CME CREDIT

LARRY W. MORELAND, MD

Associate Professor of Medicine; Vice-Chairman for Clinical Research, Department of Medicine; Director, Arthritis Clinical Intervention Program; The University of Alabama at Birmingham; investigator in several clinical trials of etanercept.

Inhibitors of tumor necrosis factor: New treatment options for rheumatoid arthritis

ABSTRACT

Infliximab and etanercept, both approved by the FDA in 1998, are examples of a new class of disease-modifying antirheumatic drugs that interfere with the action of tumor necrosis factor alpha, one of the key cytokines that promote inflammation. Infliximab is approved for Crohn disease and etanercept for rheumatoid arthritis. Both show promise in treating rheumatoid arthritis, although the long-term risks and benefits of these drugs are not yet known.

KEY POINTS

Etanercept is a soluble TNF receptor that competes with membrane binding sites for TNF; infliximab is a chimeric monoclonal anti-TNF antibody.

Etanercept is indicated for rheumatoid arthritis that is unresponsive to traditional disease-modifying antirheumatic drugs. It can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

Etanercept should not be given to patients with sepsis, and should be discontinued if a patient develops a serious infection.

THE TREATMENT OF autoimmune diseases took a big step forward in 1998 when the Food and Drug Administration (FDA) approved two drugs that, for the first time, specifically target one of the key molecular players in the inflammatory process—tumor necrosis factor (TNF).

At present, only one of these drugs, etanercept, is indicated for rheumatoid arthritis; the other, infliximab, is indicated for Crohn disease but also shows promise in rheumatoid arthritis and is expected to be reviewed by the FDA in the near future.

In the following pages I review the role of TNF in rheumatoid arthritis, how etanercept and infliximab block TNF, and how etanercept should be used in rheumatoid arthritis.

SHORTCOMINGS OF CURRENT DRUGS

To try to block the autoimmune process involved in rheumatoid arthritis, rheumatologists are increasingly turning to "disease-modifying antirheumatic drugs" such as methotrexate, hydroxychloroquine, and sulfasalazine.[1] Unfortunately, these drugs fail to achieve or maintain an adequate response for many patients. Moreover, they are fairly toxic, especially in the long term, as they are relatively nonspecific in their mechanisms of action. Both these factors limit the long-term therapeutic utility of these drugs.[1]

Investigators realized that to treat rheumatoid arthritis successfully, we needed to understand better the molecular processes taking place in the disease, and to design drugs that block specific molecules in the process.

TABLE 1

Cytokines and their effects in rheumatoid arthritis

Cytokines that promote inflammation
- Tumor necrosis factor (TNF) alpha
- TNF beta
- Interferon gamma
- Interleukin 1 (IL-1)
- IL-2
- IL-6
- IL-8
- Inducible nitric oxide synthase (iNOS)

Cytokines and associated molecules that inhibit inflammation
- Soluble TNF receptor
- Soluble IL-1 receptor
- IL-1 receptor antagonist
- Transforming growth factor beta
- IL-4
- IL-10
- IL-11

Significant progress has been achieved: the role of TNF has been elucidated and TNF antagonists have been developed and tested, bringing us closer to the goal of more effective treatment.

TNF is at or near the top of the inflammatory cascade

ROLE OF TUMOR NECROSIS FACTOR IN RHEUMATOID ARTHRITIS

The various cells of the immune system communicate at a distance by exchanging a variety of proteins called cytokines. Cytokines work by binding to receptors on the surface of immune cells and other cells, triggering specific actions inside the cell such as production of other cytokines or enzymes (eg, collagenase). The cytokines constitute a sort of regulatory system, with some cytokines promoting inflammation and some suppressing it (TABLE 1).

In rheumatoid arthritis, proinflammatory cytokines predominate in affected joints and have the net effect of prompting large numbers of immune and inflammatory cells to enter the joint. They also trigger the secretion of still other cytokines and substances that inflame the joint and damage its bone, cartilage, and other connective tissues.

TNF occupies a position at or near the top of this pyramid of activity. Named for its ability to destroy tumors in animals, TNF is now known to play a number of important roles in many immune reactions—and the list is growing. In particular, TNF:

- Regulates cell proliferation and apoptosis (programmed cell death)[2]
- Stimulates neutrophils, fibroblasts, and chondrocytes to produce proteases such as collagenase
- Stimulates production of other inflammation-promoting cytokines such as interleukin-1 (IL-1). This important role has been demonstrated by studies that show that blocking TNF activity inhibits production of IL-1 and other cytokines. Thus, TNF plays a central role in initiating and maintaining the rheumatoid arthritis process.

TNF has three isoforms, designated alpha, beta, and gamma. (For purposes of our discussion, "TNF" mainly refers to TNF alpha.) It is secreted primarily by macrophages and T lymphocytes.[3–6] TNF production has been found to be increased in the synovial fluid of patients with active rheumatoid arthritis, but not in synovial fluid from patients with inactive rheumatoid arthritis. TNF is found at the cartilage-pannus junction in affected joints,[7] and increased levels of TNF are detected in the synovial fluid.[8,9]

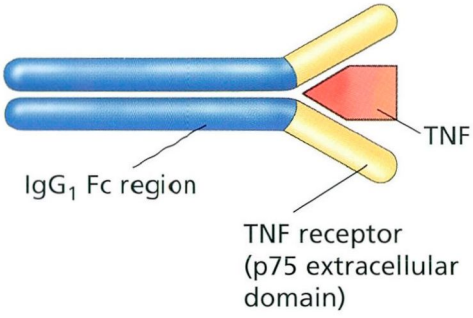
TNF binds to at least two cell-bound receptors, designated type 1 (p55 or p60) and type 2 (p80 or p75).[9,10] These receptors, which span the cell membrane, are found on several types of cells, including polymorphonuclear leukocytes, vascular endothelial cells, and fibroblasts.[2]

In addition, TNF also binds to soluble TNF receptors floating free in the blood and other fluids. Soluble TNF receptors are cleaved from the extracellular portion of the membrane-bound molecules by an enzyme called TACE (tumor necrosis factor alpha-converting enzyme).[11,12] Their levels are increased in the sera and synovial fluid of patients with rheumatoid arthritis,[13,14] and they can be detected at the cartilage-pannus junction of patients with rheumatoid arthritis and in the vicinity of TNF-containing cells.[15]

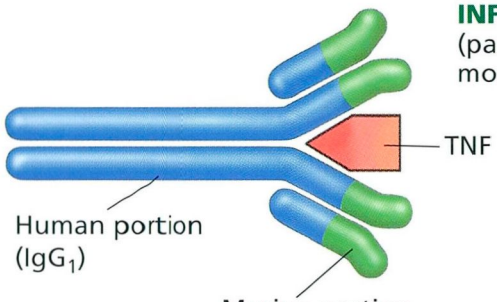
These soluble TNF receptors seem to serve as a natural counterbalance to TNF. Although patients with rheumatoid arthritis have elevated levels of circulating soluble

How etanercept and infliximab inhibit tumor necrosis factor

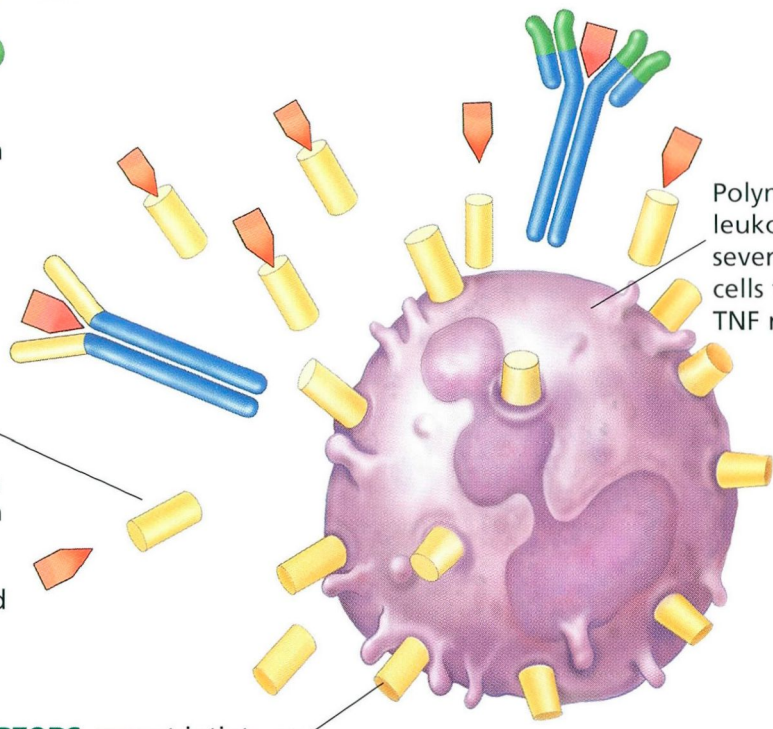
TUMOR NECROSIS FACTOR (TNF) promotes inflammation by binding to receptors on a variety of cells, stimulating them to release other inflammatory cytokines. The new anti-TNF drugs etanercept and infliximab inhibit inflammation by sopping up TNF before it reaches its cell-bound receptor, as do endogenous soluble TNF receptors.



ETANERCEPT contains two TNF receptors (specifically, the extracellular domain of the p75 type of receptor) grafted on to the Fc portion of an IgG_1 molecule by recombinant DNA technology.



INFLIXIMAB is a chimeric (part-mouse, part-human) monoclonal antibody to TNF.



ENDOGENOUS SOLUBLE TNF RECEPTORS, cleaved from the cell surface, inhibit inflammation by intercepting TNF before it can bind to cell-bound receptors. Although soluble TNF receptor levels are elevated in rheumatoid arthritis, they are overwhelmed by even higher levels of TNF.

CELL-BOUND TNF RECEPTORS cannot intiate an inflammatory response unless TNF binds to them.

FIGURE 1

TABLE 2

Efficacy of the TNF inhibitors etanercept and infliximab in refractory rheumatoid arthritis

INVESTIGATORS	REGIMEN	% OF PATIENTS WITH 20% IMPROVEMENT*	% OF PATIENTS WITH 50% IMPROVEMENT*
Moreland et al[17]	Placebo	14	7
	Etanercept 16 mg/m^2 subcutaneously twice a week	75	57
Moreland et al[18]	Placebo	23	5
	Etanercept 25 mg subcutaneously twice a week	62	40
Weinblatt et al[19]	Placebo	27	3
	Etanercept 25 mg subcutaneously twice a week	71	39
Lipsky et al[27]	Placebo	20	5
	Infliximab		
	3 mg/kg intravenously every 8 weeks	50	27
	3 mg/kg intravenously every 4 weeks	50	29
	10 mg/kg intravenously every 8 weeks	52	31
	10 mg/kg intravenously every 4 weeks	58	25

*By the criteria of the American College of Rheumatology (ACR)[22]

Soluble TNF receptors are a natural counterbalance to TNF

TNF receptors, they have even higher levels of TNF—greatly so at sites of ongoing inflammation such as the joints. Studies have suggested that in rheumatoid arthritis the overall quantity of soluble TNF receptors is inadequate to consume all of the TNF that is produced. The excess TNF combines with cell-bound TNF receptors, producing the cascade of damaging and inflammatory effects in the joints.

ETANERCEPT: A SOLUBLE TNF RECEPTOR

The findings described above suggested that drugs that block TNF would be effective in treating rheumatoid arthritis. One approach is to flood the body with exogenous soluble TNF receptors, which sop up excess TNF molecules and keep them from binding to cell-surface TNF receptors. One such agent is etanercept (FIGURE 1).

Etanercept was created by linking the DNA encoding the soluble portion of the human p75 TNF receptor to the DNA encoding the Fc portion of human IgG, and then inserting this DNA into a mammalian cell line. The resultant protein binds two TNF molecules and has a longer circulating half-life than does the TNF receptor without the Fc moiety.

Clinical trials of etanercept in adults

Early studies[16] of etanercept gave positive results, which have been replicated in several multicenter placebo-controlled trials (TABLE 2).[17–21]

In a phase 2, double-blind, placebo-controlled trial,[17] etanercept produced significant improvements in all measures of disease activity stipulated by the American College of Rheumatology (ACR) criteria,[22] particularly at the highest dose given, 16 mg/m^2 (23–30 mg). In addition, patients experienced significant reductions in pain and morning stiffness. Biochemical markers of disease activity such as the erythrocyte sedimentation rate and C-reactive protein levels decreased as well. The clinical responses to etanercept generally appeared within 1 to 2 weeks after starting therapy and nearly always occurred by 3 months.

A subsequent phase 3 study[18] verified the safety and sustained clinical efficacy of etanercept. Patients received either placebo or etan-

TABLE 3

Effect of etanercept in rheumatoid arthritis: Results from a phase 3 placebo-controlled trial

MEASURE*	MEDIAN VALUES			
	PLACEBO (N = 80)		ETANERCEPT† (N = 78)	
	BASELINE	3 MONTHS	BASELINE	3 MONTHS‡
Number of tender joints	34.0	29.5	31.2	10.0
Number of swollen joints	24.0	22.0	23.5	12.6
Physician global assessment, scale of 0–10	7.0	6.5	7.0	3.0
Patient global assessment, scale of 0–10	7.0	7.0	7.0	3.0
Pain, scale of 0–10	6.9	6.6	6.9	2.4
Disability index, scale of 0–3	1.7	1.8	1.6	1.0
Erythrocyte sedimentation rate, mm/hour	31.0	32.0	28.0	15.5
C-reactive protein level, mg/dL	2.8	3.9	3.5	0.9

*The measures listed here comprise the criteria from the American College of Rheumatology for measuring the response to therapy in clinical trials in rheumatoid arthritis[22]
†25 mg subcutaneously twice a week
‡All comparisons with placebo were statistically significant ($P < .01$) based on mean percent change from baseline; values at 6 months showed similar improvement as at 3 months

SOURCE: DATA FROM THE STUDY CONDUCTED BY MORELAND ET AL, REFERENCE 18

ercept 10 mg or 25 mg subcutaneously twice a week for 6 months. The 25-mg dose was more effective than the 10-mg dose. At 3 and 6 months, patients receiving 25 mg were doing statistically better in all ACR criteria than were controls (TABLE 3), and patients receiving either dose reported less disability, greater vitality, and higher levels of mental health, general health, and arthritis-associated health. No adverse events other than injection-site reactions were noted more commonly with either dosage compared with placebo. No abnormalities in laboratory values were noted in patients treated with etanercept.

In a recent phase 2 and phase 3 study,[19] patients with rheumatoid arthritis refractory to moderate doses of methotrexate continued to receive methotrexate while also receiving etanercept. Seventy-one percent of patients receiving the combination achieved a 20% ACR response, compared with 27% of patients who received methotrexate alone (TABLE 2). This finding indicates that the best candidates for the addition of a TNF antagonist may be patients who are having a suboptimal clinical response to a disease-modifying antirheumatic drug.

Patients who participated in placebo-controlled trials of etanercept have participated in open-label trials to determine the drug's long-term effectiveness and safety. Preliminary results indicate that etanercept has similar efficacy when given for up to 2 years at a dose of 25 mg subcutaneously twice a week as it did in short-term studies.[21] Mild injection-site reactions again were the most common side effect.

Patients can receive etanercept and methotrexate concurrently

Clinical trials of etanercept in children

In the first part of a two-part trial,[20] 69 children ages 4 to 17 with polyarticular juvenile rheumatoid arthritis received etanercept open-label for up to 3 months. All the children either could not tolerate methotrexate or had no response to it. The dosage of etanercept was 0.4 mg/kg (not to exceed 25 mg, the equivalent of 0.4 mg/kg for a 70-kg person) subcutaneously twice a week. At the end of 3 months, 51 (74%) of the patients had at least 30% improvement in at least three of six predetermined variables and 30% or greater worsening in no more than one of the variables. (These are the standard response criteria for juvenile rheumatoid arthritis.)

The 51 children who had a clinical response advanced to the second part of the trial,[20] in which 25 of them were randomly assigned to continue receiving etanercept at the same dosage and 26 received placebo, in a double-blind fashion. Treatment continued for 4 months or until a disease flare occurred, defined as at least 30% worsening in at least three of the six core variables, in at least two active joints. Significantly fewer patients treated with etanercept experienced a disease flare (7 patients treated with etanercept vs 21 patients who received placebo), and the median time to disease flare in those patients was significantly shorter (116 days for etanercept vs 28 days for placebo).

Side effects of etanercept

A variety of adverse events that potentially could be drug-related were reported in clinical trials of etanercept.

Injection-site reactions occurred in 37% of patients receiving etanercept and 10% of patients receiving placebo.[16–20] The reactions consisted of mild to moderate erythema, itching, pain, or swelling, and generally occurred during the first month of therapy and less frequently thereafter. They lasted an average of 3 to 5 days and, in most cases, did not necessitate drug discontinuation.

Other reactions included development of antinuclear and anti-double-stranded DNA antibodies, infections, and malignancies. It is not yet possible to determine whether these events are directly related to inhibition of TNF or represent complications of the underlying disease and its conventional treatment. Long-term follow-up will be necessary to determine the causal mechanisms and the true frequency of apparent side effects.

Verify that the patient can self-administer etanercept injections

Clinical use of etanercept

Indications. According to the current FDA label, etanercept is indicated for moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs. It can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

Cautions. Etanercept should not be given to patients with sepsis or with known hypersensitivity to etanercept or any of its components. It should be discontinued if a patient develops a serious infection. Allergic reactions to etanercept have been reported in less than 0.5% of patients in clinical trials. Anaphylaxis has not been observed.

No data are available on the effects of vaccination in patients receiving etanercept. In the absence of data, to prevent any potential transmission of infection, patients receiving etanercept should not receive live vaccines.

Etanercept is classified in FDA pregnancy category B. No adequate and well-controlled studies have been done in pregnant women. However, no evidence of harm to the fetus was observed in animal reproduction studies using dosages 60 to 100 times larger than that corresponding to the recommended dosage in humans.

No data are available regarding the use of etanercept in patients with a history of cancer.

Dosage. The recommended dosage of etanercept for adults with rheumatoid arthritis is 25 mg by subcutaneous injection twice weekly. Higher doses have not been studied.

The first injection should be performed under the supervision of a qualified health care professional. Patients can give themselves subsequent injections at home once they are taught the proper procedure and demonstrate that they can perform injections safely. Sites for self-injection include the thigh, abdomen, and upper arm. Injection sites should be rotated. Injections should be given at least 1 inch from previous sites and never into areas where the skin is tender, bruised, red, or hard.

INFLIXIMAB: AN ANTI-TNF ANTIBODY

Another approach to blocking TNF is to give an anti-TNF antibody. Such an agent is infliximab (Remicade), a chimeric (part-human, part-mouse) monoclonal antibody that binds to TNF (FIGURE 1).

Clinical trials of infliximab in adults

In open-label and placebo-controlled trials in patients with refractory rheumatoid arthritis, infliximab treatment resulted in significant decreases in the number of swollen joints, serum levels of C-reactive protein, and other

measures of disease activity.[23–27]

In the first placebo-controlled trial, 79% of patients treated with a single dose of infliximab 10 mg/kg intravenously achieved at least a 20% improvement in disease activity as measured by the Paulus criteria 4 weeks later.[24]

In a US phase 3 trial,[27] 58% of patients receiving infliximab 10 mg/kg intravenously every 4 weeks achieved at least a 20% improvement in disease activity as measured by the ACR criteria,[22] compared with 20% of patients receiving placebo.

Side effects of infliximab

Approximately 50% of patients develop antibodies to the murine portion of the infliximab molecule.[24,25] The immunogenicity of infliximab might be a limiting factor to treatment duration. However, recent data suggest that giving methotrexate along with infliximab may attenuate this problem.[26] In addition, the combination seems to work synergistically and seem to produce a greater therapeutic response than infliximab alone.

FDA approval of infliximab is pending for rheumatoid arthritis

Infliximab has also demonstrated efficacy in treating refractory Crohn disease and has been approved by the FDA for this indication. At present, it is not approved for treating rheumatoid arthritis but is expected to be reviewed by the FDA in the near future.

QUESTIONS REMAINING

The encouraging clinical results in short-term trials of etanercept clearly warrant further studies. Ongoing studies are addressing several questions:

- Whether TNF inhibitors can modify the destructive component of the disease in the long term
- Whether they can be given safely for long periods
- Whether starting TNF inhibitors earlier in the course of the disease may be of additional therapeutic benefit
- Whether TNF inhibitors may be more effective than current disease-modifying drugs (a phase 3 study comparing etanercept with methotrexate in early rheumatoid arthritis will be completed in the near future.)
- Whether TNF inhibitors are cost-effective. Certainly, they are more expensive than traditional antirheumatic medications, costing several thousand dollars per year. However, they may yet prove to be more cost-effective after all factors are considered, such as the costs of toxicity, laboratory monitoring, and administration of the drug, lost earnings, improved quality of life, and, hopefully, increased life span.

REFERENCES

1. **Cash JM, Klippel JH.** Second-line drug therapy for rheumatoid arthritis. N Engl J Med 1994; 330:1368–1375.
2. **Ahmadzadeb N, Shingu M, Nobunaga M.** The effect of recombinant tumor necrosis factor-alpha on superoxide and metalloproteinase production by synovial cells and chondrocytes. Clin Exp Rheumatol 1990; 8:387–391.
3. **MacNaul KL, Chartrain N, Lark M, et al.** Differential effects of IL-1 and TNF alpha on the expression of stromelysin, collagenase and the natural inhibitor, TIMP, in rheumatoid synovial fibroblasts. Matrix 1992; 1(Suppl):198–199.
4. **Moser RB, Schleiffenbaum B, Groscurth P, et al.** Interleukin 1 and tumor necrosis factor stimulate human vascular endothelial cells to promote transendothelial neutrophil passage. J Clin Invest 1989; 83:444–455.
5. **Shingu M, Nagai Y, Isayama T, et al.** The effects of cytokines on metalloproteinase inhibitors (TIMP) and collagenase production by human chondrocytes and TIMP production by synovial cells and endothelial cells. Clin Exp Immunol 1993; 94:145–149.
6. **Brennan FM, Feldmann M.** Cytokines in autoimmunity. Curr Opin Immunol 1992; 4:754–759.
7. **Chu CQ, Field M, Feldmann M, et al.** Localization of tumor necrosis factor α in synovial tissues and at the cartilage-pannus junction in patients with rheumatoid arthritis. Arthritis Rheum 1991; 34:1125–1132.
8. **Seckinger P, Zhang J, Hauptmann B, et al.** Characterization of a tumor necrosis factor α (TNF-α) inhibitor: evidence of immunological cross-reactivity with the TNF receptor. Proc Natl Acad Sci USA 1990; 87:5188–5192.
9. **Beutler B, van Huffel C.** Unraveling function in the TNF ligand and receptor families. Science 1994; 262:667–668.
10. **Banner DW, D'Arcy A, Janes W, et al.** Crystal structure of the soluble human 55 kd TNF receptor-human TNF beta complex: implications for TNF receptor activation. Cell 1993; 73:431–445.
11. **Engelmann H, Aderka, Rubinstein M, et al.** A tumor necrosis factor binding protein purified to homogeneity from human urine protects cells from tumor necrosis factor toxicity. J Biol Chem 1989; 264:11974–11980.
12. **Olsson I, Lantz M, Nilsson E, et al.** Isolation and characterization of a tumor necrosis factor binding protein from urine. Eur J Haematol 1989; 42:270–275.
13. **Cope AP, Aderka D, Doherty M, et al.** Increased levels of soluble tumor necrosis factor receptors in the sera and synovial fluid of patients with rheumatic diseases. Arthritis Rheum 1992; 35:1160–1169.

14. **Roux-Lombard P, Punzi L, Hasler F, et al.** Soluble tumor necrosis receptors in human inflammatory synovial fluids. Arthritis Rheum 1993; 36:485–489.
15. **Deleuran BW, Chu CQ, Field M, et al.** Localization of tumor necrosis factor receptors in the synovial tissue and cartilage-pannus junction in patients with rheumatoid arthritis: implications for local actions of tumor necrosis factor alpha. Arthritis Rheum 1992; 35:1170–1178.
16. **Moreland LW, Margolies GR, Heck LW Jr, et al.** Recombinant soluble tumor necrosis factor receptor (p80) fusion protein: toxicity and dose finding trial in refractory rheumatoid arthritis. J Rheumatol 1996; 23:1849–1855.
17. **Moreland LW, Baumgartner SW, Schiff MH, et al.** Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med 1997; 337:141–147.
18. **Moreland LW, Schiff MH, Baumgartner SW, et al.** Etanercept therapy in rheumatoid arthritis: A randomized controlled trial. Ann Intern Med 1999; 130:478–486.
19. **Weinblatt ME, Kremer JR, Bankhurst AD, et al.** Phase II/III trial of TNF receptor p75 fusion protein (TNFR:Fc; Enbrel) in combination with methotrexate (MTX) in RA patients [abstract]. Arthritis Rheum 1998; 41(Suppl):s189.
20. **Lovell DJ, Giannini EH, Whitmore JB, et al.** Safety and efficacy of tumor necrosis factor receptor p75 fusion protein (TNFR:Fc; Enbrel) in polyarticular course juvenile rheumatoid arthritis [abstract]. Arthritis Rheum 1998; 41(Suppl):s470.
21. **Moreland LW, Baumgartner SW, Tindall E, et al.** Long term safety and efficacy of TNF receptor (p75) Fc fusion protein (TNFR:Fc; Enbrel) in DMARD refractory rheumatoid arthritis (RA) [abstract]. Arthritis Rheum 1998; 41(Suppl):s364.
22. **Felson DT, Anderson JJ, Boers M, et al.** The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 1993; 36:729–740.
23. **Elliott MJ, Maini RN, Feldmann M, et al.** Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor α. Arthritis Rheum 1993; 36:1681–1690.
24. **Elliott MJ, Maini RN, Feldman M, et al.** Randomized double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 1994; 344:1105–1110.
25. **Elliott MJ, Maini RN, Feldmann M, et al.** Repeated therapy with monoclonal antibody to tumour necrosis factor α (cA2) in patients with rheumatoid arthritis. Lancet 1994; 344:1125–1127.
26. **Maini RN, Breedveld FC, Kalden JR, et al.** Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998; 41:1552–1563.
27. **Lipsky PE, St. Clair W, Kavanaugh A, et al.** Long-term control of signs and symptoms of rheumatoid arthritis with chimeric monoclonal anti-TNF alpha antibody (infliximab) in patients with active disease on methotrexate [abstract]. Arthritis Rheum 1998; 41(Suppl):s364.

ADDRESS: *Larry W. Moreland, MD, Department of Medicine, The University of Alabama at Birmingham, 068 Spain Rehabilitation Center, 1717 6th Avenue South, Birmingham, AL 35294-7201, e-mail larry.moreland@ccc.uab.edu.*