

A New Era in Rheumatoid Arthritis Treatment

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ABSTRACT

Rheumatoid Arthritis (RA) is a systemic autoimmune disease that primarily manifests as a chronic symmetric polyarthritis. Treatment in the past was aimed at symptomatic pain relief. The initiation of disease modifying anti-rheumatic drugs (DMARDs) was historically started only after significant disease activity was present in order to reduce side effects from drug toxicities. Unfortunately, irreversible joint damage may occur early in the disease course. Evidence of bony destruction is common on radiographs within the first 2 years after disease onset. Therefore, more aggressive treatment became the standard with earlier introduction of DMARDs in hopes of preventing joint destruction. Within the past few years, greater understanding of the pathophysiology of RA has permitted development of therapies targeted at specific cytokines. Tumor Necrosis Factor-alpha (TNF- α) is a pro-inflammatory cytokine believed to play a key role in the inflammatory response in RA. Three drugs—etanercept, infliximab, and adalimumab—are anti-TNF- α agents approved in the United States for the treatment of RA. This article is a review of indications, clinical trials, and toxicities of these 3 agents.

INTRODUCTION

Rheumatoid Arthritis (RA) is a systemic autoimmune disease with a worldwide prevalence of approximately 1%. The primary manifestation of the disease is a chronic symmetric polyarthritis secondary to inflammation of the synovium.¹ Joints most commonly involved in the early stages of disease include the proximal interphalangeals and metacarpophalangeal joints of the hands, carpal bones of the wrists, and metatar-

sophalangeals of the feet. Over the course of the disease, any joint lined by synovium may become involved. In addition, many systemic features can affect patients with RA, including fever, fatigue, anemia, serositis, and vasculitis.² As a consequence, there is significant morbidity and mortality associated with RA. Vandembroucke et al found median life expectancy was reduced by 3 years in women and by 7 years in men.³

No cure exists for RA, and the initiating events in the pathogenesis of the disease remain incompletely understood. Treatment in the past was aimed at symptomatic relief of pain with nonsteroidal anti-inflammatory drugs (NSAIDs) and the frequent addition of disease modifying anti-rheumatic drugs (DMARDs) to slow the disease progression. DMARD treatment was often delayed until significant disease activity was present in order to reduce patient exposure to toxicities. Unfortunately, damage to joints from synovial inflammation may occur early in the disease course. Evidence of bony destruction is common on radiographs within the first 2 years after disease onset.⁴ Therefore, more aggressive treatment of early disease became the standard, including initiation of DMARDs at the time of or shortly after definitive diagnosis. Of the DMARDs, methotrexate is often selected because of its tolerability, efficacy, and side effect profile.⁵

Within the past few years, greater understanding of the pathophysiology of RA has permitted development of therapies targeted at specific cytokines. Cytokines are intercellular messengers and play key roles in the inflammatory response in RA. Tumor Necrosis Factor-alpha (TNF- α) is a pro-inflammatory cytokine produced by monocytes and macrophages. Actions of TNF- α include amplification of multiple cytokines in the joint, lymphocyte chemotaxis, increased angiogenesis, and stimulation of synovial cells to release metalloproteinases causing tissue degradation.⁶ Three drugs—etanercept, infliximab, and adalimumab—are currently available in the United States as anti-TNF- α agents (Table 1).

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ETANERCEPT

Etanercept was the first approved anti-TNF- α therapy in the United States. It is a dimeric fusion protein combining the 75 kD receptor for TNF- α with the Fc portion of human IgG1.⁷ The Fc portion allows etanercept to be transported throughout the circulation. The soluble TNF- α receptor is able to bind to both circulating and membrane-bound TNF, which reduces the amount of TNF available for binding to its physiologic receptor. Indications for use of etanercept include treatment of moderate to severe rheumatoid arthritis failing adequate response to DMARDs and in combination therapy with methotrexate.⁷ Etanercept is also indicated in the treatment of psoriatic arthritis. The adult dose is 25 mg twice weekly by subcutaneous injection. Children older than age 4 are given 0.4 mg/kg twice weekly by subcutaneous route. The indications and recommended doses for etanercept were shaped by 4 clinical trials (Table 2).

Moreland et al randomly assigned 180 patients to 1 of 4 groups: etanercept subcutaneously twice a week at a dose of 0.25 mg/m², 2 mg/m² or 16 mg/m² and a placebo group.⁸ All patients had failed treatment with 1 to 4 DMARDs and had at least 12 tender joints and 10 swollen joints. Stable doses of NSAIDs and corticosteroids were permitted. The authors reported a 61% reduction in total number of tender points for the group treated with etanercept 16 mg/m² twice a week vs. placebo. This study also evaluated outcomes using the American College of Rheumatology (ACR) response criteria.⁹ These criteria are commonly used in clinical trials for determining the response to treatment at the individual level. In addition to evaluating tender joint and swollen joint count, other factors including patient perception of pain, global function and disease activity, physician assessment of global function, and levels of acute phase reactants are used in the response criteria. An ACR 20 response is defined as the minimal acceptable response to be obtained for an intervention to be deemed measurable. An ACR 20 means that an individual had greater than or equal to 20% improvement in number of tender joints and swollen joints and in at least 3 of the 5 other criteria. Similarly, an ACR 50 and ACR 70 indicate a 50% and 70% improvement, respectively, in tender joints and swollen joints in addition to 3 of the 5 criteria. In this study 57% of the group treated with etanercept 16 mg/m² twice a week met ACR 50 criteria as opposed to only 7% of the placebo-treated group.⁸

A second study by Weinblatt et al used higher doses of etanercept, 25 mg twice a week, vs. placebo in 89 in-

Table 1. TNF- α Inhibitors

Etanercept	SC injection	25 mg twice/week
Infliximab	IV infusion	3 mg/kg weeks 0, 2, 6 then every 8 weeks
Adalimumab	SC injection	40 mg every other week

Table 2. Adult Clinical Trials Using Etanercept

	ACR 20 (% response)*	ACR 50 (% response)*
Moreland et al		
0.25 mg/m ²	33	9
2 mg/m ²	46	22
16 mg/m ²	75	57
Placebo	14	7
Weinblatt et al		
25 mg + methotrexate	71	39
Placebo + methotrexate	27	3
Moreland et al		
10 mg	51	24
25 mg	59	40
Placebo	11	5

* ACR 20 and ACR 50 response criteria are defined in the body of the article.

dividuals with persistent RA and concomitant methotrexate use.¹⁰ Patients had greater than 6 tender and swollen joints to be eligible for enrollment. The primary outcome of the study was the ACR 20 at 24 weeks showing 71% of the individuals treated with etanercept meeting this response criteria vs. only 27% of the placebo group. In addition, 39% of patients treated with etanercept achieved ACR 50 criteria.

The third adult study was a randomized double-blind study involving 234 subjects with RA with sub-optimal response to DMARDs. Subjects were randomized to etanercept 10 or 25 mg twice a week vs. placebo for 26 weeks.¹¹ A washout period for the DMARDs was required, and only a stable dose of NSAIDs and/or corticosteroid was permitted. A higher dropout rate for placebo (67% vs. 24% and 32% respectively) was noted. Lack of efficacy was noted as the primary reason for withdrawal from the study. As in the other studies, etanercept had higher percentages than placebo of subjects meeting ACR response criteria. At 6 months, 59% of subjects given etanercept 25 mg twice a week met ACR 20 criteria as compared to only 11% of the placebo-treated subjects.

An open label pediatric study involving children aged 4 to 17 years with polyarticular juvenile RA found that 74% of patients had significant clinical response.¹²

Patients considered to be responders were further randomized to receive placebo or 4 additional months of etanercept.¹³ Of patients receiving placebo, 81% dropped out of the trial secondary to increased disease activity compared to only 28% of patients on etanercept.

The most common adverse effects in the adult clinical trials were injection site reactions reported as erythema associated with itching, pain, or swelling. The reaction lasted on average 3 days and most commonly occurred in the first month of treatment. Other common adverse effects included headache, diarrhea and infections (particularly upper respiratory tract infections).^{7,13,14} Of note, infections not involving the respiratory tract were similar in etanercept vs. placebo.^{13,14} Thirty cases of serious infections including sepsis prompted the FDA to issue warnings regarding its use.^{15,16} Postmarketing reports of tuberculosis (TB) have led to concerns of TNF- α inhibitors unmasking latent TB.⁷ Although no patient developed TB during the clinical trials, it is recommended that assessment of risk factors and screening for TB occur prior to initiating therapy.⁷

INFLIXIMAB

Infliximab is a chimeric monoclonal antibody that binds to soluble and transmembrane forms of TNF- α causing inhibition of binding to its receptor.¹⁷ Indications for use of infliximab include combination therapy with methotrexate for moderate to severe RA and treatment of Crohn's disease.¹⁷ The recommended adult dose for treatment of RA is an intravenous infusion of 3 mg/kg at 0, 2, and 6 weeks followed by maintenance therapy every 8 weeks.

One of the first studies using infliximab for the treatment of RA investigated the medication as a monotherapy in 20 patients with active disease and inadequate response to DMARDs.^{18,19} All DMARDs were discontinued at least 1 month prior to enrollment in the study. Patients were given 1 of 2 regimens: two 10 mg/kg infusions 2 weeks apart or four 5 mg/kg infusions every 4 days. Rapid improvement in swollen joint count was present with both regimens but relapse followed, thus demonstrating that complete remission with a short course of therapy was not an appropriate therapeutic goal.¹⁹

In the ATTRACT trial (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy), Maini et al studied 428 patients in a multi-center, randomized double-blind trial with persistent disease activity despite treatment with methotrexate.²⁰ Enrollment criteria included use of oral or parenteral methotrexate for a

minimum of 3 months with a stable dose present for at least 4 weeks prior to screening. Patients remained on their established dose of methotrexate while randomized to 1 of 3 groups: placebo and infliximab 3 mg/kg or 10 mg/kg. After receiving infusions at 0, 2, and 6 weeks, the study participants were further subdivided into groups receiving infusions every 4 weeks vs. 8 weeks. Stable low doses of corticosteroids (<10 mg per day), NSAIDs, and folic acid were also allowed during the study. The primary endpoint was an ACR 20 response at week 30. Greater than half the patients receiving infliximab in all 4 treatment regimens had an ACR 20 response as compared to only 20% in the placebo group. Furthermore, for many of the responders, a rapid response was noted within 2 weeks of initiation of treatment. Higher percentages of patients treated with infliximab also achieved ACR 50 and ACR 70 responses when compared with placebo. Of note, no appreciable difference in the percentage of patients achieving an ACR 20 response was found when comparing the lowest dose of infliximab, 3 mg/kg every 8 weeks, to the higher doses of infliximab used in the trial. However, the duration of the response increased with higher doses of infliximab and with concomitant use of methotrexate.¹⁹ Of equal importance is radiographic analysis from the ATTRACT trial demonstrating decreased progression of joint damage when compared to the placebo-treated subgroup.¹⁷

The most common reason for discontinuation of infliximab is infusion-related reactions. Typical infusion-related reactions include dyspnea, flushing, headache, and rash. Other side effects include myalgias, fever, and polyarthralgias. Absolute contraindications for use in the adult population exist for moderate to severe congestive heart failure. Warnings also exist for the increased risk of serious infections with its use and recommendations for temporary discontinuation if an acute infection is present.¹⁷

The presence of autoantibodies has been noted in multiple clinical trials. In the ATTRACT trial, antinuclear antibodies (ANAs) were detected in 23% of the patients receiving infliximab vs. only 6% of patients in the placebo arm. In addition, anti-double-stranded DNA (anti-dsDNA) antibodies were positive in 16% of the infliximab recipients but none of the patients receiving placebo.²⁰ Trials involving etanercept have also detected both ANA and anti-dsDNA in higher percentages of patients receiving etanercept.⁷ Both medications have had sporadic reports of lupus-like syndrome that resolved with discontinuation of the medications.^{7,17} Antibodies to infliximab and rarely etanercept

have also been reported with administration of these drugs.^{7,17} The clinical significance of antibody formation to the medication is unknown. Use of methotrexate with infliximab appears to reduce the formation of these antibodies.²¹

ADALIMUMAB

Adalimumab is the newest TNF- α inhibitor available for RA treatment. It is indicated for adult patients with moderate to severe RA and persistent disease despite DMARD therapy.²² Adalimumab is a recombinant human IgG1 monoclonal antibody that binds to TNF- α and blocks interaction with the receptor.²² The recommended adult dose is a 40 mg subcutaneous injection given every other week, which is possible because of adalimumab's half-life of 10 to 20 days as compared to etanercept (4 days) and infliximab (8-10 days). Adverse reactions have been similar in all the clinical trials and include injection-site reactions, increased risk of infections, rash, and headache.

The ARMADA trial (Anti-tumor Necrosis Factor Research Study Program of the Monoclonal Antibody Adalimumab in Rheumatoid Arthritis) was a 24-week, randomized, double-blind study with 271 patients with moderate to severe rheumatoid arthritis.²³ The trial's purpose was to evaluate whether patients with suboptimal response to methotrexate could achieve increased therapeutic benefit with the addition of adalimumab.²³ Enrollment criteria included a minimum of 6 months of methotrexate use at a stable dose for at least 1 month prior to initiation of the study. Active disease was defined as at least 6 swollen joints and 9 tender joints. Use of stable doses of NSAIDs, corticosteroids (≥ 10 mg per day), and salicylates were permitted for the trial's duration. Patients continued taking methotrexate and were randomized to 1 of 4 groups: placebo or adalimumab 20 mg, 40 mg, or 80 mg subcutaneously every other week. ACR 20 response rates were significantly greater for all patients treated with adalimumab vs. placebo (14.5%). Adalimumab 40 mg and 80 mg groups had response rates of 67.2% and 65.8% as compared to the 20 mg group (47.8%). ACR 50 responses of 31.9%, 55.2%, and 42.5% were also statistically significant for the 20 mg, 40 mg and 80 mg adalimumab doses respectively as compared to placebo (8.1%).

In addition to TNF- α agents, other cytokines have been investigated in hopes of finding other effective treatments for RA. Anakinra is a recombinant form of interleukin-1 receptor antagonist, which competitively binds to its physiologic receptor.²⁴ It is indicated for moderate to severe RA in adult patients who have

failed 1 or more DMARDs. The recommended dose is 100 mg per day by subcutaneous injection. Anakinra has also been associated with an increased incidence of serious infections and neutropenia. While anakinra is indicated in combination with DMARDs, use with TNF- α inhibitors increases serious infection rates and is not recommended. The most common adverse side effects are injection-site reactions typically occurring in the first month of treatment and lasting for 2 to 3 weeks.

CONCLUSION

Therapy targeted at cytokines has become a powerful tool in RA treatment. Many patients with moderate to severe disease activity refractory to DMARDs have had good responses to this class of medications. Unfortunately, like the traditional treatments for RA, TNF- α inhibitors and IL-1 inhibitors are not effective for everyone. It is estimated that 20%-40% of individuals trying these medications are nonresponders.²⁵ However, for those who do respond, the quick onset of action and encouraging results of radiographic studies offer great excitement and promise. The decrease in radiographic progression of disease will hopefully translate into preservation of clinical structure and function. Patients and their physicians must be aware of the increased risk of infections while using these agents. Clinically significant active infections and chronic infections are contraindications for this class of agents. If a new infection develops while on TNF- α inhibitor therapy, the agent should be discontinued until the infection resolves and the patient is clinically well for 1 to 2 weeks.²⁶ Patients should be screened for TB prior to initiation of therapy.

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