensitivity	**Stable dose** 44 (11%)	**Dose increase** 11 (10%)	**All** 12 (2%) 12 (2%) 9 (2%)
Significant differences in adverse events:	NR		
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*): **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 N/A		
QUALITY RATING:	**N/A**		

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

STUDY:	**Authors: Furst et al.**[27] **Year: 2003** **Study name: STAR (Safety Trail of Adalimumab in Rheumatoid Arthritis)** **Country:** USA and Canada		
FUNDING:	Abbott Laboratories, Abbot Park, Il		
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of ADA 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:**	**Adalimumab** 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		
	Adalimumab	**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:			
• Tender joint count	27.3	27.6	
• Swollen joint count	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:**	**Adalimumab**	**Placebo**	
• Upper respiratory infection	19.8%	15.1%	
• Urinary tract infection	9.1%	5.7%	
• Injection site reaction	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 injection site reaction 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*):	**Adalimumab**	**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.**[18] **Year: 2002** **Country:** Sweden		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To assess the efficacy and safety of ETA, INF, 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:**	**Etanercept** Varied 12 months 166	**Infliximab** 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		
	Etanercept	**Infliximab**	**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:	**Etanercept**	**Infliximab**	**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.**[23] **Year: 2004** **Country:** U.S.		
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-alpha agent ETA and the anti-IL1 agent AKA.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter, specialty clinic **Sample size:** 242		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Etanercept** 25 mg *twice* per week 24 weeks 80	**½ Etanercept + Anakinra** 25 mg *once* per week; 100 mg/day 24 weeks 81	**Etanercept + Anakinra** 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>Etanercept</u></td><td><u>½ Etanercept + Anakinra</u></td><td><u>Etanercept + Anakinra</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>• Tender joint count</td><td>31.0</td><td>31.0</td><td>35.9</td></tr>
<tr><td>• Swollen joint count</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:	**Etanercept**	**½ Etanercept + Anakinra**	**Etanercept + Anakinra**
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 injection site reactions and serious adverse events than patients receiving etanercept 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*):	**Etanercept**	**½ Etanercept + Anakinra**	**Etanercept + Anakinra**
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: Jobanputra et al.**[37] **Year:** 2002 **Country:** Multinational
FUNDING:	Health Technology Assessment Programme (U.K.)
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 1692 (ETA: 1062, INF: 630)
AIMS OF REVIEW:	To examine evidence for the clinical effectiveness of ETA and INF 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: add'l 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) ▪ Swollen Joint Count: -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) not reported.
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: ▪ Injection site reactions 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 ▪ Upper respiratory tract infections: 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.**[28] **Year: 2004** **Country:** US and Canada		
FUNDING:	Abbott Laboratories, Abbott Park, Illinois		
RESEARCH OBJECTIVE:	To investigate the ability of ADA to inhibit the progression of structural joint damage, reduce the signs and symptoms, and improve physical function in patients with RA receiving concomitant MTX treatment.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter (89 sites) **Sample size:** 619		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Adalimumab 40 mg biweekly** 40 mg every other week 52 weeks 207	**Adalimumab 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 rheumatoid factor 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)		

<table>
<tr><td colspan="4">Authors: Keystone et al.
Year: 2004</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>Adalimumab 40 mg biweekly</u></td><td><u>Adalimumab 20 mg weekly</u></td><td><u>Placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>56.1</td><td>57.3</td><td>56.1</td></tr>
<tr><td>Sex (% female):</td><td>76.3</td><td>75.5</td><td>73.0</td></tr>
<tr><td>Ethnicity: (% White)</td><td>83.6</td><td>85.4</td><td>83.0</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Tender joint count</td><td>27.3</td><td>27.9</td><td>28.1</td></tr>
<tr><td>• Swollen joint count</td><td>19.3</td><td>19.6</td><td>19.0</td></tr>
<tr><td>• DMARD use (%)</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• MTX use (%)</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Physician’s assessment of disease activity</td><td>62.0</td><td>61.6</td><td>613.</td></tr>
<tr><td>• Patient’s assessment of disease activity</td><td>52.7</td><td>51.9</td><td>54.3</td></tr>
<tr><td>• HAQ score</td><td>1.45</td><td>1.44</td><td>1.48</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">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;</td></tr>
<tr><td>RESULTS:</td><td colspan="3">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%)</td></tr>
</table>

Authors: Keystone et al. **Year: 2004**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**Adalimumab 40 mg biweekly**	**Adalimumab 20 mg weekly**	**Placebo**
• Serious infections	5.3%	2.4%	0.5%
• Injection site reaction	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*):	**Adalimumab 40 mg biweekly**	**Adalimumab 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.**[21] **Study name: TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes)** **Year: 2004** **Country:** Multinational (Europe)		
FUNDING:	Wyeth Research		
RESEARCH OBJECTIVE:	To compare safety and efficacy of the combination of ETA and MTX with the monotherapies in patients with RA who had failed previous DMARD treatment.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 682		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Methotrexate** 20 mg per week 52 weeks 228	**Etanercept** 25 mg twice per week 52 weeks 223	**Methotrexate + Etanercept** Same MTX + ETA doses 52 weeks 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. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate-severe		
	Methotrexate	**Etanercept**	**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: numeric index of the ACR response (ACR-N) area under the curve (AUC) over the first 24 weeks; radiographic: change from baseline in total joint damage score (modified total Sharp score) over 52 weeks **Secondary Outcome Measures:** ACR20, ACR50, ACR70 responses; disease activity score, remission (disease activity score < 1.6); and HAQ **Timing of assessments:** Baseline, 24 weeks, and 53 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. **Year: 2004**	
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: o Combination vs. MTX: 6.1 (4.5-7.8) (P < 0.0001) o ETA vs. MTX: 2.5 (0.8-4.2) (P = 0.0034) o 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 o ACR20: 85% (80-89) vs. 76% (70-81) vs. 75% (69-80); combination vs. ETA: P = 0.0151; combination vs. MTX: P = 0.0091 o ACR50: 69% (63-75) vs. 48% (42-55) vs. 43% (36-49); combination vs. ETA: P < 0.0001; combination vs. MTX: P < 0.0001 o 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 (disease activity score < 1.6): 35% (29-41) vs. 16% (11-21) vs. 13% (9-18) o (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) o (combination vs. ETA: P < 0.0001; combination vs. MTX: P < 0.0001; ETA vs. MTX: P = 0.3751) **Intermediate Outcome Measures (combination v. ETA v. MTX) (95% CI)** • Disease activity score, 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)

Authors: Klareskog et al. **Year: 2004**			
ADVERSE EVENTS:	**Methotrexate**	**Etanercept**	**Methotrexate + Etanercept**
Overall adverse effects reported:	185	192	187
• **Abdominal Pain, %**	18	12	18
• **Diarrhea, %**	9	10	8
• **Nausea**	32	10	24
• **Vomiting, %**	11	3	5
• **Headache, %**	14	15	15
• **Injection site reaction, %**	2	21	10
• **Rash, %**	9	7	10
• **Infections, number (%)**	147 (64%)	131 (59%)	154 (67%)
o **Serious**	10 (4%)	10 (4%)	10 (4%)
Significant differences in adverse events:	• Injection Site Reaction: 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		
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) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**Methotrexate**	**Etanercept**	**Methotrexate + Etanercept**
Loss to follow-up:	NR	NR	NR
Withdrawals due to adverse events:	14.0%	11.2%	10.4%
Lack of Efficacy	9.2%	7.2%	2.6%
QUALITY RATING:	**Good**		

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

STUDY:	**Authors: Kosinski et al.**[22] **Year: 2002** **Country:** USA		
FUNDING:	Wyeth-Ayerst Laboratories, Philadelphia PA and Immunex, Seattle WA		
RESEARCH OBJECTIVE:	To document the burden of early RA on health-related quality of life and compare changes in health-related quality of life across 2 treatments.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter **Sample size:** 424		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Etanercept** 25 mg (2x weekly) 52 weeks 207	**Methotrexate** 20 mg/week 52 weeks 217	
INCLUSION CRITERIA:	Diagnosis of RA of 3 years or less; no previous MTX treatment; active disease characterized by 10 or more swollen and 12 or more tender joints; erosions on baseline X-rays of hands or feet or a positive test for rheumatoid factor; stability on prednisone 10 mg or less per day		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NSAIDs		

<table>
<tr><td colspan="4">Authors: Kosinski et al.
Year: 2002</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: NR</td></tr>
<tr><td></td><td><u>Etanercept</u></td><td><u>Methotrexate</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>51</td><td>49</td><td></td></tr>
<tr><td>Sex (% female):</td><td>74</td><td>75</td><td></td></tr>
<tr><td>Ethnicity (% Caucasian):</td><td>86</td><td>88</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Rheumatoid factor positive (%)</td><td>87</td><td>89</td><td></td></tr>
<tr><td>• Mean tender joint count</td><td>31</td><td>30</td><td></td></tr>
<tr><td>• Mean swollen joint count</td><td>24</td><td>24</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: SF-36; HAQ
Secondary Outcome Measures: ASHI
Timing of assessments: Baseline; weeks 2, 4, 8, 12, 16, 20, 26, 34, 42, and 52</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No significant difference in SF-36, HAQ, and ASHI scores were found between treatment groups during weeks 16-52.
• Mean changes in SF-36, HAQ, and ASHI were significantly better in patients in the ETA group than the MTX group during the first 12 weeks. ($P < 0.0001$, $P < 0.0001$, and $P < 0.0001$ respectively; P values are based on Treatment X Time interaction term in ANOVA analysis)
• Pretreatment QoL measures significantly below that of general population ($P < 0.0001$). After 52 weeks of treatment, despite improvement, QoL measures remained below that of the general population ($P < 0.0001$).</td></tr>
</table>

Authors: Kosinski et al. **Year: 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**<u>Etanercept</u>** **NR**	**<u>Methotrexate</u>** **NR**	
Significant differences in adverse events:	N/A		
ANALYSIS:	**ITT:** NR **Post randomization exclusions:** NR		
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:** NR		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**<u>Etanercept</u>** NR	**<u>Methotrexate</u>** NR	
QUALITY RATING:	**Fair**		

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

STUDY:	**Authors: Moreland et al.**[39], **Mathias et al.**[40] **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, ETA 10 mg, or ETA 25 mg over a 26-week period; embedded in a phase III, double-blind clinical trial (Moreland 1999, Article #116)		
DESIGN:	**Study design:** RCT **Setting:** Multicenter, specialty clinic **Sample size:** 234		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 26 weeks 80	**Etanercept (low dose)** 10 mg twice per week 26 weeks 76	**Etanercept (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	**Etanercept (low dose)**	**Etanercept (high dose)**
Mean age (years):	51	53	53
Sex (% female):	76	84	74
Ethnicity (% white):	89	96	94
Other germane population qualities:			
• Tender joint count	35	34	33
• Swollen joint count	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:** o Data NR o Placebo v. ETA 10 mg and placebo v. ETA 25 mg: P < 0.05 • **SF-36: PCS-36 (n = 48)** o Data NR o At months 3 and 6, ETA groups performed significantly (P ≤ 0.01) better than the placebo group • **SF-36: MCS-36 (n = 48)** o Data NR o At month 6, ETA groups performed significantly (P < 0.02) better than the placebo group • **MOS** o Energy/Vitality: At month 6: 4.74 v. 17.38 v. 16.35 (P < 0.01) o Mental Health: At month 6: 4.41 v. 12.95 v. 13.88 (P < 0.01) • **Feeling Thermometer:** o 8.15 v. 19.97 v. 18.19 o 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**	**Etanercept (low dose)**	**Etanercept (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:	Injection site reactions- 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**	**Etanercept (low dose)**	**Etanercept (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: St. Clair et al.**[25] **Year: 2004** **Country:** Multinational		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To compare the benefits of initiating treatment with MTX and anti-TNFα with those of MTX treatment alone in patients with RA of ≤ 3 years duration		
DESIGN:	**Study design:** RCT **Setting:** University hospitals **Sample size:** 1049		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Methotrexate** N/A 54 weeks 298	**Methotrexate-Infliximab 3** 3 mg 54 weeks 373	**Methotrexate-Infiximab 6** 6 mg 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 rheumatoid factor, radiographic erosions of the hands or feet, or a serum C-reactive protein 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 tuberculosis, congestive heart failure, 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. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Early RA with moderate to severe disease activity		
	Methotrexate	**Methotrexate-Infliximab 3mg**	**Methotrexate-Infliximab 6 mg**
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
• Swollen joint count	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, Sharp score **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. **Year: 2004**	
RESULTS:	**Health Outcome Measures:** • HAQ scores improved significantly more from weeks 30-54 in the MTX-3mg and MTX-6mg 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 and MTX-6mg 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 **Intermediate Outcome Measures:** • ACR-N was significantly higher for MTX-INF 3mg and 6 mg 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 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

Authors: St. Clair et al **Year:2004**			
ADVERSE EVENTS:	**Methotrexate**	**Methotrexate-Infliximab 3 mg**	**Methotrexate-Infliximab 6 mg**
Overall adverse effects reported	NR	NR	NR
• Upper respiratory tract infections (%)	21	25	28
• Nausea (%)	18	20	17
• Sinusitis (%)	8	12	10
• Pneumonia (%)	0.7	2	3
• Tuberculosis (%)	0	0.8	0.3
• Sepsis (%)	0	0.5	0.3
• Anaphylactic reaction	0	0.5	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*):	**Methotrexate**	**Methotrexate-Infliximab 3 mg**	**Methotrexate-Infliximab 6 mg**
Loss to follow-up:	17.8%	13.4%	14%
Withdrawals due to adverse events:	3.2%	9.4%	9.3%
QUALITY RATING:	**Good**		

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

STUDY:	**Authors: van de Putte et al.**[30] **Year: 2003** **Country:** Multinational (Europe)			
FUNDING:	Abbott Laboratories			
RESEARCH OBJECTIVE:	To evaluate efficacy, dose response, safety, and tolerability of ADA 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:**	**Adalimumab** 20 mg 12 weeks 72	**Adalimumab** 40 mg 12 weeks 70	**Adalimumab** 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 tender joint count (TJC) of ≥ 12 and swollen joint count (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 C reactive protein (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			
	Adalimumab 20	**Adalimumab 40**	**Adalimumab 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:				
• Tender joint count	31.7	31.0	32.5	30.9
• Swollen joint count	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 • Injection site reactions • Hyperlipidamea	**Adalimumab 20** NR 3 11 0 29 25	**Adalimumab 40** NR 7 16 3 23 31	**Adalimumab 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 ($P \leq 0.05$) Injection site reactions 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 **Adalimumab 20** 6 0	**Adalimumab 40** 4 4	**Adalimumab 80** 1 3	**Placebo** 1 1
QUALITY RATING:	**Fair**			

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

STUDY:	**Authors: van de Putte et al.**[29] **Year: 2004** **Country:** Multinational (3)				
FUNDING:	Abbott				
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of monotherapy with ADA 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	**Adalimumab** 20 mg biweekly (BW) 26 weeks 106	**Adalimumab** 20 mg week (W) 26 weeks 112	**Adalimumab** 40 mg week 26 weeks 113	**Adalimumab** 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 tuberculosis 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	**Adalimumab20BW**	**Adalimumab20W**	**Adalimumab40W**	**Adalimumab 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:					
• Tender joint count	35.5	33.9	35.3	33.7	33.8
• Swollen joint count	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 ≤ 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 ≤ 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 ≤ 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	**Adalimumab20BW** NR	**Adalimumab20W** NR	**Adalimumab40W** NR	**Adalimumab40BW** 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
• Injection site reaction	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%), injection site reactions (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: Weinblatt et al.**[26] **Year: 2003** **Country:** US and Canada			
FUNDING:	Abbott Labs and Knoll Pharmaceuticals			
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of ADA administered subcutaneously every other week to patients with active RA despite long term therapy with MTX			
DESIGN:	**Study design:** RCT **Setting:** Multicenter (35 sites) **Sample size:** 271			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Adalimumab** 20 mg every 2 weeks 24 weeks 69	**Adalimumab** 40 mg every 2 weeks 24 weeks 67	**Adalimumab** 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**					
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate				
		Placebo	**Adalimumab20**	**Adalimumab40**	**Adalimumab80**
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:					
• Tender joint count		28.7	28.5	28.0	30.3
• Swollen joint count		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**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** ACR20; And improvements in tender joint count, swollen joint count, patients assessment of pain, patients global assessment of disease activity, physicians global assessment of disease activity, HAQ and serum levels of C-reactive protein. **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 $P < 0.001$) **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:	**Adalimumab20**	**Adalimumab40**	**Adalimumab80**	**Placebo**
Overall adverse effects reported (%):	NR	NR	NR	NR
• Nausea	18.8	4.5	9.6	6.5
• Injection site pain	8.7	10.4	11.0	3.2
• Injection site reaction	4.3	1.5	11.0	0
• Dizziness	11.6	3.0	1.4	1.6
Significant differences in adverse events:	• Injection site reactions 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*):	**Overall loss to follow-up:** 110/271 (40.6%) **Loss to follow-up differential high:** Yes			
ATTRITION (*treatment specific*):	**Adalimumab**	**Placebo**	***loss to follow was not reported in treatment specific fashion only as overall	
Loss to follow-up:	NR	NR		
Withdrawals due to adverse events:	2	5		
Withdrawals due to lack of efficacy	23,27,27	35		
QUALITY RATING:	**Fair**			

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

STUDY:	**Authors: Horneff et al.**[50] **Year: 2004** **Country:** Germany
FUNDING:	Wyeth-Pharma
RESEARCH OBJECTIVE:	To assess efficacy and safety of ETA 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:**	**Etanercept** 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: 2005**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease characteristic:** – Polyarticular, systemic & oligoarticular
	Etanercept
Mean age (years):	NR
Sex (% female):	NR
Ethnicity:	NR
Other germane population qualities:	
• Tender joint count (%)	7
• Swollen joint count (%)	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: 2005**	
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	**Etanercept** 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:**	**Etanercept** 17.7% 3.4%
QUALITY RATING:	**N/A**

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

STUDY:	**Authors: Lovell et al.**[49, 89] **Year: 2000 and 2003** **Country:** US		
FUNDING:	Immunex Corporation, Children's Hospital Foundation of Cincinnati, NIH		
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of ETA in children with polyarticular juvenile RA (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	**Etanercept** 0.4 mg/kg body weight/2x weekly 4 months 25	**Extension** 0.4 mg/kg body weight/2x weekly up to 2 years 58
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		

<table>
<tr><td colspan="4">Authors: Lovell et al.
Year: 2000 and 2003</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease characteristic: Polyarticular</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>Etanercept</u></td><td><u>Extension</u></td></tr>
<tr><td>Mean age (years):</td><td>12.2</td><td>8.9</td><td>10</td></tr>
<tr><td>Sex (% female):</td><td>58</td><td>76</td><td>67</td></tr>
<tr><td>Ethnicity: white (%)</td><td>88</td><td>56</td><td>74</td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td><td></td></tr>
<tr><td>• Disease duration mean (years)</td><td>6.4</td><td>5.3</td><td>5.9</td></tr>
<tr><td>• Tender joint count</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• Swollen joint count</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• DMARD use (%)</td><td>73</td><td>64</td><td>74</td></tr>
<tr><td>• MTX use (%)</td><td>69</td><td>64</td><td>72</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>50</td><td>24</td><td>38</td></tr>
<tr><td>• DAS score</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>• HAQ score</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">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</td></tr>
<tr><td>RESULTS:</td><td colspan="3">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</td></tr>
</table>

Authors: Lovell et al. **Year: 2000 and 2003**				
ADVERSE EVENTS:	**Open label**	**Double-blind portion**		**Extension**
Overall adverse effects reported:	NR	NR		NR
▪ **Serious adverse events requiring hospitalization**	3%	NR		16% NR
• Injection site reaction	39%	4%		NR
• URTI	35%	NR		NR
• Headache	20%	NR		NR
• Abdominal pain	16%	NR		NR
• Vomiting	14%	NR		NR
• Rash	10%	NR		NR
• Varicella-Zoster virus	NR	NR		5% requiring hospitalization
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**	**Etanercept**	**Placebo**	**Extension**
Loss to follow-up:	5	6 (24%)	19 (63%)	10 (17%)
Withdrawals due to adverse events:	1	6- Disease flare	18-Disease flare	2-Adverse events 7-Suboptimal response
QUALITY RATING:	**Fair**			

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

STUDY:	**Authors: Braun et al.**[55, 60-62], **Listing et al.**[59] **Year: 2002, 2004, 2003** **Country:** Multinational		
FUNDING:	Schering-Plough		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of INF treatment of AS		
DESIGN:	**Study design:** RCT **Setting:** Multi-center **Sample size:** 70		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Infliximab** 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</td></tr>
<tr><td></td><td><u>Infliximab</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>

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

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

STUDY:	**Authors: Calin et al.**[52] **Year: 2004** **Country:** Multinational		
FUNDING:	Wyeth		
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of ETA to treat adult patients with AS		
DESIGN:	**Study design:** RCT **Setting:** Multicenter (14 sites) **Sample size:** 84		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Etanercept** 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		
	Etanercept	**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:** • Injection site reaction • Haemorrhage, injection site • Headache • Nausea • Asthenia	**Etanercept** NR 15 8 6 3 5	**Placebo** NR 6 4 4 4 1	
Significant differences in adverse events:	Only injection site reactions.		
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:**	**Etanercept** 2 0	**Placebo** 0 0	
QUALITY RATING:	**Fair**		

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

STUDY:	**Authors: Davis et al.**[54] **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 ankylosing spondylitis.		
DESIGN:	**Study design:** RCT, placebo-controlled, parallel-group **Setting:** Multicenter **Sample size:** 277		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Etanercept** 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		
	Etanercept	**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 swollen joint counts, 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: (etanercept 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	**Etanercept** NR 28% 41% 17% 8% 5%	**Placebo** NR 16% 13% 6% 3% 10%	
Significant differences in adverse events:	Injection-site reactions, upper respiratory tract infections, and accidental injury were the only reported adverse events achieving a statistically significant difference between the etanercept and placebo groups. Patients receiving etanercept 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:**	**Etanercept** 14% 5.1%	**Placebo** 9% 0.7%	
QUALITY RATING:	**Good**		

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

STUDY:	**Authors: Gorman et al.**[53] **Year: 2002** **Country:** US		
FUNDING:	NIH and Immunex		
RESEARCH OBJECTIVE:	To evaluate the efficacy of ETA for the treatment of AS		
DESIGN:	**Study design:** RCT **Setting:** Rheumatology practices in Northern California **Sample size:** 40		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Etanercept** 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		
	Etanercept	**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 • Injection site reactions • Diarrhea • Neurological	**Etanercept** 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 **Etanercept** 1 0	**Placebo** 2 0	
QUALITY RATING:	**Fair**		

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

STUDY:	**Authors: van der Heijde et al.**[56] **Year: 2005** **Country:** Multinational		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of INF in patients with AS.		
DESIGN:	**Study design:** RCT **Setting:** 33 sites **Sample size:** 279		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Infliximab** 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 tuberculosis (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 congestive heart failure; 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 methotrexate 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</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>Infliximab</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**	**Infliximab**	
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**	**Infliximab**	
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.**[69] **Year: 2005** **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	**Infliximab** 5 mg/kg at weeks 0,2,6,14 16 weeks 52	**Placebo/infliximab** 5 mg/kg every 8 weeks 34 weeks 50	**Infliximab/infliximab** 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 rheumatoid factor 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 rheumatoid factor 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</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>Infliximab</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
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</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</td></tr>
</table>

Authors: Antoni et al. **Year: 2005**			
ADVERSE EVENTS (%):	**Placebo (-week 16)**	**Infliximab 5 mg (-week 16)**	**Infliximab 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**	**Infliximab**	
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.[66] and Kavanaugh et al.[67]** **Year: 2005** **Country:** Multinational		
FUNDING:	Centocor Inc and Schering-Plough		
RESEARCH OBJECTIVE:	The evaluation of INF 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	**Infliximab** 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 rheumatoid factor in their serum.		
EXCLUSION CRITERIA:	Latent or active tuberculosis (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 congestive heart failure; or if they had used TNF$_\alpha$ 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		
	Placebo	**Infliximab**	
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**	**Infliximab 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**	**Infliximab**	
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.**[63] **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:**	**Etanercept** 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		

Authors: Mease et al. **Year: 2000**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** NR		
	Etanercept	**Placebo**	
Median age (years):	46	43.5	
Sex (% female):	40	47	
Ethnicity (% white):	83	90	
Other germane population qualities:			
• Tender joint count	22.5	19	
• Swollen joint count	14	14.7	
• DMARD # previous usage	1.5	2	
• MTX use (%)	47	47	
• Corticosteroids use (%)	20	40	
• DAS score	N/A	N/A	
• HAQ score	1.3	1.2	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PsARC; PASI **Secondary Outcome Measures:** ACR20/50/70; CRP; tender and swollen joint count; HAQ ESR **Timing of assessments:** Baseline, 4, 8, and 12 weeks		
RESULTS:	**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		

Authors: Mease et al. **Year: 2000**			
ADVERSE EVENTS: **Overall adverse effects reported:** • URI • Pharynigitis • Rhinitis • Sinusitis • Influenza syndrome • Injection site bruise • Injection site reaction • Fatigue	**Etanercept** 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:**	**Etanercept** 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.**[64] **Year: 2004** **Country:** US		
FUNDING:	Immunex		
RESEARCH OBJECTIVE:	To evaluate the safety, efficacy, and effect on radiographic progression of ETA 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	**Etanercept** 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 ankylosing spondylitis-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		
	Placebo	**Etanercept**	
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	51	
• NSAID use (%)	38	41	
• MTX use (%)	83	88	
• Corticosteroids use (%)	41	42	
• DAS score	15	19	
• HAQ score	N/A	N/A	
	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 (%):	**Placebo**	**Etanercept**	
Overall adverse effects reported:	NR	NR	
• Injection site reaction	9	36	
• URTI	23	21	
• Injection site ecchymosis	11	12	
• Accidental injury	5	8	
• Headache	5	8	
• Sinusitis	8	6	
• Urinary tract infection	6	6	
• Rash	7	5	
Significant differences in adverse events:	Yes- Injection site reaction (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*):	**Placebo**	**Etanercept**	
Loss to follow-up:	31%	8%	
Withdrawals due to adverse events:	1%	1%	
QUALITY RATING:	**Fair**		

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

STUDY:	**Authors: Mease et al.**[68] **Year: 2005** **Country:** Multi-national		
FUNDING:	Abbott Laboratories		
RESEARCH OBJECTIVE:	Evaluation of efficacy and safety of ADA 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	**Adalimumab** 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 tuberculosis (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 tender joint counts 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		
	Placebo	**Adalimumab**	
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	**Adalimumab** 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%)	**Adalimumab** 11 (7.3%) 5(3.3%)	
QUALITY RATING:	**Fair**		

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

STUDY:	**Authors: D'Haens et al.**[73] **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	**Infliximab5** 5 mg/kg 4 weeks 7	**Infliximab10** 10 mg/kg 4 weeks 7	**Infliximab20** 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, methotrexate 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>Infliximab 5</u></td><td><u>Infliximab 10</u></td><td><u>Infliximab 20</u></td></tr>
<tr><td>Mean age (years):</td><td>34.4</td><td>30.1</td><td>30.7</td><td>33.1</td></tr>
<tr><td>Sex (% female):</td><td>63</td><td>57</td><td>57</td><td>63</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>• Mean baseline CDAI</td><td>276.9</td><td>314.4</td><td>336.8</td><td>300.9</td></tr>
<tr><td>• Azathioprine use (%)</td><td>38</td><td>43</td><td>14</td><td>63</td></tr>
<tr><td>• Corticosteroids use (%)</td><td>63</td><td>57</td><td>43</td><td>50</td></tr>
<tr><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 infliximab 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
• Infliximab 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 infliximab treatment groups all showed a significant improvement compared to the placebo group in their CRP (mg/dL) at week 4.</td></tr>
</table>

Authors: D'Haens et al. **Year: 1999**				
ADVERSE EVENTS: **Overall adverse effects reported:** • None specified	**Placebo** 2 (inferred)	**Infliximab 5** NR	**Infliximab 10** NR	**Infliximab 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**	**Infliximab5**	**Infliximab10**	**Infliximab20**
Loss to follow-up:	2	NR	NR	NR
Withdrawals due to adverse events:	1 (inferred)	NR	NR	NR
QUALITY RATING:	**Fair**			

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

STUDY:	**Authors: Hanauer et al.[74], Lichtenstein et al.[80], Feagan et al.[81]** **Year: 2002, 2003, 2003** **Country:** Multinational		
FUNDING:	Centocor, Malvern PA		
RESEARCH OBJECTIVE:	To assess the benefit of maintenance INF therapy in patients with active Crohn's disease who respond to a single infusion of INF, the impact of remission on patients' employment, quality of life, and hospitalization to validate clinical remission and health related quality of life.		
DESIGN:	**Study design:** RCT **Setting:** Multicenter (55 sites) **Sample size:** 573		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Infliximab dose 1** 5 mg/kg at weeks 2,6 & every 8 weeks thereafter 54 weeks 192	**Infliximab dose 2** 5 mg/kg injections at weeks 2, 6, then 10 mg/kg every 8 weeks 54 weeks 193	**Placebo** N/A (responded to one initial dose of INF) 54 weeks 188
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; methotrexate		

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 **Timing of assessments:** Weeks 0,2,6,10,14,22,30,38,46,54; SF-36 taken at wk 10, 30, and 54
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 had discontinued corticosteroids in the active treatment groups than the placebo group. Odds ratio: 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; odds ratio: 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 ($P = 0.0002$)

Authors: Hanauer et al. **Year: 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Infections • Intestinal Stenosis • Infusion reactions • Serum sickness like reactions	**Infliximab 5mg/kg** 72 (37%) 3 (2%) 44 (23%) 5 (3%)	**Infliximab 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:**	**Infliximab dose 1** 49 (26%) 29 (15%)	**Infliximab 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.**[70] **Year: 2004** **Country:** Sweden
FUNDING:	NR
RESEARCH OBJECTIVE:	To assess the use of INF 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 **Setting:** Multicenter (11 medical centers) **Sample size:** 217
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Infliximab** 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
	Infliximab
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	**<u>Infliximab</u>** 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.**[75] **Year: 1999** **Country:** Multinational		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To determine the efficacy of using INF 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	**Infliximab** 5 mg/kg 34 weeks 31	**Infliximab** 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>Infliximab (5 mg/kg)</u></td><td><u>Infliximab (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%	**Infliximab (5 mg/kg)** 21 (65%) 1 (3%) 5 (16%) 2 (6%) 2 (6%)	**Infliximab(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%)	**Infliximab** 2 (3%) 1 (2%	
QUALITY RATING:	**FAIR**		

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

STUDY:	**Authors: Rutgeerts et al.**[76] **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:**	**Infliximab** 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>Infliximab</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 C-reactive protein (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 infliximab 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	**Infliximab** 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:**	**Infliximab** 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.**[127] **Year: 2002** **Country:** Canada		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To determine whether the clinical efficacy and safety of INF 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:**	**Infliximab** 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 rowspan="2">POPULATION CHARACTERISTICS:

Median age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• MTX use (%)
• Corticosteroids use (%)</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: NR</td></tr>
<tr><td><u>Infliximab</u>
42.5
48%
NR

26%
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	**<u>Infliximab</u>** 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:	**Fair**		

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

STUDY:	**Authors: Sandborn et al.**[72] **Year: 2001** **Country:** USA		
FUNDING:	Immunex Corporation		
RESEARCH OBJECTIVE:	Evaluation of ETA 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:**	**Etanercept** 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.		

Authors: Sandborn et al. **Year: 2001**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease severity:** Moderate - severe		
	Etanercept	**Placebo**	
Median age (years (Range)):	37.4	39.3	
Sex (% female):	50	30.4	
Ethnicity:	N/ R	N/R	
Other germane population qualities:			
• Previous surgery for CD (%)	57	45	
• Patients with fistulae (%)	17	5	
• Median baseline CDAI (range)	303 (226-499)	265 (115-453)	
OUTCOME ASSESSMENT:	**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)		
RESULTS:	**Health Outcome Measures:** • Only 4 etanercept and 1 placebo patient had fistulas; only 1 etanercept 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)		

Authors: Sandborn et al. **Year: 2001**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Headache • New injection site reactions • Asthenia • Abdominal pain • Mild anemia • Skin disorders	**Etanercept (%)** 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 not reported but it was done by Immunex Corporation		
ADEQUATE ALLOCATION CONCEALMENT:	Method not reported		
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:**	**Etanercept** 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.,**[77, 82] **Lichtenstein et al.**[83] **Year: 2004, 2004, 2005** **Country:** Multinational		
FUNDING:	Centocor and NIH		
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of INF in maintaining closure of draining fistulas among patients who had a response to a three dose induction regimen of INF		
DESIGN:	**Study design:** RCT **Setting:** 45 sites **Sample size:** 282		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Placebo** N/A 54 weeks 144	**Infliximab** 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 infliximab		
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>Infliximab</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

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)</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%)	**Infliximab** 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 not reported		
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%)	**Infliximab** NR 5 (4%)	
QUALITY RATING:	**Good**		

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

STUDY:	**Authors: Targan et al.**[78] **and Lichtenstein et al.**[79] **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 INF at 10mg/kg			
DESIGN:	**Study design:** RCT **Setting:** Multi-center (18 sites) **Sample size:** 108			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Infliximab** Single infusion at 5 mg/kg 12 weeks 27	**Infliximab** Single infusion at 10 mg/kg 12 weeks 28	**Infliximab** 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="2">POPULATION CHARACTERISTICS:</td><td colspan="4">Groups similar at baseline: Yes
Disease severity: Moderate - severe</td></tr>
<tr><td></td><td><u>Infliximab 5</u></td><td><u>Infliximab10</u></td><td><u>Infliximab20</u></td><td><u>Placebo</u></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• Previous surgery for CD (%)
• Mean baseline CDAI</td><td>37.0
48
NR

44
312</td><td>39.3
54
NR

50
318</td><td>36.0
54
NR

50
307</td><td>38.5
40
NR

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 - Adverse Events***

STUDY:	**Authors: Baeten et al.**[99] **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:**	**Infliximab** 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 tuberculosis • 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 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Bergstrom et al.**[100] **Year: 2004** **Country:** US		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To assess if patients who were treated with tumor necrosis factor α(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:**	**Infliximab** 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		
	Infliximab	**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
• Tender joint count	NR	NR	NR
• Swollen joint count	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 (relative risk 5.23, 95% confidence interval 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:	**FAIR**

Evidence Table 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Brown et al.**[107] **Year: 2002** **Country:** USA		
FUNDING:	Authors are from FDA and National Cancer Institute		
RESEARCH OBJECTIVE:	To investigate the occurrence of lymphoproliferative disorders in patients treated with ETA and INF.		
DESIGN:	**Study design:** Case series **Setting:** N/A **Sample size:** 26		
INTERVENTION: **Dose:** **Cases:**	**Etanercept** Various 18	**Infliximab** Various 8	
INCLUSION CRITERIA:	MedWatch reports submitted to the Food and Drug Administration (FDA) for the biologic products etanercept and infliximab. 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		

<table>
<tr><td colspan="4">Authors: Brown 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>Etanercept</u></td><td><u>Infliximab</u></td><td></td></tr>
<tr><td>Median age (years):</td><td>64</td><td>62</td><td></td></tr>
<tr><td>Sex (% female):</td><td>61</td><td>33.5</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>• RA indication (%)</td><td>83</td><td>37.5</td><td></td></tr>
<tr><td>• PA indication (%)</td><td>11.1</td><td>0</td><td></td></tr>
<tr><td>• Crohn’s indication (%)</td><td>0</td><td>62.5</td><td></td></tr>
<tr><td>• Not specified indication (%)</td><td>5.6</td><td>0</td><td></td></tr>
<tr><td>• MTX use (%)</td><td>72.2</td><td>25</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures:
Associated lymphomas with treatment</td></tr>
<tr><td>RESULTS:</td><td colspan="3">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</td></tr>
</table>

Authors: Brown et al. **Year: 2002**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**Etanercept** N/A	**Infliximab** 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:**	**Etanercept** N/A	**Infliximab** N/A	
QUALITY RATING:	**N/A**		

Evidence Table 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Cheifetz et al.**[95] **Year: 2003** **Country:** US
FUNDING:	NR
RESEARCH OBJECTIVE:	To assess the incidence and management of infusion reactions to INF in patients with Crohn's Disease.
DESIGN:	**Study design:** Observational **Setting:** Single center (Mt. Sinai Medical Center) **Sample size:** 165
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Infliximab** 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
	Infliximab
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:**	**Infliximab** 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 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Chung et al.**[112] **Year: 2003** **Country:** US		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To assess the effectiveness and safety of INF in patients with congestive heart failure		
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	**Infliximab** 5 mg/kg 28 weeks 50	**Infliximab** 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 infliximab or other therapeutic agents that could interfere with the actions of TNFα (eg, etanercept, pentoxifylline, thalidomide, or D2E7)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Vasodilators or nitrates		

<table>
<tr><td colspan="4">Authors: Chung et al.
Year: 2003</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: Moderate-severe</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>Infliximab5</u></td><td><u>Infliximab10</u></td></tr>
<tr><td>Mean age (years):</td><td>60 ± 12</td><td>62 ± 15</td><td>62 ± 13</td></tr>
<tr><td>Sex (% female):</td><td>24</td><td>14</td><td>16</td></tr>
<tr><td>Ethnicity (% white):</td><td>88</td><td>88</td><td>84</td></tr>
<tr><td>Current or prior angina (%):</td><td>29</td><td>18</td><td>24</td></tr>
<tr><td>Myocardial infarction (%):</td><td>63</td><td>50</td><td>67</td></tr>
<tr><td>Diabetes mellitus (%):</td><td>41</td><td>28</td><td>37</td></tr>
<tr><td>NYHA Class III/IV (%):</td><td>96/4</td><td>96/4</td><td>92/8</td></tr>
<tr><td>LVEF (%):</td><td>0.25 ± 0.07</td><td>0.23 ± 0.07</td><td>0.24 ± 0.06</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Change in clinical status, assessed by the clinical composite score, which categorized each patient as improved, worse, or unchanged using pre-specified criteria

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

Authors: Chung et al. **Year:2003**			
ADVERSE EVENTS: **Overall adverse effects reported (# of patients with 1 or more) n (%):** • Dizziness • Dyspnea • Hypotension • Angina • Serious AEs • Serious infections	**Placebo** 40 (83.3) 2 (4.2) 6 (12.5) 0 (0.0) 1 (2.1) (29.2) (2.1)	**Infliximab5** 47 (92.2) 16 (31.4) 10 (19.6) 3 (5.9) 3 (5.9) (23.5) (5.9)	**Infliximab10** 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, not reported separately	**Overall loss to follow-up:** NR **Loss to follow-up differential high**: NR **Placebo** 1	**Infliximab5** 2	**Infliximab10** 5
QUALITY RATING:	**Fair**		

Evidence Table 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Colombel et al.**[93] **Year: 2004** **Country:** US	
FUNDING:	NR	
RESEARCH OBJECTIVE:	Short and long term safety of INF treated Crohn's disease patients in clinical practice	
DESIGN:	**Study design:** Case series **Setting:** Mayo Clinic **Sample size:** 500	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Infliximab** 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	

<table>
<tr><td colspan="3">Authors: Colombel et al.
Year: 2004</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="2">Groups similar at baseline: N/A
Disease severity: Mild – severe</td></tr>
<tr><td></td><td><u>Infliximab</u></td><td></td></tr>
<tr><td>Median age (years):</td><td>37</td><td></td></tr>
<tr><td>Sex (% female):</td><td>56</td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td></td></tr>
<tr><td>Other germane population qualities:</td><td></td><td></td></tr>
<tr><td>• Previous surgery for CD (%)</td><td>NR</td><td></td></tr>
<tr><td>• Patients with fistulae (%)</td><td>24</td><td></td></tr>
<tr><td>• Mean baseline CDAI</td><td>N/A</td><td></td></tr>
<tr><td>• Mercaptopurine/Azathioprine use (%)</td><td>75</td><td></td></tr>
<tr><td>• Corticosteroids use (%)</td><td>31</td><td></td></tr>
<tr><td>• HAQ score</td><td>N/A</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="2">Primary Outcome Measures: Adverse events

Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="2">Health Outcome Measures:
• See adverse events</td></tr>
</table>

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	**Infliximab** 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*): **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 **Infliximab** N/A N/A		
QUALITY RATING:	**N/A**		

Evidence Table 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Fleischmann et al.,[90] Schiff et al.,[92] Tesser et al.[91]** **Year: 2003 and 2004** **Country:** Multinational	
FUNDING:	Amgen Inc., Thousand Oaks, CA	
RESEARCH OBJECTIVE:	To evaluate the safety of AKA in a large population of patients with RA, typical of those seen in clinical practice. Additionally to determine the safety in a sub-population of patients with comorbid conditions; and to examine concomitant medication's effect on adverse events.	
DESIGN:	**Study design:** RCT **Setting:** Multicenter (169 sites) **Sample size:** 1414 (1399 enrolled)	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Anakinra** 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	
	Anakinra	**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:		
• Tender joint count	22.6	22.6
• Swollen joint count	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 injection site reactions, 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-AKA antibodies detected in 0.8% of AKA patients not reported 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 • Injection site reactions • Infectious episode • Serious infection • URTI • Sinusitis • Influenza-like • UTI • Bronchitis • Infection (resistance mechanism body system)	**Anakinra** 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 Injection site reactions.)	
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:**	**Anakinra** 21.6% 13.4%	**Placebo** 18.7% 9.2%
QUALITY RATING:	**Fair**	

Evidence Table 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Gomez-Reino et al.**[103] **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:**	**Infliximab and/or Etanercept** 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	
	Infliximab and/or Etanercept	
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	**Infliximab and/or Etanercept** 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:**	**Infliximab and/or Etanercept** 228 discontinued therapy (14%) 118 (8%)	
QUALITY RATING:	**N/A**	

Evidence Table 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Keane et al.**[86] **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 tuberculosis based on data from MedWatch		
DESIGN:	**Study design:** Retrospective database review **Setting:** N/A **Cases:** 70		
INTERVENTION: **Dose:** **Duration:** **Cases:**	**Infliximab** all 1 to 52 weeks 70		
INCLUSION CRITERIA:	If during or after treatment with infliximab, patient received a diagnosis of tuberculosis 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		
	Tuberculosis patients		
Median age (years):	57 (18-83)		
Sex (% female):	64		
Ethnicity:	NR		
Other germane population qualities:			
• Crohn's disease	26		
• RA	67		
• JRA	3		
• Ankylosing spondylitis	3		
• Behcet's disease	1		
• Extrapulmonary tuberculosis	56		
• Disseminated tuberculosis	24		
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Incidence rate of tuberculosis in patients receiving infliximab		
RESULTS:	**Health Outcome Measures:** • Estimated incidence for patients with RA who have been treated with infliximab 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		

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 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Kwon et al**.[110] **Year: 2003** **Country:** USA
FUNDING:	U.S. 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:**	**Etanercept or Infliximab** 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 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Lebwohl et al**.[109] **Year: 2005** **Country:** USA
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 rheumatoid arthritis receiving ETA for up to 5 years.
DESIGN:	**Study design:** Retrospective observational study with historical controls **Setting:** Clinical trial participants receiving etanercept from private and institutional practices **Sample size:** 1442 (4257 patient-years)
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Etanercept** NR Mean 3.7 years 1442 (4257 pt-yrs)
INCLUSION CRITERIA:	Participant in one of various studies* of ETA in patients with rheumatoid arthritis; 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>Etanercept</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 etanercept 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 etanercept
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 etanercept 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 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Lee et al**.[88] **Year: 2002** **Country:** USA (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 INF and ETA.		
DESIGN:	**Study design:** Database analysis **Setting:** Clinics **Sample size:** 10		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Etanercept** any any 9	**Infliximab** 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 rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: N/A
Disease severity: NR</td></tr>
<tr><td><u>Etanercept</u></td><td><u>Infliximab</u></td><td></td></tr>
<tr><td>Age range (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• % concomitant immunosuppressive</td><td>11-78
4/9
NR
N/A
100%</td><td>38
0/1
NR
N/A
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 infliximab
o One case among patients receiving etanercept
• Through August 2001, number of patients treated
o With infliximab: ~150,000
o With etanercept: ~96,500
• Histoplasmosis case rates per 100,000 patients receiving drug
o Infliximab: ~6/100,000
o Etanercept: ~1/100,000
• Deaths due to histoplasmosis
o Infliximab: 1/10
o Etanercept 0/1
Summary: More cases of histoplasmosis were reported to the AERS by July 2001 among patients receiving infliximab than for those receiving etanercept. When accounting for the actual number of patients taking each of the drugs, the histoplasmosis case rate was ~6 times higher among patients receiving infliximab than among those receiving etanercept.</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 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Ljung et al**.[70] **Year: 2004** **Country:** Sweden
FUNDING:	NR
RESEARCH OBJECTIVE:	To assess the use of INF 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 **Setting:** Multicenter (11 medical centers) **Sample size:** 217
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Infliximab** 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
	Infliximab
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	**<u>Infliximab</u>** 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 6 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Lovell et al.**[49, 89] **Year: 2000 and 2003** **Country:** US		
FUNDING:	Immunex Corporation, Children's Hospital Foundation of Cincinnati, NIH		
RESEARCH OBJECTIVE:	To evaluate the safety and efficacy of ETA in children with polyarticular juvenile RA (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	**Etanercept** 0.4 mg/kg body weight/2x weekly 4 months 25	**Extension** 0.4 mg/kg body weight/2x weekly up to 2 years 58
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 and 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Disease characteristic:** Polyarticular		
	Placebo	**Etanercept**	**Extension**
Mean age (years):	12.2	8.9	10
Sex (% female):	58	76	67
Ethnicity: white (%)	88	56	74
Other germane population qualities:			
• Disease duration mean (years)	6.4	5.3	5.9
• Tender joint count	NR	NR	NR
• Swollen joint count	NR	NR	NR
• DMARD use (%)	73	64	74
• MTX use (%)	69	64	72
• Corticosteroids use (%)	50	24	38
• DAS score	NR	NR	NR
• HAQ score	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		

Authors: Lovell et al. **Year: 2000 and 2003**				
ADVERSE EVENTS:	**Open label**	**Double-blind portion**		**Extension**
Overall adverse effects reported:	NR	NR		NR
▪ **Serious adverse events requiring hospitalization**	3%	NR		16% NR
• Injection site reaction	39%	4%		NR
• URTI	35%	NR		NR
• Headache	20%	NR		NR
• Abdominal pain	16%	NR		NR
• Vomiting	14%	NR		NR
• Rash	10%	NR		NR
• Varicella-Zoster virus	NR	NR		5% requiring hospitalization
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**	**Etanercept**	**Placebo**	**Extension**
Loss to follow-up:	5	6 (24%)	19 (63%)	10 (17%)
Withdrawals due to adverse events:	1	6- Disease flare	18-Disease flare	2-Adverse events 7-Suboptimal response
QUALITY RATING:	**Fair**			

Evidence Table 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Maini et al**.[46, 47] **Year: 2004** **Country:** Multinational				
FUNDING:	Centocor				
RESEARCH OBJECTIVE:	Efficacy and safety of repeated administration of INF plus MTX over a 2-year period in patients with rheumatoid arthritis who previously experienced an incomplete response to MTX.				
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 methotrexate 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:					
• Tender joint count	N/A	N/A	N/A	N/A	N/A
• Swollen joint count	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

Secondary Outcome Measures: HAQ, SF-36

Timing of assessments: 102 weeks

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 ($P < 0.001$)

Authors: Maini et al. **Year: 1999 and 2004**					
ADVERSE EVENTS: at 30 weeks **Overall adverse effects reported:** **More than 80% in all**	**Placebo** NR	**Infli3/8 + MTX** NR	**Infli3/4 + MTX** NR	**Infli10/8 + MTX** NR	**Infli10/4 + MTX** NR
• Upper respiratory tract infection	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%)
• Urinary tract infection	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**	**Infli3/8 + MTX**	**Infli3/4 + MTX**	**Infli10/8 + MTX**	**Infli10/4 + 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 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Mohan et al**.[113] **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:**	**Etanercept** NR 4 months NR	**Infliximab** 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		

<table>
<tr><td colspan="4">Authors: Mohan et al
Year: 2001</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: NR
Disease severity: NR</td></tr>
<tr><td><u>Etanercept</u></td><td><u>Infliximab</u></td><td></td></tr>
<tr><td>Mean age (years):
Sex (% female):
Ethnicity:
Other germane population qualities:
• Tender joint count
• Swollen joint count
• DMARD use (%)
• MTX use (%)
• Corticosteroids use (%)
• DAS score
• HAQ score</td><td>NR
NR
NR

NR
NR
NR
NR
NR
NR
NR</td><td>NR
NR
NR

NR
NR
NR
NR
NR
NR
NR</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: N/A

Secondary Outcome Measures: N/A

Timing of assessments: patients were identified from FDA database after ETA and INF therapy</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:

• 17 cases of demyelination after ETA and 2 cases after INF treatment were detected in MedWatch</td></tr>
</table>

Authors: Mohan et al **Year: 2001**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Fever • Confusion • Gait disturbance • Parasthesias • Optic neuritis • Bladder problems • Visual	**Etanercept/Infliximab** 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*): **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 N/A N/A		
QUALITY RATING:	**N/A**		

Evidence Table 6 ***Targeted Immune Modulators – Adverse Events***

STUDY:	**Authors: Nuki et al**.[117] **Year: 2002** **Country:** Multinational (Europe)		
FUNDING:	Amgen, INC		
RESEARCH OBJECTIVE:	Long-term safety and maintenance in the treatment of RA with AKA. 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 (309)		
INTERVENTION: Extension phase **Dose:** **Duration:** **Sample size:**	**Anakinra** 30 mg 52 weeks 111	**Anakinra** 75 mg 52 weeks 103	**Anakinra** 150 mg 52 weeks 95
INCLUSION CRITERIA:	Patients that had completed the initial 24 week study		
EXCLUSION CRITERIA:	NR		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: Nuki et al.
Year: 2002</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: Mild-moderate-severe</td></tr>
<tr><td></td><td><u>Placebo to Anakinra (76)</u></td><td><u>Anakinra to Anakinra (233)</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>53.1</td><td>52.7</td><td></td></tr>
<tr><td>Sex (% female):</td><td>69.7</td><td>76.8</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>• Tender joint count</td><td>32.7</td><td>33.7</td><td></td></tr>
<tr><td>• Swollen joint count</td><td>24.5</td><td>26.4</td><td></td></tr>
<tr><td>• Mean disease duration</td><td>3.7</td><td>4.1</td><td></td></tr>
<tr><td>• DMARD use (%)</td><td>73.7</td><td>71.7</td><td></td></tr>
<tr><td>• MTX use (%)</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>• Corticosteroids use (%)</td><td>40.8</td><td>47.6</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>1.5</td><td>1.5</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: ACR20; radiographs; safety

Timing of assessments: 24th week of extension for efficacy and 52nd week for safety analysis</td></tr>
<tr><td>RESULTS:</td><td colspan="3">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)</td></tr>
<tr><td></td><td colspan="3"></td></tr>
</table>

Authors: Nuki et al. **Year: 2002**	**Extension phase – Weeks 24 to 76**		**Placebo phase – Weeks 0 to 24**	
ADVERSE EVENTS:	**Placebo to Anakinra (76)**	**Anakinra to Anakinra (233)**	**Placebo**	**Anakinra**
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 Anakinra (76)**	**Anakinra to Anakinra (233)**		
Loss to follow-up:	21 (28%)	70(30%)		
Withdrawals due to adverse events:	14 (18%)	32 (14%)		
QUALITY RATING:	**N/A**			

Evidence Table 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Schaible**[94] **Year: 2000** **Country:** NR		
FUNDING:	NR but author is employee of Centocor		
RESEARCH OBJECTIVE:	Long term safety of INF		
DESIGN:	**Study design:** Retrospective analysis of clinical trials data **Setting:** NR **Sample size:** 913		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**Infliximab** 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		

Authors: Schaible **Year: 2000**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** Mild-moderate-severe		
	Infliximab	Control	
Mean age (years):	NR	NR	
Sex (% female):	NR	NR	
Ethnicity:	NR	NR	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Long term safety		
RESULTS:	**Health Outcome Measures:** • N/A		

Authors: Schaible **Year: 2000**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Infections • Pneumonia • Cellulites • Sepsis • Skin ulceration • UTI • Abscess • New malignancies • Recurrent malignancies	**Infliximab** 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 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Slifman et al.**[84] **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:**	Infliximab or etanercept 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
	Infliximab or etanercept
Median age (years):	69.5
Sex (% female):	53
Ethnicity:	NR
Other germane population qualities:	
• Infliximab (%)	93.3
• Etanercept (%)	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.

Authors: Slifman et al. **Year: 2003**	
ADVERSE EVENTS: **Overall adverse effects reported:** •	Infliximab or etanercept 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:**	Infliximab or etanercept N/A N/A
QUALITY RATING:	**N/A**

Evidence Table 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Vermeire et al.**[115] **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:**	**Infliximab** 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 methotrexate, 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
	Infliximab
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	**Infliximab** 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:**	**Infliximab** NR NR		
QUALITY RATING:	**N/A**		

Adverse Events ***Targeted Immune Modulators***

STUDY:	**Authors: Wallis et al.**[85] **Year: 2003** **Country:** Multinational	
FUNDING:	Amgen	
RESEARCH OBJECTIVE:	The relationship between the use of tumor necrosis factor antagonists and onset of granulomatous infection was examined	
DESIGN:	**Study design:** Database analysis (MedWatch)/case series **Setting:** Multicenter **Sample size:** >346,000	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	Infliximab Various Various 566 cases (>233,000 treated)	Etanercept 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: 2003**		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Disease severity:** N/A	
	Infliximab	Etanercept
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). ▪ Tuberculosis 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: 2003**	
ADVERSE EVENTS: **Overall adverse effects reported:** •	Infliximab or etanercept N/A
Significant differences in adverse events:	N/A
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** NA
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:**	Infliximab or etanercept N/A N/A
QUALITY RATING:	**NA**

Evidence Table 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Wolfe and Michaud**[108] **Year: 2004** **Country:** USA			
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 **Setting:** Multicenter (908 practices) **Sample size:** 18,572			
INTERVENTION:	**Infliximab**	**Etanercept**	**Methotrexate**	**No MTX/ No biologics**
Dose:	N/A	N/A	N/A	N/A
Duration:	N/A	N/A	N/A	N/A
Sample size:	6433	2729	5593	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:	N/A			

Authors: Wolfe et al.
Year: 2004

POPULATION CHARACTERISTICS:

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

	Infliximab	Etanercept	Methotrexate	No MTX/ No biologics
Mean age (years):	60.7	56.4	61.2	60.4
Sex (% female):	77.3	79.3	75.7	75.7
Ethnicity:	NR	NR	NR	NR
Other germane population qualities:				
• Tender joint count	NR	NR	NR	NR
• Swollen joint count	NR	NR	NR	NR
• Mean disease duration	13.7	14.1	13.5	13.5
• DMARD use (%)	NR	NR	NR	NR
• MTX use (%)	NR	NR	NR	NR
• Corticosteroids use (%)	NR	NR	NR	NR
• DAS score	1.2	1.2	1.1	1.0
• HAQ score				

OUTCOME ASSESSMENT:

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

RESULTS:

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 confidence interval 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.

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 6 ***Targeted Immune Modulators - Adverse Events***

STUDY:	**Authors: Wolfe et al.**[104] **Year: 2004** **Country:** Multinational	
FUNDING:	Centocor	
RESEARCH OBJECTIVE:	To determine the baseline rate of tuberculosis (TB) in RA prior to the introduction of inf and to determine the rate of TB among those currently receiving inf.	
DESIGN:	**Study design:** Observational **Setting:** Multicenter **Sample size:** 17,242	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	Pre-infliximab Various N/A 10,782	Infliximab Various 2.5 years 6,640
INCLUSION CRITERIA:	Rheumatoid arthritis and use of inf	
EXCLUSION CRITERIA:	N/A	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR	

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

Authors: Wolfe et al. **Year: 2004**	
ADVERSE EVENTS: **Overall adverse effects reported:** •	Pre-infliximab or infliximab 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:**	Infliximab N/A N/A
QUALITY RATING:	**Fair**

Evidence Table 7 ***Targeted Immune Modulators - Subgroups***

STUDY:	**Authors: Chung et al**.[112] **Year: 2003** **Country:** US		
FUNDING:	Centocor		
RESEARCH OBJECTIVE:	To assess the effectiveness and safety of infliximab in patients with congestive heart failure		
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	**Infliximab** 5 mg/kg 28 weeks 50	**Infliximab** 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 infliximab or other therapeutic agents that could interfere with the actions of TNFα (eg, ETA, pentoxifylline, thalidomide, or D2E7)		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Vasodilators or nitrates		

<table>
<tr><td colspan="4">Authors: Chung et al.
Year: 2003</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Disease severity: Moderate-severe</td></tr>
<tr><td></td><td><u>Placebo</u></td><td><u>Infliximab5</u></td><td><u>Infliximab10</u></td></tr>
<tr><td>Mean age (years):</td><td>60 ± 12</td><td>62 ± 15</td><td>62 ± 13</td></tr>
<tr><td>Sex (% female):</td><td>24</td><td>14</td><td>16</td></tr>
<tr><td>Ethnicity (% white):</td><td>88</td><td>88</td><td>84</td></tr>
<tr><td>Current or prior angina (%):</td><td>29</td><td>18</td><td>24</td></tr>
<tr><td>Myocardial infarction (%):</td><td>63</td><td>50</td><td>67</td></tr>
<tr><td>Diabetes mellitus (%):</td><td>41</td><td>28</td><td>37</td></tr>
<tr><td>NYHA Class III/IV (%):</td><td>96/4</td><td>96/4</td><td>92/8</td></tr>
<tr><td>LVEF (%):</td><td>0.25 ± 0.07</td><td>0.23 ± 0.07</td><td>0.24 ± 0.06</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Change in clinical status, assessed by the clinical composite score, which categorized each patient as improved, worse, or unchanged using pre-specified criteria

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

Authors: Chung et al. **Year:2003**			
ADVERSE EVENTS: **Overall adverse effects reported (# of patients with 1 or more) n (%):** • Dizziness • Dyspnea • Hypotension • Angina • Serious AEs • Serious infections	**Placebo** 40 (83.3) 2 (4.2) 6 (12.5) 0 (0.0) 1 (2.1) (29.2) (2.1)	**Infliximab5** 47 (92.2) 16 (31.4) 10 (19.6) 3 (5.9) 3 (5.9) (23.5) (5.9)	**Infliximab10** 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, not reported seperately	**Overall loss to follow-up:** NR **Loss to follow-up differential high**: NR **Placebo** 1	**Infliximab5** 2	**Infliximab10** 5
QUALITY RATING:	**Fair**		

Evidence Table 7 ***Targeted Immune Modulators - Subgroups***

STUDY:	**Authors: Fleischman et al.**[121] **Year: 2003** **Country:** USA		
FUNDING:	Immunex Corporation		
RESEARCH OBJECTIVE:	Safety and efficacy of ETA 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 7 ***Targeted Immune Modulators - Subgroups***

STUDY:	**Authors: Fleischman et al.**[120] **Year: 2005** **Country:** USA
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="4">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:
Median age (years):
Sex (% female):
Ethnicity (%white):
Other germane population qualities:
</td><td>
2772
47
77
78.6
NR
</td><td>
579
70
73
89.5
NR
</td><td>
251
46
46
89.2
NR
</td><td>
14
70
71.4
100
NR
</td><td>
273
42
24.5
92.7
NR
</td><td>
4
65
0
100
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, tuberculosis, 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)**	**Etanercept (n=2652)**	**Control (n= 170)**	**Etanercept (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)**	**Etanercept (n=2652)**	**Control (n= 1020)**	**Etanercept (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 7 ***Targeted Immune Modulators - Subgroups***

STUDY:	**Authors: Kwon et al**.[110] **Year: 2003** **Country:** USA
FUNDING:	U.S. 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:**	**Etanercept or Infliximab** 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 7 ***Targeted Immune Modulators - Subgroups***

STUDY:	**Authors: Rudwaleit et al.**[119] **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:**	**Infliximab** NR 12 weeks 69	**Etanercept** 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>Infliximab</u></td><td><u>Etanercept</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 7 ***Targeted Immune Modulators – Subgroups***

STUDY:	**Authors: Vermeire et al**.[118] **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 INF 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 infliximab 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**

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