

Tumor Necrosis Factor Inhibitors: New Options for Treating Rheumatoid Arthritis

Larry W. Moreland MD

Department of Medicine, University of Alabama at Birmingham, Birmingham, AM, USA

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Abstract

There is accumulating evidence that tumor necrosis factor plays a major role in the pathogenesis of rheumatoid arthritis. Recent biotechnological advances have allowed for the development of agents that directly target TNF, a pro-inflammatory cytokine. In the last 2 years, the U.S. Food and Drug Administration and the European Union's Commission of the European Communities have approved two biological agents for the treatment of refractory RA, etanercept and infliximab. Etanercept is a fusion protein, composed of the Fc portion of immunoglobulin G1 and the extracellular domain of a TNF receptor (p75). Infliximab is a chimeric monoclonal antibody composed of murine variable and human constant regions. In placebo-controlled trials, both agents have proven to be effective and well tolerated in RA patients.

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For Editorial see page 669

Rheumatoid arthritis affects approximately 1% of the U.S. population, and along with osteoarthritis represents one of the leading causes of disability in the western world [1]. RA is characterized by a symmetrical inflammatory synovitis, often leading to progressive joint destruction and a step-wise functional decline. In addition to disease-associated morbidity, RA leads to premature mortality [2]. The financial burden of the disease is enormous, with lifetime costs comparable to those of coronary artery disease.

An important advance in treatment is the availability of several new agents, including the first biological agents available for use in RA. Etanercept, a TNF α inhibitor, was the first biological agent approved for the treatment of RA [3-9]. Infliximab, an anti-TNF monoclonal antibody, has also demonstrated efficacy and good tolerability in clinical trials [10-14] and represents another potentially important disease-modifying anti-rheumatic drug. Infliximab was approved by the FDA for use in the treatment of RA in November 1999.

The TNF precursor, a 26 kDa transmembrane protein, is found in a variety of cells throughout the body. Macrophages appear to be the primary site of TNF production in RA with the active form of TNF, a 17 kDa soluble protein fragment formed via TNF α -converting enzyme-mediated cleavage of the precursor molecule. After being shed from the cell surface, these soluble TNF molecules aggregate into trimolecular complexes that subsequently bind receptors found on a variety of cells, including fibroblasts, leukocytes and endothelial cells. Two TNF receptors have been described, the p55 (also called p60) receptor and the p75 (also called p80) receptor.

TACE acts not only on the TNF precursor molecule, but also cleaves the extracellular domain of its complementary ligand, forming soluble TNF receptors. These circulating sTNFRs are then free to bind the trimolecular TNF complexes, rendering them biologically inactive; thus, the sTNFRs function as natural inhibitors of TNF-mediated inflammation. Not surprisingly, sTNFR levels are increased in both the serum and synovial fluid of patients with RA [15]. These soluble receptors have an extremely short half-life – only seconds to several minutes.

A variety of physiologic functions have been ascribed to TNF-TNF receptor interactions. Also called cachexin, TNF blocks the action of lipoprotein lipase, causing severe cachexia in experimental models of chronic infection. Additionally, TNF induces programmed cell death (apoptosis) and stimulates the release of several pro-inflammatory cytokines, including interleukins 6, 8 and 1. TNF also induces the release of matrix metalloproteinases from fibroblasts, chondrocytes and neutrophils, and up-regulates the expression of endothelial adhesion molecules, leading to the migration of leukocytes into extra-vascular tissues.

Because of its array of pro-inflammatory effects, TNF has been implicated as playing a major role in several chronic inflammatory disorders, including RA, multiple sclerosis, Crohn's disease, systemic vasculitis, allograft rejection and graft-versus-host disease. There is accumulating evidence that TNF is indeed a key element in RA pathogenesis. Transgenic mice that overexpress TNF develop a chronic inflammatory arthritis [16]. Treatment of the arthritic mice with an anti-TNF monoclonal antibody ameliorates the arthritis. Anti-TNF thera-

TNF = tumor necrosis factor
RA = rheumatoid arthritis
FDA = Food and Drug Administration

TACE = TNF α -converting enzyme
sTNFRs = soluble TNF receptors

Table 1. Summary of placebo-controlled trials for infliximab and etanercept for the treatment of rheumatoid arthritis

	Phase	Study duration (wk)	Active treatment	Control treatment	Clinical response**
Infliximab (Remicade)					
Elliott et al. [22]	II	4	10 mg/kg i.v., single infusion	Placebo	79 vs. 8%
Maini et al. [24]	II	26	3 and 10 mg/kg i.v. at weeks 0,2,6,10 and 14	Placebo*	60 vs. 15%
Kavanaugh et al. [25]	Ib	12	5,10,20 mg/kg i.v. single infusion	Placebo*	81 vs. 14%
Maini et al. [26]	Phase III ATTRACT trial	30	3 mg/kg i.v. every 8 weeks	Placebo*	50 vs. 20%
Etanercept					
Moreland et al. [31]	II	12	16 mg/m ² s.c. twice weekly	Placebo	75 vs. 14%
Moreland et al. [32]	III	12	25 mg s.c. twice weekly	Placebo	62 vs. 23%
Finck et al. [35]	Phase III ERA trial	48	25 mg s.c. twice weekly	MTX	72 vs. 65%
Weinblatt et al. [34]	III	24	25 mg s.c. twice weekly	Placebo*	71 vs. 27%

* All patients (placebo and active treatment groups) were receiving concomitant weekly MTX.

** ACR criteria for 20% improvement. Active treatment vs. control treatment.

pies have also been shown to be effective in delaying the onset of collagen-induced arthritis [17]. In RA patients, synovial fluid levels of TNF are 4 to 5 times higher than peripheral blood levels, a discrepancy not seen in normal controls [18]. Advances in recombinant DNA technology have allowed investigators to specifically target TNF, not only in arthritic animal models, but also in patients with active RA. The success of these agents in humans has provided unequivocal support for the role of TNF-mediated inflammation in RA.

Etanercept

Etanercept (Enbrel) (Immunex, USA) is a dimeric fusion protein consisting of the extracellular domain of the p75 TNF receptor linked to the Fc portion of human IgG1 [Figure 1]. Fusion to the Fc component results in a much longer serum half-life. Administered subcutaneously, the standard adult dose is 25 mg twice weekly (0.4 mg/kg to a maximum dose of 25 mg in children). Serum levels of etanercept may increase by a factor of 2 to 5 with repeated dosing. The median half-life of the drug is 4.8 days (range 4.1–12.5 days).

In phase I and II trials etanercept has proven to be both well tolerated and effective in the treatment of RA. In the initial phase I dose-finding study, 16 patients with long-standing RA were given twice weekly subcutaneous injections for 4 weeks following a single intravenous loading dose at trial onset [3]. Etanercept administration was associated with a 45% mean improvement in pain and joint scores compared to 22% in patients receiving placebo. In a subsequent phase II placebo-controlled trial, 180 patients with long-standing active disease

were randomized to receive either twice weekly subcutaneous etanercept (at doses of 0.25, 2, or 16 mg/m²) or placebo [5]. High dose etanercept was clinically superior to lower doses, with 75% of patients receiving 16 mg/m² and attaining 20% improvement (American College of Rheumatology criteria) [19] by the trial's conclusion compared to only 14% in the placebo group ($P < 0.001$) [Table 1]. Clinical responses were frequently rapid, with a majority of patients showing significant response as early as one month into the trial.

In the pivotal phase III trial, fixed doses of etanercept (10 and 25 mg s.c. twice weekly) versus placebo were evaluated in RA patients over a 6 month period [6]. The trial again involved patients with long-standing, DMARD-refractory RA. Clinical response was again rapid with responders meeting criteria for improvement often within the first month of therapy. At 6 months, 59% of patients given high dose etanercept experienced at least 20% improvement, with 40% meeting criteria for 50% improvement [Table 1] Functional activity, as defined by the

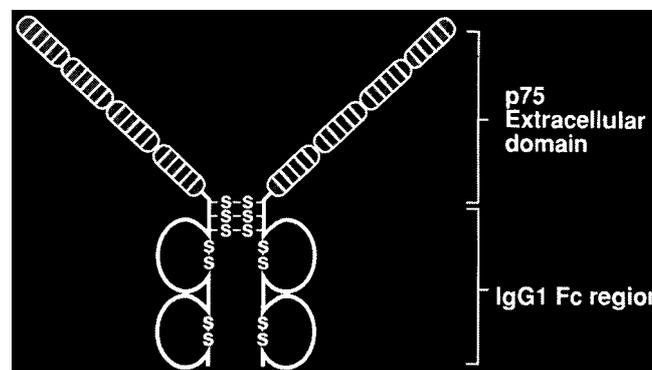


Figure 1. Etanercept is composed of the Fc portion of human IgG1 linked to the extracellular domain of a TNF receptor (p75).

IgG1 = immunoglobulin G1

DMARD = disease-modifying anti-rheumatic drug

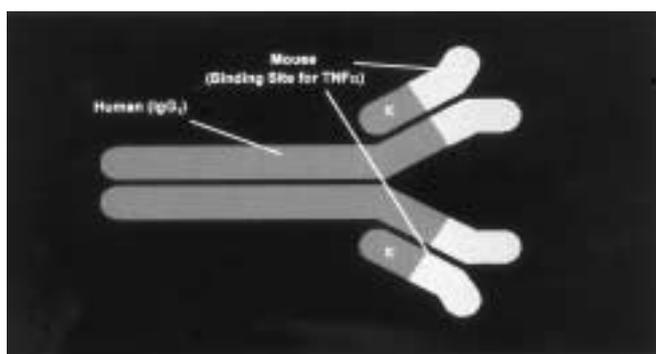


Figure 2. Infliximab is a chimeric monoclonal antibody composed of human constant and murine variable regions.

health assessment questionnaire, showed significant improvement at 3 and 6 months compared to placebo, with improvement observed as early as 2 weeks after the initiation of etanercept.

In addition to use as a single agent, etanercept has been studied in combination with methotrexate. In a 24 week double-blind trial, patients with MTX-refractory disease were randomized to receive additional therapy with either etanercept or placebo [8]. At 24 weeks, 71% of patients receiving the etanercept-MTX regimen had experienced 20% improvement compared to only 27% of patients receiving placebo plus MTX ($P < 0.001$) [Table 1]. Additionally, 39% met criteria for 50% improvement compared to only 3% of those randomized to placebo plus MTX. Patients receiving the combination of etanercept and MTX had better outcomes in all measures of disease activity, including pain and joint scores, physician and patient global assessment, HAQ scores, erythrocyte sedimentation rate, and C-reactive protein.

Until recently, experience with TNF inhibition has been largely limited to RA patients with long-standing refractory arthritis. In the recently reported ERA trial (The Use of Etanercept in Early RA), etanercept was compared to MTX over a 12 month period in patients with early disease (disease duration of less than 3 years) [9]. Clinical responses, as measured by ACR criteria, were similar at the trial's conclusion with significant differences at early time points (0–6 months), favoring etanercept. At 12 months, 72% of patients receiving etanercept (25 mg dose) attained 20% improvement and 25% met the criteria for a 70% improvement [Table 1]. However, when assessed by measuring an area under the curve, calculated from a mean numeric ACR response, the overall clinical outcome was superior for patients receiving etanercept. Additionally, patients receiving etanercept were less likely to show radiographic disease progression in terms of bony erosions when compared to those receiving MTX. These

MTX = methotrexate

HAQ = health assessment questionnaire

ACR = American College of Rheumatology

promising results suggest that etanercept may prove to be a valuable treatment option early in the course of disease.

In clinical trials the most common adverse outcome associated with etanercept use has been minor injection site reactions. Recently available safety data come from long-term, open-label follow-up of patients involved in the placebo-controlled clinical trials [7]. A large cohort of patients ($n = 713$) receiving etanercept has now been followed longitudinally for a total of 1,152 patient-years. Not only has the agent displayed maintained efficacy, but there has also been no evidence of cumulative toxicity with extended use.

Infliximab

Infliximab (Remicade) (Centocor, USA) is a chimeric anti-TNF mAb composed of a constant region from human immunoglobulin and a variable region from murine (mouse) immunoglobulin. Previously approved for the treatment of Crohn's disease, infliximab received FDA approval for the treatment of RA in November 1999. Clinical trials summarized below have confirmed both the efficacy and tolerability of the agent when used in patients with DMARD-refractory RA, both alone and in combination with MTX [11–14].

In the initial phase I open-label trial, Elliott [11] studied the use of infliximab in 20 patients with active long-standing RA. Patients had a median disease duration of 10.5 years and had failed a median of four previous DMARDs. Patients received a total of 20 mg/kg of intravenous infliximab given in divided doses over the course of 12–14 days. Clinical response to the treatment was substantial. Morning stiffness decreased from a median of 180 minutes at study entry to a median of 5 minutes at week 6. Pain scores decreased from 7.1 to 1.9 (range 0–10) over the same time period, representing an improvement of 73%. Swollen joint count dropped from 18 to 5, while serum C-reactive protein levels fell from a median of 39.5 mg/dl at study entry to 8 mg/dl at week 6. Functional capacity, as measured by HAQ score, improved significantly from a median of 2.0 at study entry to 1.1 by 6 weeks. Patients showed sustained benefit following the last dose of infliximab, with response duration ranging from 8 to 25 weeks (median 14).

The phase II trial [11] included 73 patients who, similar to those in the phase I trial, had long-standing DMARD-refractory RA. Results in this trial were similar. Patients in the active treatment groups received only a single intravenous infusion of infliximab, either 1 mg/kg or 10 mg/kg. At the 4 week assessment 79% of patients receiving 10 mg/kg reported at least 20% improvement in symptoms, and half had at least 50% improvement (measured by the Paulus criteria) [20].

In both the phase I and phase II trials, infliximab was well tolerated without reports of any clinically significant adverse events. No patients had evidence of human anti-chimeric antibodies subsequent to infliximab administration when assessed at the 4 week examination [15]. In a continuation of this phase II trial [12], 8 of the original 20 patients from the phase I open-label trial returned after a 4 week interval and were

retreated with up to three additional doses of infliximab. The timing of the additional doses was determined by disease relapse. Repeat administration resulted in significant clinical improvement with minimal adverse effects. The interval between doses, however, became progressively shorter during the course of the study. Additionally, four of the eight patients developed human anti-chimeric antibodies. Antibody development may well account for the decreasing response duration observed during the course of the study.

Maini and colleagues [13] recently published data on the combination of infliximab and low dose weekly MTX in the treatment of RA. In a double-blind placebo-controlled trial, 101 patients were given intravenous infliximab (1, 3, or 10 mg/kg) with or without MTX (7.5 mg/week) or MTX plus intravenous placebo. Sixty percent of patients receiving infliximab, with or without MTX, experienced at least 20% improvement using the Paulus criteria. Importantly, co-administration of low dose MTX significantly prolonged the duration of response seen with low dose (1 mg/kg) infliximab. Co-administration of MTX with higher doses of infliximab (3 and 10 mg/kg) also prolonged response duration, although not in a statistically significant fashion. All treatment arms were associated with minimal toxicity; headache was the most commonly observed adverse effect in patients receiving combination therapy. The overall incidence of human anti-chimeric antibodies was 17% for patients receiving infliximab (with and without MTX), with the incidence inversely proportional to the dose of infliximab. Half of the patients receiving low dose infliximab (1 mg/kg) without MTX developed human anti-chimeric antibodies, compared with 7% of those receiving 10 mg/kg. Concurrent administration of low dose MTX greatly diminished development of human anti-chimeric antibodies (by approximately threefold), suggesting that MTX induces an immunologic tolerance to infliximab. Although there were no reports of drug-induced lupus, 8% of patients receiving infliximab developed antibodies to double-stranded DNA.

Maini et al. [14] conducted a 54 week double-blind placebo-controlled trial of infliximab in combination with MTX, in which infliximab (3 mg/kg or 10 mg/kg intravenously) or placebo was given at 4 to 8 week intervals to patients with active RA who were also receiving MTX. They found that 59% of patients receiving 10 mg/kg and 42% of those receiving 3 mg/kg at 4 to 8 week intervals experienced 20% improvement by ACR criteria. There were no statistically significant differences in percentage of responders among the infliximab groups. When compared to placebo, there was no increase in the incidence of adverse effects. The combination resulted in a statistically significant reduction in radiographic progression (as measured by the Sharp score) when compared with MTX treatment alone.

Conclusions

Anti-TNF therapies have provided patients and physicians with a new and exciting means of treating RA and other allied conditions. With continued advances in our understanding of

cytokine biology, new ways of blocking TNF are likely to evolve. Selective TACE inhibition, by preventing release of its cell-surface subunit, may be a potential mechanism of TNF blockade. Gene-delivery systems may someday provide another effective way of modulating the action of TNF and TNF receptors.

With the availability of two TNF inhibitors for the treatment of RA, the major task facing physicians is finding ways to predict response to these agents as well as to other standard DMARDs and DMARD combinations. The unique mode of action of these biological agents makes them potentially attractive agents for use in combination regimens with either traditional DMARDs or potentially with other cytokine inhibitors. Additionally, the relatively rapid onset of action of these agents may make them ideal "induction" therapies. The availability of TNF inhibitors has dramatically changed the treatment paradigm for patients with RA.

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Correspondence: Dr. L.W. Moreland, Dept. of Medicine, University of Alabama at Birmingham, 1717 6th Avenue South, SRC 068, Birmingham, AL 35294-7201, USA. Phone: (1- 205) 934-7727, Fax: (1-205) 975-5554, email: larry.moreland@ccc.uab.edu