
Psoriatic arthritis: The role of TNF inhibition and the effect of its inhibition with etanercept

P. Mease

Department of Medicine, University of Washington, Seattle, Washington, USA.
Philip Mease, MD, Seattle Rheumatology Associates, Swedish Hospital Medical Center Division of Clinical Research; Clinical Professor, Department of Medicine, University of Washington, Seattle, Washington, USA.

Address for correspondence: Philip Mease, MD, Seattle Rheumatology Associates, 1101 Madison St., Suite 230, Seattle, WA 98102, USA.

E-mail: pmease@u.washington.edu

Clin Exp Rheumatol 2002; 20 (Suppl. 28): S116-S121.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2002.

Key words: Etanercept, psoriatic arthritis, psoriasis, controlled clinical trial, tumor necrosis factor, cytokine.

ABSTRACT

Etanercept has demonstrated excellent safety and efficacy in the treatment of patients with psoriatic arthritis (PsA), which is a chronic inflammatory arthritis. Composed of 2 soluble TNF receptor (p75) domains fused to human immunoglobulin, etanercept neutralizes the inflammatory cytokines TNF and lymphotoxin- α .

In a phase 2, randomized, placebo-controlled trial of 60 patients with PsA, etanercept 25 mg subcutaneously twice weekly resulted in significantly more improvement in arthritis and skin symptoms than placebo. At 12 weeks, 87% of etanercept-treated patients achieved a clinical response by the Psoriatic Arthritis Response Criteria compared with 23% of the placebo group. The percent of those patients achieving an American College of Rheumatology 20% (ACR20), ACR 50, and ACR70 response were 73%, 50% and 13%, respectively, compared to 13%, 3%, and 0% in the placebo group. The median improvement in skin disease activity (assessed by the Psoriasis Area and Severity Index) in the etanercept group was 46% versus 9% in the placebo group. In a 6-month open-label extension of this study, patients who originally had received placebo rapidly achieved responses to etanercept that were comparable to responses in the group originally randomized to the active drug; in the group originally on etanercept, efficacy was maintained, and a large proportion of patients decreased or discontinued concomitant prednisone or methotrexate. Etanercept was generally well tolerated throughout this trial. A phase 3 trial confirmed the efficacy and safety of etanercept in PsA, with 59% of etanercept-treated patients meeting the ACR20 improvement criteria at 12 weeks compared with 15% of placebo-treated patients. Significant improvements in skin lesions relative to

placebo were also observed. No adverse events were significantly more common with etanercept than with placebo.

Several case studies add to our body of knowledge of etanercept in PsA. Etanercept is well suited to long-term therapy and provides a valuable treatment option for PsA.

Introduction

Psoriatic arthritis (PsA) is a chronic disease with potentially severe functional consequences (1,2). Treatment options for this disease have been relatively limited and of variable efficacy (3). In 2001 etanercept became the first agent to be specifically approved by the US Food and Drug Administration (FDA) for reducing the signs and symptoms of PsA. This agent is currently awaiting approval for treatment of PsA in Europe. Etanercept is a tumor necrosis factor (TNF) inhibitor and thus has a unique mechanism of action that distinguishes it from other therapies commonly used for PsA. The biologic basis for the use of etanercept in PsA and clinical data supporting this use will be reviewed here.

Tumor necrosis factor: A pivotal role in inflammatory arthritis

Tumor necrosis factor is a proinflammatory cytokine found at high levels in the joint fluid and tissue of patients with inflammatory arthritis, including rheumatoid arthritis (RA) and PsA (4-7). Tumor necrosis factor induces the production of other proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (8-11). In addition, TNF mediates multiple biologic processes that can cause joint damage, most notably bone resorption, inhibition of bone formation and proteoglycan synthesis, and induction of metalloproteinases and prostaglandin E₂ (12-15).

One way that the body attempts to regulate excess TNF is through the release of soluble TNF receptors, which are found at high levels in the sera of patients with RA and PsA (16-18). These soluble receptors serve as natural TNF inhibitors by binding to TNF in solution and preventing the cytokine from interacting with cell-bound receptors.

Etanercept: Structure and mechanism of action

Etanercept is a fully human, dimeric fusion protein consisting of 2 soluble TNF receptor (p75) domains linked to the Fc portion of human IgG1. This molecule is 50 to 1000 times more potent in inhibiting TNF bioactivity than the monomeric soluble p75 TNF receptor (19). In addition to binding and neutralizing free and membrane-bound TNF, etanercept also binds to a related molecule, lymphotoxin- α (also known as TNF- β) (20). Lymphotoxin- α is known to play an important role in immune functioning and inflammation (21), but its possible involvement in PsA has not been reported. Unlike therapeutic antibodies, etanercept does not lyse cells in the presence or absence of complement (20, 22).

Controlled clinical trials of etanercept in PsA and psoriasis

Phase 2 trial

The first controlled clinical trial of etanercept in PsA was a randomized, double-blind, placebo-controlled trial of 60 patients who received either placebo or etanercept 25 mg subcutaneously (SC) twice weekly for 12 weeks (23). Patients in this study had long-standing disease (psoriasis for a median of approximately 20 years and PsA for a median of 10 years). Patients achieving partial benefit from methotrexate (MTX) were allowed to continue on MTX therapy; randomization distributed this subgroup of 47% of patients evenly between the placebo and etanercept groups. Background use of nonsteroidal anti-inflammatory drugs (NSAIDs) or prednisone 10 mg per day or less was allowed. All other disease-modifying antirheumatic drugs (DMARDs) and topical medicines for psoriasis were discontinued.

Table I. Efficacy end points for etanercept clinical trials.

Measures of Arthritis Disease Activity

Psoriatic Arthritis Response Criteria (PsARC)³⁸

Improvement in 2 of the following 4 criteria, 1 of which must be tender- or swollen-joint score

- Physician global assessment (1 unit on 0 to 5 Likert scale)
- Patient global assessment (1 unit on 0 to 5 Likert scale)
- Tender joint score (30% improvement)
- Swollen joint score (30% improvement)

No worsening in any criteria

American College of Rheumatology (ACR) Response Criteria³⁹ To meet the ACR20 response criteria, a 20% improvement must be observed in

Tender joint count

Swollen joint count

3 of the following 5 core set measures

- Patient global assessment
- Physician global assessment
- Pain
- Disability
- Acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein)

For an ACR50 response, the level of improvement must be at least 50%, and for an ACR70, the level of improvement must be at least 70%.

Measures of Psoriasis Disease Activity

Psoriasis Area and Severity Index (PASI)⁴⁰

Composite index of disease severity

Features evaluated

- Scale
- Erythema
- Induration
- Score weighted by
- Severity
- Body surface area

Target Lesion Assessment

Prospectively defined psoriatic lesion

Features evaluated

- Scale
- Erythema
- Plaque elevation

The major study end points employed in etanercept PsA clinical trials are described in Table I. In the phase 2 study, the primary end point for arthritic activity was the proportion of patients meeting the Psoriatic Arthritis Response Criteria (PsARC). For psoriasis, the proportion of patients achieving a 75% improvement in psoriasis activity from baseline as measured by the Psoriasis Area and Severity Index (PASI) was the primary efficacy end point. Secondary end points for arthritis were the American College of Rheumatology (ACR) 20, 50, and 70 responses, while improvement in preselected target psoriasis lesions was the secondary end point for psoriasis activity.

The benefit of etanercept treatment was striking. At the end of 12 weeks, 87% of patients in the etanercept group (n =

30) had achieved a PsARC response compared with 23% in the placebo group (n = 30; $P < 0.0001$). The response to etanercept occurred rapidly; by the 4-week time point, 77% of the patients in the etanercept group had achieved the PsARC (Fig. 1) (23). A similarly high level of response was observed with ACR 20 response criteria; 73% of etanercept-treated patients attained this level of response compared with 13% of placebo-treated patients ($P < 0.0001$). All individual measures of disease activity showed significant improvement in the etanercept group compared with the placebo group. Disability, as assessed by the Health Assessment Questionnaire (HAQ), improved by 83% from baseline in the etanercept group compared to 3% in the placebo group ($P < 0.0001$). Ten patients (34%) in the

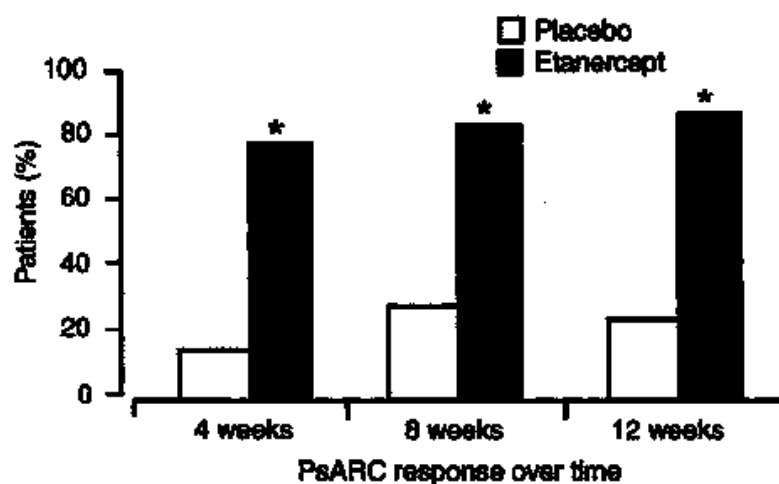


Fig. 1. PsARC response over time in a randomized, placebo-controlled clinical trial of etanercept in PsA.

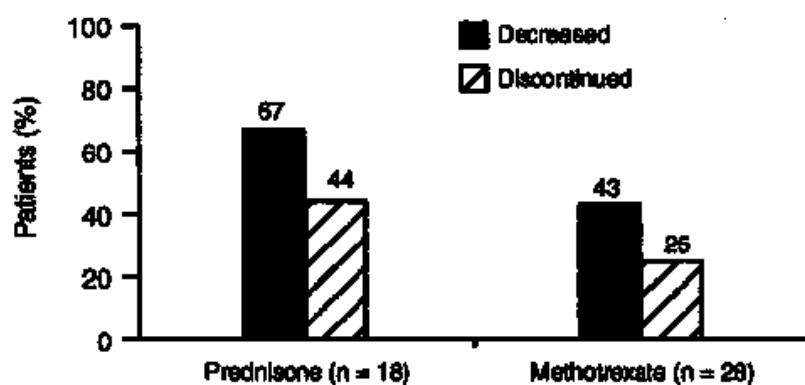


Fig. 2. Effect of etanercept therapy on concomitant medication during a 6-month open-label extension study. Data from Mease, 2001 (ref. 24). None of the patients increased their dose of prednisone or methotrexate during this study.

etanercept group achieved HAQ scores of 0, while only 1 patient (3%) in the placebo group met this goal (23). Significant improvements in psoriasis relative to placebo were also observed in the etanercept group. Patients with 3% or more of body surface involvement were evaluated for the impact of therapy on psoriasis (19 patients in each group). Of these patients, 5 etanercept-treated patients (26%) showed a 75% improvement in PASI at 12 weeks, while none of the placebo patients (0%) fulfilled this criterion ($P = 0.0154$) (23). The median improvement in PASI scores in etanercept-treated patients at 3 months was 46% compared with 9% in the placebo group. The corresponding median improvement in target lesion score was 50% and 0%, respectively. Etanercept was well tolerated through-

out the trial, with all 30 patients in the etanercept group completing the 12-week course of therapy. The most common adverse events in the study were upper respiratory tract events, which were equivalent in frequency between etanercept and placebo patients, and mild injection-site reactions, which were more frequently seen in etanercept patients and were not a cause for interruption of therapy. No serious adverse events were reported in patients receiving etanercept, and none of the patients developed infections that required hospitalization or intravenous antibiotics.

Open-label extension study

Patients who completed this phase 2 study ($n = 58$) were allowed to enter a 6-month open-label extension study of etanercept 25 mg SC twice weekly

(24). At the end of this 6-month period, 81% of these etanercept-treated patients met the PsARC criteria for improved arthritis symptoms, and 74% achieved the ACR 20. The original placebo patients demonstrated rapid response to etanercept, while the original etanercept patients showed further improvements. For instance, in this group the proportion achieving an ACR20 response after 3 months of therapy was 73%, increasing to 87% after 9 months of treatment. The patients who were evaluable for psoriasis ($n = 37$) achieved a median improvement of 62% in the PASI and 50% in the target lesion response. A large proportion of patients decreased or discontinued concomitant steroids or MTX during this open-label extension (Fig. 2). Etanercept continued to be well tolerated during the 6-month extension period.

Phase 3 trial

The efficacy and safety of etanercept in patients with PsA were confirmed in a randomized, double-blind, multicenter, placebo-controlled phase 3 clinical trial of 205 patients (25). Patients were randomized to receive either placebo ($n = 104$) or etanercept 25 mg SC ($n = 101$) twice weekly for 24 weeks, with randomization stratified by concomitant MTX use. The primary end point was joint response, as determined by ACR20 criteria, at 12 weeks. This end point was achieved by 59% of patients in the etanercept group and 15% of those in the placebo group ($P < 0.001$; Fig. 3). A similar difference was observed when PsARC criteria were used to assess clinical response at 12 weeks, with 72% of etanercept-treated patients achieving a clinical response compared with 31% of placebo patients ($P < 0.001$). Significantly greater responses in the etanercept group compared with the placebo group were also observed at 24 weeks (Fig. 3). An ACR20 response was achieved by 50% of patients in the etanercept group versus 13% in the placebo group at 24 weeks ($P < 0.001$), indicating that responses were generally maintained over the 6-month period (25). Functional improvement also occurred: etanercept treated

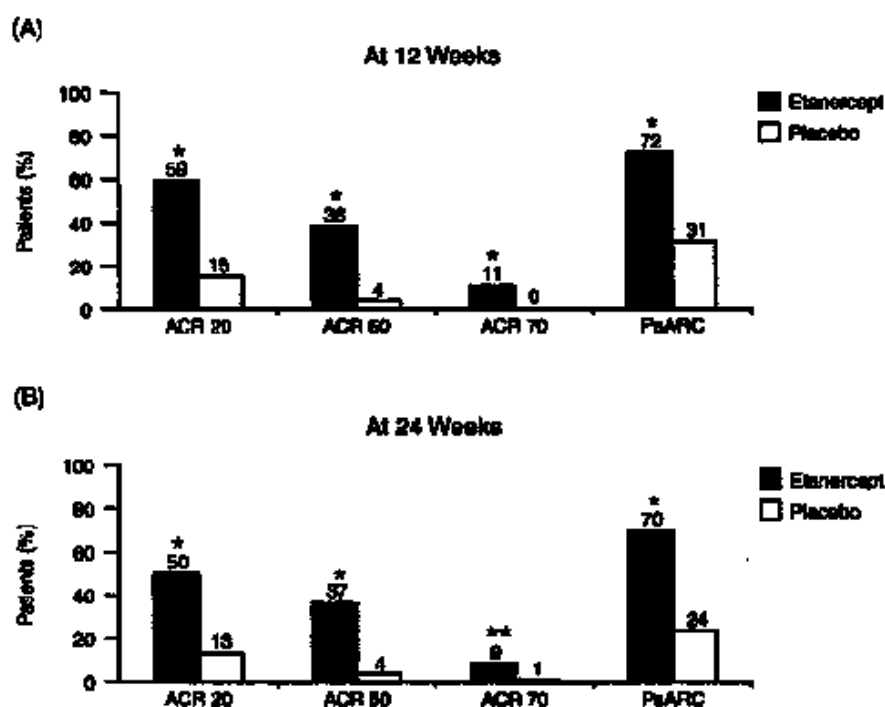


Fig. 3. Effect of etanercept vs placebo on arthritic symptoms in a phase 3 clinical trial. (A) 12-week data (primary end point); (B) 24-week data. Data from Mease, 2001 (ref. 25). * $P < 0.001$; ** $P < 0.01$.

patients demonstrated 63% median improvement of HAQ scores compared to 0% in the placebo group at 12 weeks (Mease – personal communication). Patients treated with etanercept also showed significant improvements in skin lesions compared with placebo. The median improvement in target lesion at 24 weeks was 33% in etanercept-treated patients versus 0% in placebo-treated patients ($P < 0.001$). In patients who were evaluable for psoriasis, a 47% median improvement in PASI scores was observed in the etanercept group ($n = 66$) versus no improvement in the placebo group ($n = 62$; $P < 0.001$). Etanercept was well tolerated, with no increase in the number of serious adverse events relative to placebo.

Phase 2 clinical trial in psoriasis

Etanercept has also shown efficacy in a controlled clinical trial of patients with refractory chronic psoriasis (26). In this study, 112 patients were randomized to receive placebo or etanercept 25 mg SC twice weekly for 24 weeks. At 12 weeks, 30% of patients in the etanercept group ($n = 57$) had achieved a 75% improvement in PASI compared

with 2% of patients in the placebo group ($n = 55$; $P < 0.0001$). Etanercept-treated patients continued to improve during the second 12-week period, with 56% achieving a PASI 75 versus 5% of placebo-treated patients ($P < 0.0001$). Similar improvements were observed in target lesion assessments. The adverse event profile was unremarkable, and no drug-related serious adverse events were observed in the etanercept group.

Additional clinical experience with etanercept in PsA: Case studies

In addition to controlled clinical trials, several case studies involving the use of etanercept in PsA have been reported (27-30). Two reports described patients who were dependent on a wheelchair and who regained the ability to walk modest distances during etanercept therapy (27, 28). In addition to the concomitant MTX use by some patients in the controlled clinical trials, etanercept has also been used in combination with cyclosporine, MTX, and calcipotriene cream in patients with psoriasis and PsA (31). No added toxicities were noted in patients receiving these combination regimens. Long-

term data (up to 2 years) on 8 patients with severe PsA resistant to DMARDs and immunosuppressives indicated that etanercept resulted in a satisfactory and sustained response (32). Etanercept was found to be effective in a case study of human immunodeficiency virus (HIV)-associated PsA that was refractory to other therapies (33). Immunologic and viral parameters remained stable; however, the occurrence of frequent polymicrobial infections necessitated the discontinuation of etanercept. Etanercept should be used with caution in HIV-infected patients.

Management of PsA patients on etanercept

Not all patients with PsA will be candidates for biologic therapy. Milder disease may be managed with nonsteroidals. Although etanercept has proven useful and is used for treatment of early RA (34), many insurance programs dictate that a patient first be tried on a less costly medication such as methotrexate before an anti-TNF agent may be allowed, even though efficacy and side effect profile of the latter is favorable. Etanercept is typically considered for patients with moderate to severe disease who have not adequately responded to a medication such as methotrexate, or who have had side effects with such medication. Standard dosing is 25 mg twice weekly, administered subcutaneously. Patients adopt self-administration readily and appreciate the ease and sense of self-control of this approach.

Arthritis response is often seen within the first month of therapy and is typically fully seen within the first three months. Skin response is often slower and may not have reached its full level of improvement at six months. Roughly a third may experience mild injection-site reactions that tend to dissipate over a short period of time. Patients should be counseled about temporarily discontinuing the medication if a severe infection should develop and the potential ability to reinstate the medication when the infection has been controlled. The potential for atypical infections, including tuberculosis,

should also be discussed, albeit with some reassurance about their relative rarity. Patients should be advised that exacerbation of pre-existing multiple sclerosis, as well as occurrence of new-onset multiple sclerosis, has been described as rare phenomena in the context of anti-TNF therapy, although whether the association is a causal relationship remains uncertain. Rarely, drug-induced lupus has been reported with anti-TNF therapy. Routine laboratory monitoring is not required with etanercept therapy.

Conclusions/Future directions

Controlled clinical trial data have demonstrated that etanercept is highly effective in relieving the joint and skin symptoms of PsA and improving patient functionality. Although there are no accepted criteria for assessment of radiologic progression of PsA, radiographs are being obtained in current PsA trials so that as criteria are established, we will be able to ascertain if reduction of progression can be achieved.

Etanercept has several features that make it well suited to the therapy of chronic conditions. First, it is highly efficacious and results in a rapid response. Secondly, it can be self-administered by most patients. Thirdly, it can allow reduction or discontinuation of worrisome therapeutic agents, including corticosteroids and disease modifying drugs such as methotrexate, that may cause side effects over the long term. Finally, and of most importance, etanercept has a favorable adverse event profile and is generally well tolerated during long-term therapy. In RA patients treated with etanercept monotherapy for up to 5 years, no cumulative toxicities or increases in serious adverse events were noted (35,36). An excellent safety profile was similarly observed in patients receiving etanercept plus MTX for up to 34 months (37). The high degree of efficacy exhibited by etanercept has helped create interest in the use of novel agents to treat PsA. Other agents that interrupt the pathophysiologic processes of inflammation are either being actively investigated for their potential use in PsA or will

likely be tested in the near future, including new anti-TNF inhibitors, IL-1 inhibitors such as anakinra, the LFA3-CD2 modulator alefacept, anti-inflammatory cytokines, such as recombinant IL-10, and other biologics in development. If etanercept is to serve as a general example, such agents will likely make a significant contribution to the treatment of PsA.

References

- GLADMAN DD, STAFFORD-BRADY F, CHANG C-H, LEWANDOWSKI K, RUSSELL ML: Longitudinal study of clinical and radiological progression in psoriatic arthritis. *J Rheumatol* 1990; 17: 809-12.
- TORRE-ALONSO JC, RODRIGUEZ PEREZ A, ARRIBAS CASTRILLO JM, BALLINA GARCIA J, RIESTRA NORIEGA JL, LOPEZ LARREA C: Psoriatic arthritis (PA): a clinical, immunological and radiological study of 180 patients. *Br J Rheumatol* 1991; 30: 245-50.
- JONES G, CROTTY M, BROOKS P: Interventions for treating psoriatic arthritis (Cochrane Review). In: *The Cochrane Library*. Issue 1. Oxford, Update Software; 2001.
- PARTSCH G, STEINER G, LEEB BF, DUNKY A, BRÖLL H, SMOLEN JS: Highly increased levels of tumor necrosis factor- α and other proinflammatory cytokines in psoriatic arthritis synovial fluid. *J Rheumatol* 1997; 24: 518-23.
- HUSBY G, WILLIAMS RC Jr: Synovial localization of tumor necrosis factor in patients with rheumatoid arthritis. *J Autoimmun* 1988; 1: 363-71.
- DELEURAN BW, CHU CQ, FIELD M *et al.*: Localization of interleukin-1 α , type 1 interleukin-1 receptor and interleukin-1 receptor antagonist in the synovial membrane and cartilage/pannus junction in rheumatoid arthritis. *Br J Rheumatol* 1992; 31: 801-9.
- RITCHLIN C, HAAS-SMITH SA, HICKS D, CAPPUCCIO J, OSTERLAND CK, LOONEY RJ: Patterns of cytokine production in psoriatic synovium. *J Rheumatol* 1998; 25: 1544-52.
- NAWROTH PP, BANK I, HANDLEY D, CASIMERIS J, CHESS L, STERN D: Tumor necrosis factor/cachectin interacts with endothelial cell receptors to induce release of interleukin 1. *J Exp Med* 1986; 163: 1363-75.
- BRENNAN FM, CHANTRY D, JACKSON A, MAINI R, FELDMANN M: Inhibitory effect of TNF- α antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet* 1989; 2: 244-7.
- BUTLER DM, MAINI RN, FELDMANN M, BRENNAN FM: Modulation of proinflammatory cytokine release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti TNF- α antibody with the interleukin-1 receptor antagonist. *Eur Cytokine Netw* 1995; 6: 225-30.
- HAWORTH C, BRENNAN FM, CHANTRY D, TURNER M, MAINI RN, FELDMANN M: Expression of granulocyte-macrophage colony-stimulating factor in rheumatoid arthritis: regulation by tumor necrosis factor- α . *Eur J Immunol* 1991; 21: 2575-9.
- SAKLATVALA J: Tumour necrosis factor alpha stimulates resorption and inhibits synthesis of proteoglycan in cartilage. *Nature* 1986; 322: 547-9.
- BERTOLINI DR, NEDWIN GE, BRINGMAN TS, SMITH DD, MUNDY GR: Stimulation of bone resorption and inhibition of bone formation *in vitro* by human tumour necrosis factors. *Nature* 1986; 319: 516-8.
- SHINMEI M, MASUDA K, KIKUCHI T, SHIMOMURA Y: The role of cytokines in chondrocyte mediated cartilage degradation. *J Rheumatol* 1989; 6 (Suppl. 18): 32-4.
- DAYER JM, BEUTLER B, CERAMI A: Cachectin/tumor necrosis factor stimulates collagenase and prostaglandin E₂ production by human synovial cells and dermal fibroblasts. *J Exp Med* 1985; 162: 2163-8.
- PARTSCH G, WAGNER E, LEEB BF, DUNKY A, STEINER G, SMOLEN JS: Upregulation of cytokine receptors sTNF-R55, sTNF-R75, and sIL-2R in psoriatic arthritis synovial fluid. *J Rheumatol* 1998; 25: 105-10.
- 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: 1160-9.
- ROUX-LOMBARD P, PUNZI L, HASLER F *et al.*: Soluble tumor necrosis factor receptors in human inflammatory synovial fluids. *Arthritis Rheum* 1993; 36: 485-9.
- MOHLER KM, TORRANCE DS, SMITH CA *et al.*: Soluble tumor necrosis factor (TNF) receptors are effective therapeutic agents in lethal endotoxemia and function simultaneously as both TNF carriers and TNF antagonists. *J Immunol* 1993; 151: 1548-61.
- ENBREL® [package insert]. Seattle, Wash: Immunex Corporation; 2002.
- RUDDLE NH: Lymphoid neo-organogenesis: lymphotoxin's role in inflammation and development. *Immunol Res* 1999; 19: 119-25.
- BARONE D, KRANTZ C, LAMBERT D, MAGGIORA K, MOHLER K: Comparative analysis of the ability of etanercept and infliximab to lyse TNF-expressing cells in a complement dependent fashion [abstract]. *Arthritis Rheum* 1999; 42 (Suppl.): S90.
- MEASE PJ, GOFFE BS, METZ J, VANDERSTOEP A, FINCK B, BURGE DJ: Etanercept in the treatment of psoriatic arthritis and psoriasis: A randomised trial. *Lancet* 2000; 356: 385-90.
- MEASE PJ, GOFFE BS, METZ J, VANDERSTOEP A, BURGE DJ: Enbrel® (etanercept) in patients with psoriatic arthritis and psoriasis [poster]. Presented at: *European League Against Rheumatism (EULAR)/European Congress of Rheumatology*, June 13-16, 2001; Prague, Czech Republic.
- MEASE P, KIVITZ A, BURCH F, SIEGEL E, COHEN S, BURGE D: Improvement in disease activity in patients with psoriatic arthritis receiving etanercept (Enbrel®): Results of a phase 3 multicenter clinical trial [abstract]. *Arthritis Rheum* 2001; 44 (Suppl.): S90.
- GOTTLIEB AB, LOWE NJ, MATHESON RT, LEBSACK ME: Efficacy of etanercept in patients with psoriasis [poster]. Presented at: *American Academy of Dermatology*, Febru-

- ary 24-26, 2002, New Orleans, LA.
27. KURSCHAT P, RUBBERT A, POSWIG A, SCHARFFETTER-KOCHANKE K, KRIEG T, HUNZELMANN N: Treatment of psoriatic arthritis with etanercept [letter]. *J Am Acad Dermatol* 2001; 44: 1052.
 28. ELKAYAM O, YARON M, CASPI D: From wheels to feet: a dramatic response of severe chronic psoriatic arthritis to etanercept [letter]. *Ann Rheum Dis* 2000; 59: 839.
 29. YAZICI Y, ERKAN D, LOCKSHIN MD: A preliminary study of etanercept in the treatment of severe, resistant psoriatic arthritis. *Clin Exp Rheumatol* 2000; 18: 732-4.
 30. CUELLAR ML, MENDEZ EA, COLLINS RD, BURFORD S, ESPINOZA LR: Efficacy of etanercept in refractory psoriatic arthritis (PsA) [abstract]. Presented at: *64th Annual Scientific Meeting of the American College of Rheumatology and the 35th Annual Scientific Meeting of the Association of Rheumatology Health Professionals*, October 28 - November 2, 2000, Philadelphia, Pa. Abstract 235.
 31. IYER S, YAMAUCHI P, LOWE NJ: Etanercept for severe psoriasis and psoriatic arthritis: observations on combination therapy. *Br J Dermatol* 2002; 146: 118-21.
 32. YAZICI Y, ERKAN D, LOCKSHIN MD: Etanercept in the treatment of severe, resistant psoriatic arthritis: Continued efficacy and changing patterns of use after two years [letter]. *Clin Exp Rheumatol* 2002; 20: 115.
 33. ABOULAFIA DM, BUNDOW D, WILSKIE K, OCHS UI: Etanercept for the treatment of human immunodeficiency virus-associated psoriatic arthritis. *Mayo Clin Proc* 2000; 75: 1093-8.
 34. BATHON JM, MARTIN RW, FLEISCHMANN RM *et al.*: A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis [published errata appear in *N Engl J Med* 2001; 344: 76 and *N Engl J Med* 2001; 344: 240]. *N Engl J Med* 2000; 343: 1586-93.
 35. MORELAND LW, COHEN SB, BAUMGARTNER SW, SCHIFT MH, TINDALL EA, BURGE DJ: Long-term use of Enbrel® (etanercept) in patients with DMARD-refractory rheumatoid arthritis [abstract]. Presented at: *European League Against Rheumatism (EULAR)/European Congress of Rheumatology*, June 13-16, 2001, Prague, Czech Republic. Abstract FRI0080.
 36. MORELAND LW, COHEN SB, BAUMGARTNER SW *et al.*: Longterm safety and efficacy of etanercept in patients with rheumatoid arthritis. *J Rheumatol* 2001; 28: 1238-44.
 37. KREMER JM, WEINBLATT ME, FLEISCHMANN RM, BANKHURST AD, BURGE DJ: Etanercept (Enbrel®) in addition to methotrexate (MTX) in rheumatoid arthritis (RA): Long-term observations [abstract]. *Arthritis Rheum* 2001; 44 (Suppl.): S78.
 38. CLEGG DO, REDA DJ, MEJIAS E *et al.*: Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis: A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* 1996; 39: 2013-20.
 39. FELSON DT, ANDERSEN JJ, BOERS M *et al.*: American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 727-35.
 40. FREDRIKSSON T: Oral treatment of psoriasis and pustulosis palmo-plantaris with Ro 10-9359. *Dermatologica* 1978; 157 (Suppl. 1): 13-18.
 41. FRANKLIN CM: Clinical experience with soluble TNF p75 receptor in rheumatoid arthritis. *Semin Arthritis Rheum* 1999; 29: 172-82.