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REVIEW ARTICLE

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Efficacy and safety of the anti-TNF biologic agents

Abstract The last decade has seen a marked increase in the elucidation of cellular and molecular factors involved in chronic inflammatory processes that contribute to the pathogenesis of rheumatoid arthritis (RA). Multiple lines of evidence have demonstrated a critical role for the proinflammatory cytokine tumor necrosis factor (TNF) in the perpetuation of inflammatory synovitis and the subsequent destruction of cartilage and bone that leads to the functional disability observed in RA. In the light of these discoveries, new therapeutics have been developed to target TNF. The consistent efficacy demonstrated by these agents for the treatment of RA has validated TNF as an important mediator of the chronic inflammatory events and structural damage that occur with the disease. Three of these agents (etanercept, infliximab, and adalimumab) have been approved by the United States Food and Drug Administration (FDA) over the last 5 years for treatment of moderately to severely active RA. This article will first explain the role of TNF in inflammation and RA, and then compare and contrast the mechanisms of action, efficacy, and safety profiles of the various FDA-approved TNF inhibitors, as well as offer potential explanations for the clinical differences observed between these agents, especially with regard to safety.

Key words Efficacy · Monoclonal antibodies · Safety · Soluble receptors · Tumor necrosis factor (TNF) inhibitors

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TNF: its role in inflammation and rheumatoid arthritis

Tumor necrosis factor (TNF) is a potent, pleiotropic cytokine that has recently been described as a member of a protein family whose functions represent a physiological "double-edged" sword.[1] While TNF expression is required for many normal biologic processes such as regulation of the immune system and protection against microbial infection, inappropriate expression of TNF has been associated with autoimmunity, chronic heart failure, accelerated bone resorption, transplant rejection, and atherosclerosis, among others.[1]

TNF exists as a homotrimer in both soluble and transmembrane forms and exerts many of its effects by binding (in either form) to a 55-kD cell membrane receptor termed TNF receptor-1 (TNFR-1) or a 75-kD cell membrane receptor termed TNFR-2. The binding of TNF to its receptors leads to signal transduction and a variety of cellular activities including apoptosis, proliferation, activation, recruitment, and differentiation.[1] Many, and possibly all, of these TNF-induced events can be identified as relevant to the inflammatory and pathological processes of RA.

TNF is produced mainly by cells of the monocyte/macrophage lineage, but also by T and B cells, endothelial cells, and fibroblasts.[2–4] The first reports of an association between expression of TNF and its receptors in the joints and synovial fluid of patients with RA were made more than a decade ago.[4–8] Husby and Williams[6] first reported a strongly positive tissue distribution of TNF within synovial lining cells of patients with RA, and also within interstitial monocytes/macrophages within inflammatory infiltrates. They also reported that the levels of TNF within the synovial lining appeared to parallel the extent of inflammatory cells within the tissues. Expression of TNF and its receptors have also been demonstrated within cells comprising the deeper layers of the synovium and the cartilage–pannus junction.[4,5]

The tissue localization and expression levels of TNF in patients with RA support an important role for this cytokine in the development, and chronic nature, of RA. Many of the inflammatory (hyperplasia, increased vascular-

ity, cellular infiltration) and destructive (bone and cartilage degradation) aspects of RA can be accounted for, at least in part, by the dysregulated biologic actions of TNF on cell types involved in the immune response and those contributing to the maintenance of bone and cartilage integrity.

One of the mechanisms by which TNF promotes inflammation is through the induction of synthesis of other proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8, and granulocyte–monocyte colony-stimulating factor.[3,9,10] TNF may also sustain inflammation by facilitating the infiltration of leukocytes into areas of tissue damage. It has been shown to increase the expression of synovial vessel adhesion molecules that interact with leukocyte cell-surface receptors.[11] These adhesion molecule interactions are required for leukocyte extravasation into inflamed tissues. Upregulation of these adhesion molecules may promote the sustained infiltration of immune cells into the damaged tissue, thereby contributing to the chronic nature of the inflammation.

In patients with RA, angiogenesis ensures the development and persistence of the pannus by increasing the supply of nutrients, cytokines, and inflammatory cells to the synovial membrane.[12] There is emerging evidence that TNF plays a role in angiogenesis and the resultant increase in vascularity which is observed early in the development of RA.[13,14]

In addition to initiating and sustaining inflammation in RA, TNF likely plays a critical role in the degradation of bone and cartilage. The imbalance between bone resorption and bone formation that leads to focal bone loss in RA is driven primarily by osteoclasts. TNF acts both indirectly and directly to promote osteoclast differentiation.[15] Bone-lining cells respond to TNF by releasing factors that promote the differentiation of osteoclast precursors. TNF acts directly on osteoclasts by enhancing their resorbing activity, and has been shown to increase the expression of receptor activator of NF-κB ligand, a potent regulator of osteoclastogenesis.[15,16] TNF further enhances bone loss in RA by inducing osteoblast apoptosis.[17]

TNF also appears to play a critical role in cartilage loss in RA by stimulating the production of matrix metalloproteinases and other tissue-degrading substances such as nitric oxide, while decreasing the synthesis of cartilage-specific collagens and proteoglycans.[18–20]

In vivo evidence supporting the role of TNF in inflammatory arthritis was first shown in animal studies. Multiple studies employing the murine collagen-induced arthritis model demonstrated that systemic administration of soluble TNFR-Fc fusion proteins, or anti-TNF antibodies, after disease onset led to an amelioration of joint disease.[21–23] In addition, mice carrying a modified human TNF transgene (resulting in dysregulated expression of TNF) develop a chronic inflammatory polyarthritis that can be prevented with a human anti-TNF antibody.[24] These studies provided a strong basis for the study of TNF-blocking strategies for the treatment of RA in humans. The following sections discuss the various therapeutic options to target TNF that have been approved for use by the United States Food and Drug Administration (FDA).

Mechanisms of action, dosing, and pharmacokinetics of FDA-approved TNF inhibitors

TNF inhibitors represent an advance over more traditional therapeutic regimens. Traditional disease-modifying antirheumatic drugs (DMARDs) are limited by a number of different factors, such as unpredictable responses, slow onset of action, high rates of discontinuation, unproven long-term benefits, and toxicity. Inhibition of TNF provides a selective regulation of the immune responses contributing to the pathogenesis of RA, rather than the systemic suppression of the immune system that is observed with methotrexate (MTX), for example.

As previously mentioned, various therapeutics have been developed to target TNF. Most of the clinical experience in RA to date has centered on the use of two classes: a soluble TNFR fusion protein (etanercept), and monoclonal antibodies to TNF (infliximab [chimeric], adalimumab [human]). Etanercept, infliximab, and adalimumab have all been approved for the treatment of RA, but the indications for each agent differ (Table 1).[25–27] In addition, although these classes of therapeutics share the ability to inhibit the biologic action of TNF, the mechanism by which this occurs is quite different, and there are a number of molecular dissimilarities that result in vastly different pharmacokinetics. Some of the important functional and clinical characteristics of these agents are summarized in Table 2.

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kD (p75) TNFR-2 linked to the Fc portion of human IgG1. Conjugation of soluble receptors to human Fc (a proteolytic fragment of IgG1) can extend the plasma half-life of these agents to approximately that of immunoglobulin.[28] Etancercept binds to both soluble and cell membrane-associated TNF as well as to lymphotoxin-α, and inhibits their interactions with cell-surface receptors. Etanercept does not lyse cells that express transmembrane TNF in either the presence or the absence of complement.[27]

The recommended dosing regimen of etanercept for adult patients with RA is 50 mg per week, administered as two 25-mg subcutaneous (SC) injections or a single 50-mg injection. For pediatric patients with active polyarticular-course juvenile RA (ages 4–17), the recommended dose is 0.8 mg/kg weekly (25 mg per week maximum). The mean half-life of a single SC injection of 25 mg etanercept is approximately 4.8 days according to pharmacokinetic (PK) analysis in 25 patients with RA.[27] Clearance of etanercept was measured at a rate of 160 ± 80 ml/h in these patients, with a maximum serum concentration (C_{max}) of 1.1 ± 0.6 μg/ml. Time to C_{max} was 69 ± 34 h. There are no sex- or age-related differences in the PK parameters of etanercept.[27] Concomitant use of MTX does not affect the PK of etanercept.[29]

Infliximab is a chimeric IgG1 monoclonal antibody composed of human constant and murine variable domains that binds to soluble and cell membrane-associated TNF and inhibits their interactions with TNFRs.[26] Infliximab does not bind to lymphotoxin-α.[26] Unlike etanercept, infliximab has

Table 1. FDA approved indications for TNF inhibitors

Drug	FDA-approved indication(s) for RA	Year of first approval for RA	Other approved indications (year of approval)
Etanercept (Enbrel)	Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. Etanercept can be used in combination with methotrexate in patients who do not respond adequately to MTX or alone.[27]	1998	Juvenile RA (1999) Psoriatic arthritis (2002) Ankylosing spondylitis (2003)
Infliximab (Remicade)	Infliximab, in combination with MTX, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to MTX.[26]	1999	Crohn's disease (1998)
Adalimumab (Humira)	Indicated for reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs. Adalimumab can be used alone or in combination with MTX or with other DMARDs.[25]	2002	None

Table 2. Characteristics of TNF inhibitors

	Etanercept	Infliximab	Adalimumab
Structure	Human TNFR fusion protein	Chimeric (mouse/human) monoclonal antibody	Human monoclonal antibody
Administration	Subcutaneously	Intravenously	Subcutaneously
Dose	25 mg BIW *or* 50 mg Q 1 week	3–10 mg/kg Q 4–8 weeks	40 mg Q 1–2 weeks
Concomitant MTX required	No	Yes	No
MTX effects on PK	None	Increase in serum concentration	Decrease in clearance
Half-life	4.8 days	9.5 days	12–14 days
In vitro complement fixation	No	Yes	Yes
In vitro lysis of cells expressing cell-surface TNF	No	Yes	Yes
Antigenicity	No	Yes; human antichimeric antibodies (HACA)	Yes; human antihuman antibodies (HAHA)

been shown to lyse cells expressing transmembrane TNF via antibody-dependent cellular toxicity and complement-mediated cytotoxicity effector mechanisms.[30] Lysis of cells expressing transmembrane TNF (such as macrophages) in the joints of patients with RA may have deleterious results, the potential consequences of which are discussed in the accompanying section on the long-term safety of the TNF inhibitors.

Infliximab must be used concomitantly with MTX to decrease the formation of human antichimeric antibodies (HACAs),[26] which may explain the increased serum levels of infliximab that have been observed with concomitant MTX compared with infliximab used alone.[31] The recommended dosing regimen for infliximab is a single 3-mg/kg infusion followed by two 3 mg/kg doses at weeks 2 and 6, and every 8 weeks thereafter.[26] Doses of infliximab may be adjusted up to 10 mg/kg or administered as more frequent (every 4 weeks) infusions in patients who do not exhibit a complete response.[26] Median PK results for doses of 3–10 mg/kg in patients with RA indicate that the terminal half-life of infliximab is 8.0–9.5 days.[26] The effect of human antichimeric antibodies on the half-life of infliximab has not been studied.

No systemic accumulation of infliximab has been reported to occur upon continued repeated treatment with 3 or 10 mg/kg at 4- or 8-week intervals, despite its long half-life.[26] No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or sex.[26]

Adalimumab is a human IgG1 monoclonal antibody whose constant and variable regions consist of human sequences. In vitro and in vivo studies indicate that adalimumab binds to TNF and inhibits its interaction with cell-surface receptors.[32] Adalimumab does not bind to lymphotoxin-α. Consistent with its antibody structure, adalimumab is capable of lysing cells expressing cell-surface TNF in the presence of complement.[25]

The recommended dosing regimen of adalimumab for patients with RA is one 40-mg SC injection every 2 weeks. However, the frequency of dosing may be increased to one 40-mg SC injection every week in cases of incomplete responses. The development of human antihuman antibodies (HAHA) to adalimumab has been observed, but the relationship between the formation of these antibodies and the need for more frequent dosing has not been defined.

The terminal half-life of adalimumab has been estimated to be approximately 14 days.[32] In healthy volunteers, a C_{max} of 4.7 ± 1.6 μg/ml was achieved within 131 ± 56 h after a single SC injection of adalimumab.[25] Systemic clearance of adalimumab is approximately 12 ml/h. However, MTX reduces the clearance of single and multiple doses of adalimumab by 29% and 44%, respectively.[25] Population PK analyses suggest that the presence of antibodies against adalimumab increases its clearance.[25] There are no gender-related PK differences among patients on adalimumab after correcting for patient body weight, but there does appear to be an age-related decrease in drug clearance (i.e., in patients aged 40 years and older).[25]

Efficacy of TNF inhibitors

Soluble receptors

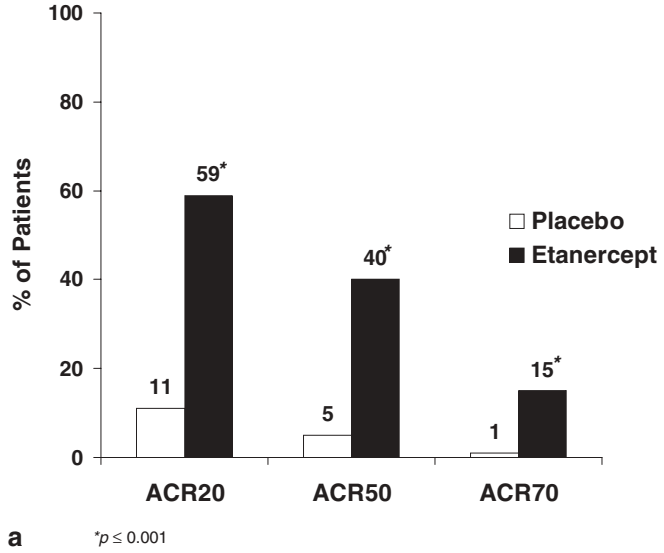
Etanercept

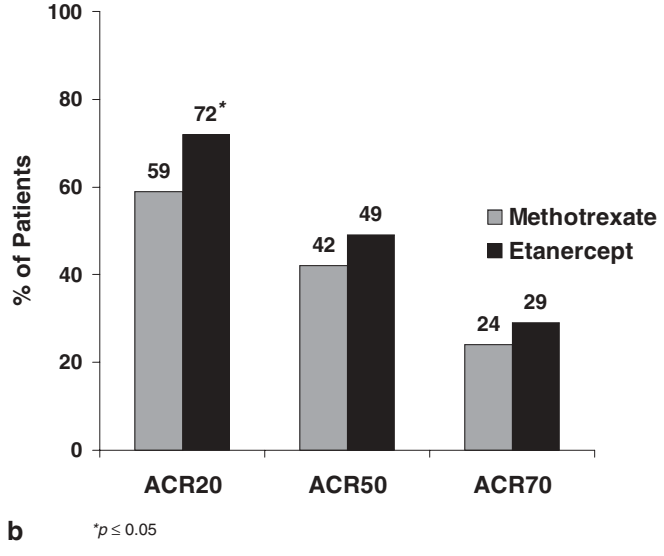
Etanercept has demonstrated its efficacy as a monotherapy in patients whose long-standing disease is inadequately controlled with traditional DMARDs (hydroxychloroquine, oral or injectable gold, MTX, azathioprine, penicillamine, or sulfasalazine), and in patients with early RA (disease duration <3 years) who haved never received MTX.[33–36] Etanercept has also proven efficacious in combination with MTX for patients whose disease remains persistently active despite at least 6 months of MTX therapy.[37,38] In addition, a trial (TEMPO: Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) that directly compared the efficacy of etanercept or MTX monotherapy to the efficacy of combination etanercept and MTX has also been completed. This trial demonstrated the clinical superiority of the combination of etanercept and MTX therapy compared with either etanercept or MTX monotherapy. The clinical trials demonstrating these results are described in greater detail below.

Based on encouraging results in an initial 3-month dose-finding study in 180 DMARD-refractory patients (mean disease duration, >5 years), a second, multicenter, randomized, double-blind, placebo-controlled study was undertaken to confirm the benefit of etanercept over a longer duration (6 months) in patients with DMARD-refractory RA (mean disease duration, 12 years). While the previous trial had employed body surface area-based dosing, this trial was designed to test the potential for fixed dosing also.[36] Doses of 10 and 25 mg were chosen for this phase 3 trial based on the results of the 3-month phase 2 study.

The primary efficacy endpoints in the phase 3 trial were 20% and 50% improvement at 3 and 6 months, respectively, according to the American College of Rheumatology (ACR) response criteria. Patients receiving etanercept (25 mg) achieved significantly higher ACR 20, 50, and 70 responses at 3 and 6 months compared with placebo (Fig. 1a). Consistent with the phase 2 trial, the responses were evident as early as 2 weeks. In the 25-mg group, differences in the ACR 20 and 50 responses were already statistically higher at this time compared with placebo.

Patients receiving etanercept (10 or 25 mg) also had significant reductions in the number of tender and swollen joints compared with placebo at 6 months of treatment, with 17% (25 mg) and 14% (10 mg) assessed as having minimal disease (0–5 tender or swollen joints) compared with 3% of the placebo group ($P < 0.005$ for each etanercept group compared with placebo). These changes in the etanercept patients were reflected in improvements in quality-of-life measures recorded on all components of the health assessment questionnaire (HAQ). All components of the HAQ were significantly ($P < 0.05$) improved at 6 months in patients receiving 25 mg twice weekly compared with the placebo group.





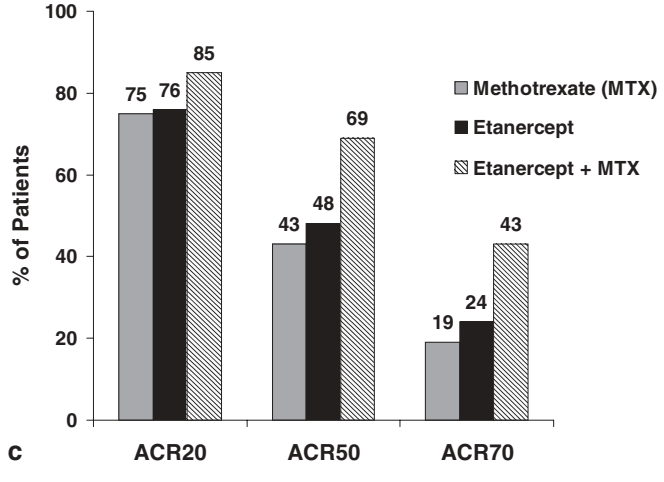


Fig. 1. a Etanercept monotherapy; ACR responses at 6 months. **b** Etanercept for early RA; ACR responses at 2 years. **c** Etanercept and MTX vs. etanercept or MTX monotherapy; ACR responses at 1 year

Etanercept has also demonstrated sustained efficacy as well as the ability to inhibit disease progression in patients with early RA.[33,34] In early RA trials, patients were chosen who were at risk of rapidly progressive joint damage and whose disease, if untreated, was predicted to progress at a rate of 4–5 points per year on the Sharp erosion subscale, and 4 points per year on the joint space-narrowing subscale.[33] In the first trial, 632 patients with a mean disease duration of approximately 12 months, who had never previously been treated with MTX, were randomized to receive either twice weekly etanercept (10 or 25 mg) or MTX for 12 months.[33] MTX doses were rapidly escalated from 7.5 mg at the time of entry to 20 mg at week 8 (the mean dose of MTX at this time was 19 mg). In the open-label extension of this trial, 512 patients continued to receive the therapy to which they had been randomized for up to 1 additional year. Importantly, more patients in the 25-mg etanercept group remained in the study for 2 years (74%) than did patients randomized to receive MTX (59%).

Early clinical responses were observed in the group receiving 25 mg that were sustained over the entire 24 months of treatment. Early responses were consistent with previous trials of patients with long-standing RA and with a rapid onset of action for etanercept. Significant differences in clinical responses between the group receiving 25-mg etanercept and the group receiving MTX were evident at most evaluations within the first 6 months of treatment despite rapid dose escalation of MTX within the first 8 weeks of treatment.[33] Although these differences were less apparent between months 6 and 12 of the study, the open-label extension trial demonstrated that at 24 months significantly more patients receiving 25-mg twice weekly met the ACR 20 criteria than patients receiving MTX (72% vs. 59%, respectively, $P = 0.005$) (Fig. 1b).[34]

The effects of etanercept on radiographic-evident disease progression were also impressive over the course of the two trials.[33,34] These effects were monitored by the analysis of erosion, joint-space narrowing, and total Sharp scores. Nearly three-quarters of the patients (72%) in the 25-mg group had no increase in the erosion score over 6 months compared to 60% of the patients receiving MTX ($P = 0.007$), and the mean increase in the erosion score at 6 months in the etanercept group (25 mg) was half that of the MTX group (0.3 and 0.68, respectively, $P = 0.001$). The changes at 12 months were 0.47 and 1.03, respectively ($P = 0.002$). Both etanercept and MTX prevented joint-space narrowing, and mean joint-space narrowing scores were comparable between etanercept and MTX over 12 months. The mean increases in the total Sharp scores were 0.57 in the 25-mg etanercept group and 1.06 in the MTX group at 6 months ($P = 0.001$), and 1.00 and 1.59, respectively ($P = 0.11$) at 12 months.[33] The mean changes in total Sharp and erosion scores continued to be significantly lower in the 25-mg etanercept group (1.3 and 0.66 units, respectively) compared with the MTX group (3.2 and 1.86, respectively) at 24 months ($P = 0.001$ for etanercept vs. MTX for both comparisons).[34]

Consistent with earlier trials, etanercept improved patient quality of life as measured by the HAQ.[33,34] Patients in

the early RA trial had moderate disability at the beginning of the study (HAQ scores 1.4–1.5 units). A 0.25 unit change in the HAQ score is considered to be a clinically significant change in the level of disability.[39] Slightly more than half (~55%) of the patients in both the etanercept (25 mg) and MTX groups had at least a 0.5 unit increase in the HAQ score at 12 months. At 24 months, however, the 25-mg dose of etanercept was significantly more effective than MTX in improving patient quality of life. The same proportion (55%) of patients in the etanercept group had at least a 0.5 unit increase, while only 37% of the MTX patients maintained this level after 24 months ($P < 0.001$).[34]

Patients with persistently active RA despite MTX therapy also experience a significant clinical response when etanercept is added to their regimen of MTX.[37,38] Eighty-nine patients with active RA (median of 28 tender and 18 swollen joints) despite 6 months of treatment were randomized to have either 25 mg etanercept twice weekly or placebo added to their regimen of MTX for a period of 6 months. At the end of the controlled trial, all patients were offered the opportunity to receive etanercept in an open-label extension of this trial that assessed the longer-term benefits of this therapy as well as whether the combination allowed for a dose reduction or discontinuation of MTX or corticosteroids while maintaining a clinical response.[37]

The primary endpoint of the blind study was the proportion of patients achieving an ACR 20 response at 6 months. Patients in this multicenter, double-blind trial had a mean duration of RA of 13 years. The mean weekly doses of MTX were 18 mg in the placebo/MTX group and 19 mg in the etanercept/MTX group.

Patients who had etanercept added to MTX had significantly superior ACR 20, 50, and 70 responses at both 3 and 6 months (blind phase). Seventy-one percent and 27% of the etanercept/MTX and placebo/MTX patients, respectively, had an ACR 20 response at 6 months ($P < 0.001$).[38] In addition, median scores for both swollen and tender joint counts at 6 months decreased substantially in the etanercept/MTX group compared with the placebo/MTX group (7 vs. 17 tender; 6 vs. 11 swollen). Patients receiving etanercept/MTX had significantly greater improvements in all other individual measures of disease activity at 3 and 6 months. Consistent with clinical and disease activity responses observed in the etanercept/MTX group, measures of disability also improved. HAQ scores had improved by 47% at 6 months in the etanercept/MTX group (from 1.5 to 0.8), while the score in the placebo/MTX group did not change significantly (1.5 to 1.1; 27% improvement).

Seventy-nine patients who were on background MTX enrolled in the open-label extension of the combination therapy trial and had received treatment with etanercept for a median of 44 months.[37] Seventy-six patients were evaluated for 1-year efficacy, 63 for 2-year efficacy, and 57 for 3-year efficacy. Of the 57 patients assessed at 3 years, 77% had achieved an ACR 20 response, 44% had an ACR 50 response, and 23% had an ACR 70 response. These patients had a median of three tender and six swollen joints at the 3-year assessment. Eighteen percent of these patients also had HAQ disability scores of zero.

Etanercept/MTX therapy allowed for a dose reduction of corticosteroids (after at least 3 months of combination therapy) in 83% and a discontinuation in 56% of 30 patients assessed after 3 years in the extension study. Sixty-two percent and 29% of 66 patients assessed were able to decrease or discontinue MTX, respectively. The response to etanercept was maintained in patients who decreased or discontinued corticosteroids or MTX.

The efficacy of etanercept or MTX monotherapy has also been directly compared with a combination of etanercept and MTX in 682 patients with active RA (disease duration up to 20 years) and an inadequate response to at least one DMARD other than MTX. Patients in this international, randomized, double-blind, parallel-group study received one of three treatments: twice-weekly etanercept (25 mg), MTX (up to 20 mg/week), or etanercept and MTX for 52 weeks. Radiographic analysis was performed on a total of 642 patients.

The clinical responses observed in this trial are shown in Fig. 1c. Thirty-seven percent of the patients treated with the combination of etanercept and MTX ($n = 212$) achieved clinical remission as measured by the disease activity score (DAS) criteria (DAS < 1.6) at 1 year compared with 18% of patients treated with etanercept alone ($n = 212$) and 14% of patients treated with MTX alone ($n = 212$).[40]

Eighty percent of the patients in the combination group experienced no progression of joint damage (unit change of total Sharp score (TSS) <0.5) in the radiographic analysis compared with 68% and 57% of etanercept monotherapy and MTX monotherapy-treated patients, respectively, at 1 year. Fifty-one percent of the patients in the combination group also reported significant improvements in functionality at 1 year.[40]

Monoclonal antibodies

Infliximab

Infliximab must be used concomitantly with MTX for the treatment of RA. While initial studies examined the potential of infliximab monotherapy,[41,42] it subsequently became evident that sustained efficacy with this drug required the use of concurrent MTX, presumably to reduce serum levels of HACAs that form against the murine components of the antibody. Indeed, low-dose MTX has been shown to greatly diminish the appearance of HACAs in RA patients treated with repeated doses of 1 mg/kg to 10 mg/kg intravenous infliximab.[43]

The first trial to demonstrate the superior efficacy of multiple doses of infliximab when used in combination with MTX was a 26-week, randomized, double-blind, placebo-controlled trial involving 101 patients with long-standing active RA.[43] Patients in this trial had previously exhibited an incomplete response or flare of disease activity while on low-dose MTX (7.5–15 mg/week) for a minimum of 6 months, and were subsequently randomized to receive 1, 3,

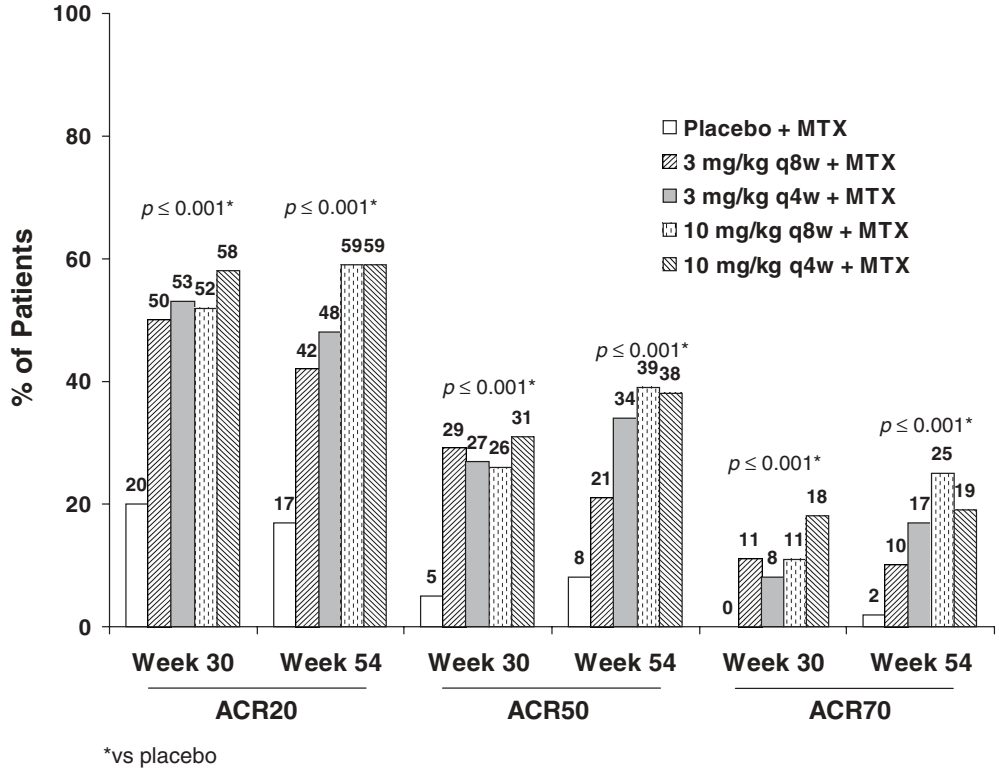


Fig. 2. Infliximab and MTX; ACR responses at weeks 30 and 54

or 10 mg/kg infliximab or placebo at weeks 0, 2, 6, 10, and 14, along with a fixed MTX dose of 7.5 mg/week. The primary endpoint of this phase 2 trial was the total time (in weeks) that a patient exhibited a response to treatment using the composite index defined by the Paulus 20% criteria.

When used in combination with MTX, 1 mg/kg of infliximab produced a longer duration of response as well as a higher response rate than infliximab (1 mg/kg) alone. This observation was consistent across the range of infliximab doses studied. The median duration of response in patients receiving 1 mg/kg without MTX was 2.6 weeks, while those receiving concomitant MTX had a median response duration of 16.5 weeks ($P < 0.006$). A peak response rate of 60% at week 2 declined rapidly (to placebo rates by week 6) in patients receiving 1 mg/kg infliximab alone, whereas patients who were also receiving MTX had response rates in the range of 60% to 80% during the treatment period, but which declined to 20% by week 26.

No dose-related increase in response rates was observed in the trial. However, patients with Paulus 20% and 50% responses between weeks 8 and 16 receiving higher doses of infliximab (3 or 10 mg/kg) did appear to have a longer duration of response that was sustained until the end of the study (26 weeks).

Infliximab also demonstrated efficacy in patients with MTX-refractory disease in a larger phase 3 trial.[44] Patients in this randomized, double-blind, placebo-controlled trial ($n = 428$) who had received continuous MTX for at least 3 months, and at a stable dose for at least 4 weeks, were randomized to receive intravenous doses of 3 or 10 mg/kg infliximab at weeks 0, 2, and 6, and every 4–8 weeks thereafter for 30 weeks. Patients in this trial had a mean disease duration of 7.2–9 years, and median MTX doses of 15 mg/week (range, 10–35 mg/week). Approximately one-half of the patients in each treatment group had been on MTX for ≥3 years.

More patients in each infliximab treatment group achieved the primary endpoint (ACR 20 response at 30 weeks) than in the group receiving only MTX ($P < 0.001$ for each comparison, Fig. 2). Approximately one-half of the responders had attained an ACR 20 by week 2, and nearly 90% by week 6. Total response rates were between 50% and 60% up to 30 weeks. Clinical measures of disease activity also improved in the infliximab groups, with trends toward more significant improvements with higher and more frequent dosing.[44]

To examine the capacity of the approach used in the Maini et al.[44] study to effect a more sustained clinical benefit as well as to assess the longer-term effect on joint damage, patients in the 6-month trial were eligible to continue on the same weekly doses of MTX and infliximab or placebo every 4 or 8 weeks for a total of 54 weeks of treatment.[45] Clinical responses were assessed using the ACR criteria. Radiographic joint damage was measured according to the van der Heijde-modified Sharp scoring system.

At the end of 1 year, 50% of the patients in the MTX group had discontinued treatment, largely due to lack of efficacy (36%), compared with 21% in all infliximab groups (12% for lack of efficacy). ACR 20, 50, and 70 responses at week 54 were significantly higher in infliximab-treated patients treated with 3 mg/kg every 4 weeks, and in both 10 mg/kg groups when compared with the placebo (MTX) group. ACR 20 responses in the group receiving 3 mg/kg every 8 weeks were also significantly higher at 54 weeks

($P < 0.001$), but ACR 50 and 70 responses in this group did not reach statistical significance (Fig. 2).

Consistent with clinical response, patients treated with infliximab had significantly less progression of joint damage from baseline when compared with the MTX group ($P < 0.001$). While MTX patients had a 9% to 10% increase in the total radiographic score at 54 weeks, infliximab-treated patients had no significant change in the mean score when baseline values were compared with those at 54 weeks.

In a subsequent analysis of the treatment outcomes from this trial as a function of serum infliximab concentrations, it was found that 22% to 30% of the patients in the group receiving 3 mg/kg every 8 weeks had undetectable trough serum levels of infliximab before each infusion. Further analyses demonstrated that improvements in clinical, laboratory, and radiographic measures were related to higher trough serum concentrations, and suggested that some patients might require higher or more frequent dosing of infliximab.[45]

Adalimumab

Adalimumab has undergone an extensive clinical development program to define its optimal dosing regimen and therapeutic potential in RA. To date, all adalimumab clinical trials have enrolled adult patients with RA with long-standing, DMARD-refractory disease. Efficacy in these trials has been assessed by a number of response criteria, including the ACR, the European League Against Rheumatism, and DAS criteria. Results from clinical trials of adalimumab that included doses currently recommended by the FDA are discussed.

A 12-week, phase 2, double-blind, placebo-controlled study evaluated the efficacy and dose response effect of adalimumab monotherapy in 238 patients with active, DMARD-refractory RA. After a 4-week, DMARD wash-out period, patients were randomized to receive SC injections of adalimumab (20, 40, or 80 mg weekly or placebo). At week 12, ACR 20 response rates for 20, 40, and 80 mg of adalimumab (49%, 57%, and 56%, respectively) were significantly greater than those for placebo (10%) ($P \leq 0.001$ for each comparison). Improvements in ACR 20 response rates were maintained over the 12-week period. Each of the ACR core criteria significantly improved with each adalimumab dose.[46]

This 12-week trial was followed by a 40-week, double-blind continuation phase, during which patients initially randomized to placebo were switched to adalimumab at 40 mg weekly. A total of 229 patients with a mean disease duration of nearly 10 years, and approximately four previous DMARDs per patient, then entered a 12-month, open-label continuation phase of 40 mg weekly adalimumab. Patients who entered the open-label phase had sustained ACR 20, 50, and 70 responses from 12 to 24 months, as well as mean disability scores as measured by the HAQ of 1.12 at both 12 and 24 months.[47]

The ability of adalimumab monotherapy to provide a clinical benefit in active, DMARD-refractory RA was also examined in a 26-week, double-blind, randomized, placebo-controlled trial.[48] This trial also compared the efficacy of weekly versus every-other-week (EOW) administration of 20 or 40 mg adalimumab and placebo. After a 4-week DMARD wash-out period, 544 patients with a mean disease duration of 11 years were randomized to one of the five treatment groups.

All adalimumab dosing regimens demonstrated significantly superior efficacy versus placebo at week 26, although weekly dosing of 40 mg resulted in the in best ACR responses.[48] For example, an ACR 20 response was achieved by 53% of the patients receiving 40 mg weekly, compared with 46% receiving 40 mg EOW, 39% receiving 20 mg weekly, and 36% receiving 20 mg EOW ($P < 0.01$ for each comparison to a 19% placebo response). Week 2 ACR 20 responses to all four adalimumab regimens were significantly better than those with placebo. Disability also improved in all adalimumab treatment groups as assessed by the HAQ. Consistent with ACR responses, the highest mean decrease in the HAQ occurred in the group receiving weekly injections of 40 mg (0.49 vs. 0.07 in the placebo group, $P < 0.01$).

The efficacy of adalimumab in combination with MTX was also assessed in a 24-week, randomized, double-blind, placebo-controlled trial including 271 patients with active RA (mean disease duration 12.5 years) despite at least 6 months of treatment with MTX at stable doses.[49] Patients were randomized to receive placebo or 20, 40, or 80 mg adalimumab EOW. The mean weekly dose of MTX was 16.5 mg in the placebo group, and 16.8 mg in the adalimumab group. The primary efficacy end-point was ACR 20 at 24 weeks.

All groups receiving MTX and adalimumab achieved a significantly higher ACR 20 response compared with placebo at week 24 compared with the placebo/MTX group (Fig. 3). Responses to adalimumab were rapid, and the proportion of patients achieving ACR 20 responses was greatest at the first scheduled visit (week 1). Each of the seven ACR core components was also significantly improved from baseline in all adalimumab/MTX groups at week 24 compared with the placebo/MTX group. The HAQ disability index decreased by at least 0.54 (absolute change) in each adalimumab dosage group compared with 0.27 for placebo.

Adalimumab has also been shown to inhibit radiographic disease progression when added to stable doses of MTX in patients with MTX-refractory disease in a 52-week, randomized, double-blind, placebo-controlled trial.[50] Six hundred and nineteen patients with a mean disease duration of 11 years were randomized to receive adalimumab at doses of 20 mg weekly, 40 mg EOW, or placebo weekly. The mean dose of MTX was approximately 17 mg/week.

At week 52, the mean changes in the modified Sharp and erosion scores were significantly lower in the adalimumab groups compared with the placebo group. In addition, significantly more patients taking adalimumab had no new erosions compared wth placebo (20 mg weekly, 57.9%; 40 mg EOW, 61.8%; placebo, 46.0%; $P \leq 0.05$ and $P \leq 0.001$, respectively).[50]

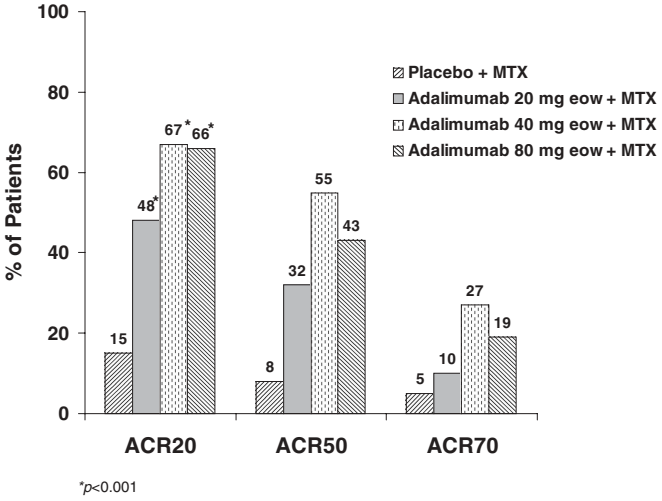


Fig. 3. Adalimumab and MTX; ACR responses at 24 weeks

Long-term safety of TNF inhibitors

Long-term maintenance of both efficacy and tolerability are particularly important in therapeutic strategies for RA considering the chronic, progressive nature of the disease. Given the natural biologic role that TNF plays in immune function, particular attention has been paid to overall rates of infection and malignancy in patients treated with TNF inhibitors. However, in some cases, a direct association between these events and treatment with a specific TNF inhibitor has been difficult given that the overall rates of infection and malignancy, most notably lymphoma, appear to be higher in patients with RA.[51–57]

There are a number of relative contraindications for the use of TNF inhibitors. These include systemic lupus erythematosus, multiple sclerosis, optic neuritis, current active serious infections, chronic recurrent infections, a history of tuberculosis (TB) or positive purified protein derivative (PPD) skin tests, and congestive heart failure.

Soluble receptors

Etanercept

More long-term safety data exist for etanercept than for the other TNF inhibitors. In controlled trials, there were no differences in rates of infection among patients with RA treated with etanercept and those treated with placebo or MTX. The most common type of infection was upper respiratory infection, which occurred at approximately the same rate in etanercept- and placebo-treated patients.[27]

A recent report on observations from 2054 North American ($n = 1442$) and European ($n = 612$) patients participating in etanercept RA trials, some of whom had received etanercept for more than 5 years (6654 patient-years), concluded that the overall rate of adverse events in these patients remains low. The frequency of infections requiring hospitalization or intravenous antibiotics was 0.04 per patient-year in the total population (6654 patient-years), which is equivalent to the rate in control groups in clinical trials. The incidence of malignancies was also similar to that projected by the Surveillance, Epidemiology, and End Results database (57 observed vs. 55 predicted).[58]

Rare cases of demyelinating disease, cytopenia, lupus-like syndromes, and serious infections, including TB, have occurred with treatment with TNF inhibitors. Owing to the potential of TNF inhibitors in general to increase the susceptibility of infection, a bold-type warning on the etanercept package insert states that administration should be discontinued if the patient develops a serious infection or sepsis, and treatment should not be initiated in patients with active infection.[27]

Monoclonal antibodies

Infliximab and adalimumab

Long-term safety with infliximab is generally good. In a 2-year study, there was no increase in previously reported adverse events, and there have been no reports of increased rates of lymphoma.[59] However, there does appear to be an increased rate of severe infections with infliximab treatment, including granulomatous infections such as histoplasmosis, aspergillosis, listeriosis, and TB.[60–62] A recent abstract presented at the ACR's annual meeting reported at least a 10-fold increase in the number of cases of listeriosis, histoplasmosis, tuberculosis, and *Pneumocystic carinii* infections for patients treated with infliximab compared with etanercept-treated patients until June 2002 (these events were recorded in the FDA adverse events reporting system).[62] In light of this increased incidence, a black box warning has been added to the infliximab package insert regarding TB (frequently disseminated or extrapulmonary at presentation) and invasive fungal and opportunistic infections. Patients being considered for infliximab treatment must be evaluated for latent TB, and those with a positive tuberculin skin test should be treated for TB prior to initiating infliximab therapy.

The incidence of TB and other granulomatous infections in infliximab-treated patients appears to be considerably higher than in etanercept-treated patients, which argues against the occurrence of these infections as a general consequence of TNF inhibition. A number of possible explanations have been put forward to explain potential points of differentiation between the two agents, such as differences in pharmacokinetics, binding properties, complement activation, cell lysis, or effects on circulating leukocytes. Some of these suggestions may also hold true for differences between etanercept and adalimumab. Adalimumab has also been mandated by the FDA to include a black box warning in its package insert owing to an increased incidence of TB.

TNF appears to be involved in both the initiation of formation, as well as in the maintenance, of granuloma. It

increases the phagocytic ability of macrophages, enhances the killing of mycobacterium, induces apoptosis of permissive macrophages, and stimulates the production of chemokines and endothelial adhesion molecules which are crucial to sustaining the recruitment of inflammatory cells, leading to their focused accumulation within granuloma.[63] Therefore, it would appear that the amount of TNF-inhibition required to affect a clinical response in inflammatory diseases such as RA must be balanced with the amount of circulating TNF that is required to mount an effective immune response against granulomatous infections. Infliximab possesses a number of characteristics that might lead to oversuppression of circulating TNF, and therefore an increased risk of the development of these infections.

Infliximab forms very stable complexes with both soluble and transmembrane TNF, and does not appear to release TNF once bound.[64] This property, coupled with the long serum half-life of infliximab, may result in complete neutralization of TNF. In comparison, in vitro studies have suggested that etanercept may bind transmembrane TNF less robustly and has a faster dissociation rate than infliximab.[64] It has been suggested that etanercept may act as a TNF "sink," trapping it where concentrations are high and shedding where concentrations are low.[63]

As mentioned previously, infliximab has a half-life of 9.5 days. When dosed every 8 weeks, its peak and trough concentrations vary 55-fold. This fluctuation may lead to efficacy and safety issues brought on by blocking too much TNF at peak times and too little at trough times. The half-life of etanercept is 4.8 days. When dosed twice a week, it demonstrates a 1.5-fold variation between peak and trough values, potentially leading to tighter control of TNF blockade.

Infliximab is also capable of cross-linking transmembrane TNF, which may result in caspase-dependent apoptosis of monocytes.[65] When bound to transmembrane TNF, infliximab also promotes complement-mediated cell lysis.[30] The lysis of macrophages infected with *M. tuberculosis* may then result in the dissemination of mycobacteria from the lesion.[63] The ability to promote complement-mediated cell lysis is shared by adalimumab.

Long-term safety data on adalimumab are not available, and the long term-effects on the development of both infection and malignancy remain to be seen. As mentioned previously, there is evidence that rates of TB infection are increased in adalimumab-treated patients. While the FDA has expressed concern over increased rates of malignancies in patients treated with adalimumab, no definitive association has been made to date.

Conclusion

Inhibition of TNF-mediated pathology continues to be a powerful mechanism not only for improving the signs and symptoms of RA, but also, in some cases, for preventing further progression and improving the quality of life and physical function in patients with this disease. The targeted mechanism and rapid onset of action of the agents described in this review offer an improvement over more traditional drugs that may be hampered by efficacy- limiting properties such as global immunosuppression, toxicity, and delayed responses.

Although TNF inhibitors are often mistakenly considered a "class" of therapeutics, there are clear differences in their overall structures and mechanisms of action, as well as in their PK properties, that may explain divergences in their safety profiles and, ultimately, in their long-term efficacy. More data, and perhaps head-to-head studies of these agents, will be required before direct comparisons can be made. Continued vigilance in defining the biology of RA, as well as identifying patients who will respond to particular treatments, will increase the likelihood of success for all patients who suffer from this chronic, debilitating disease.

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