

Etanercept: A New Era in the Treatment of Psoriatic Arthritis

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Abstract

Psoriatic arthritis (PsA) can exact a devastating physical and emotional toll from its sufferers. For decades, patients have been understandably dismayed by the shortcomings of the therapeutic approaches that have been available. Now, equipped with a greater understanding of the role of cytokines such as tumor necrosis factor in the origins of PsA, researchers have been able to develop cytokine inhibitors aimed precisely at the mechanisms of cutaneous and articular inflammation. When used in combination with physical rehabilitation, pharmacologic therapy can slow or arrest the progression of PsA and profoundly improve the quality of life of PsA patients.

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Psoriatic arthritis (PsA) is an inflammatory disease of the skin and joints that occurs in association with psoriasis. The clinical and socioeconomic impact of PsA has only recently begun to be appreciated. PsA is a debilitating disease that affects between 7% and 40% of patients with psoriasis.¹

Over the past 5 years, there have been significant advances in our understanding of the immunology and molecular biology of PsA, particularly the pathogenic role of cytokines such as tumor necrosis factor (TNF). Furthermore, we have observed dramatic and long-term clinical benefits in patients with rheumatoid arthritis (RA) treated with TNF inhibitors.²⁻⁶ PsA is not the same disease as RA, and the ability to differentiate RA from PsA is important in the management of patients who present

with clinical features consistent with an arthropathy.

Pharmacologic therapy combined with a physical rehabilitation program is the most effective available treatment for PsA. Early initiation of pharmacologic therapy, documented to help prevent damage and disability in RA, is likely helpful in PsA. Unfortunately, conventional disease-modifying antirheumatic drugs (DMARDs) in many cases have yielded suboptimal and inconsistent clinical improvement as well as treatment-limiting toxicities.

Advances in our understanding of the role of cytokines such as TNF in the pathogenesis of PsA have led to the development of TNF inhibitors that directly target the mechanisms of articular inflammation. Several clinical studies in RA have shown that TNF-inhibitor therapy can slow or halt the progression of disease and dramatically improve quality of life.²⁻⁶ TNF inhibition has been hailed as the first quantum leap in the pharmacotherapy of PsA in more than 2 decades.

Conventional Treatment Options for Psoriasis and PsA

Pharmacologic therapy combined with a physical rehabilitation program is the most effective available treatment for PsA. Early initiation of pharmacologic therapy is needed to avoid joint damage and disability.

NSAIDs. In mild cases, nonsteroidal anti-inflammatory drugs (NSAIDs) are used alone or in combination with local corticosteroid injections. NSAIDs possess

analgesic and anti-inflammatory properties, but do not alter the course of disease or prevent joint destruction.

Clinicians often select an NSAID for treatment based on a combination of factors, including cost, dosing frequency, patient preference, and side-effect profile.⁷ These side effects can be considerable, and range from mild abdominal discomfort to life-threatening ulcer disease. Gastrointestinal toxicity, in fact, is the major factor in limiting long-term NSAID use. Other limiting factors are renal and hepatic dysfunction. Even the new cyclooxygenase-2-inhibiting NSAIDs have not been shown definitively to avoid the risk of such toxicities when used on a long-term basis, and must carry the class labeling of all NSAID products, warning against the possibility of these toxicities.

DMARDs. PsA can be a debilitating disease when associated with significant skin disease and significant radiographic progression, even in the setting of ongoing therapy with conventional DMARDs. Moderate-to-severe or uncontrolled disease requires the use of traditional DMARDs such as methotrexate, cyclosporine, and gold salts. Unfortunately, all can be associated with significant adverse effects.⁸⁻¹³

Methotrexate is a folic acid antagonist that blocks DNA synthesis and inhibits the proliferation of immunologically active cells, thus inhibiting proliferative psoriatic skin lesions and joint inflammation. Cyclosporine is useful against the skin manifestations of psoriasis, and modestly useful for the joint manifestations of PsA, but relapses occur soon after cessation of treatment. The mechanism of action of cyclosporine against PsA is unclear, but it is probably related to its immunosuppressive effects on T lymphocytes. Gold salts, administered orally or intramuscularly, are marginally effective in treating PsA and are slow acting; 2 to 6 months of treatment may be needed before a clinical response is observed. A variety of other DMARDs, including D-penicillamine, antimalarial preparations, and azathioprine, are also used to treat PsA, but most trials of these agents have been uncontrolled

and definitive data regarding efficacy are lacking. Furthermore, use of antimalarial medications has been associated with worsening of psoriasis.

The selection of a specific DMARD is driven primarily by balancing efficacy and relative safety against individual patient factors. Specific DMARD factors that influence selection include the dose, schedule, and route of administration; long-term monitoring requirements; and safety profile. All currently available DMARDs are relatively slow acting and may cause serious adverse reactions.

Retinoids. Acitretin and etretinate are derivatives of retinoic acid that suppress DNA synthesis in psoriatic epidermis. They are sometimes used to treat the skin manifestations of PsA. Use of retinoids is limited by side effects, which may include arthralgias, mucocutaneous problems, teratogenicity, and hyperostosis that can mimic psoriatic spine lesions.

Systemic Corticosteroid Therapy. Systemic corticosteroid therapy is effective in treating the skin manifestations of some patients with PsA, but may lead to postcessation flares. Because of this, most clinicians advocate the use of systemic corticosteroids only for patients with severe skin manifestations who are acutely ill.

Phototherapy. Phototherapy for the skin manifestations of PsA is available in 2 forms. Pure ultraviolet (UV) B phototherapy, which encompasses the sunburning wavelengths of 300 to 320 nm, is the oldest therapeutic modality for patients with psoriasis. Intensive UVB may be combined with coal-tar therapy for patients with moderate-to-severe disease.

Photochemotherapy, the second form of phototherapy, combines the photosensitizing drug psoralen with UVA radiation (320 to 400 nm), and is referred to as PUVA therapy. PUVA is usually given 2 to 3 times per week in an office or clinic, for a total of about 10 weeks, followed by maintenance therapy that involves less frequent treatment. PUVA therapy is gen-

erally an effective treatment for the skin manifestations of PsA. In most patients, skin lesions disappear after 20 to 30 treatments. The duration of remission in patients who terminate maintenance therapy after 2 to 3 months ranges from 6 to 12 months.¹⁴ Short-term adverse effects associated with PUVA therapy include nausea, burning, and pruritus. Long-term problems include an increased risk of photodamage to skin and an increased risk of skin cancer related to the cumulative exposure to UVA radiation. Intensive PUVA therapy can also induce wrinkling, irregular pigmentation, lentigines, benign keratoses, and premalignant lesions.¹⁵

Topical Therapy. Topical therapy, like phototherapy, treats the skin manifestations but not the articular manifestations of PsA.

Topical corticosteroids are a commonly used treatment for psoriasis because of their short-term efficacy, high degree of acceptability to patients, and relative low cost.¹⁶ Patient compliance is much greater with topical corticosteroids than with other topical treatments such as anthralin or coal tar because there is no skin irritation or staining of the skin or clothing.

Anthralin is a synthetic anthrone that appears to be antimetabolic, but through a different mechanism than corticosteroids or tar. Unfortunately, it has irritant and staining properties that limit its usefulness. It soils clothing and bed linen, and may even stain the skin and produce long-standing pigmentary changes. Anthralin should be avoided in acute inflammatory psoriasis, flexural areas, and the face. Severe chemical conjunctivitis may occur with accidental contact with the eyes. Anthralin is often used in conjunction with a daily coal-tar bath and UVB phototherapy.

Coal tar is perhaps the most widely prescribed noncorticosteroid preparation used in the treatment of psoriasis.¹⁷ Although wood tars such as pine tar soap or oil of cade (juniper) are occasionally used, the most common products contain crude or refined coal tar. Coal tar is a by-product of the process of heating coal in

the absence of oxygen to produce coke that is used to fire steel furnaces. The substance is an ill-defined mixture of complex hydrocarbons. Each batch of coal tar, depending on the source of coal and the temperature of the coking ovens, has a variable concentration of naphthalene, cresol, phenol, anthracene, and as many as 10,000 other undefined substances.¹⁸ Like anthralin therapy, coal-tar treatment is usually combined with UVB phototherapy. Numerous coal-tar preparations are available as creams, ointments, gels, shampoos, and emulsions.

The application of an emollient that hydrates and softens the scaly, hyperkeratotic surface of psoriatic plaques is an active, but weak treatment. In about one third of patients, itching, soreness, redness, scaling, and lesional extension are reduced by the twice-daily application of emollients such as soft yellow paraffin or aqueous cream.¹⁹ This effect may be a result of a reversal of the inflammatory consequences of damage to the stratum corneum.²⁰ Greasier emollients, such as petrolatum or aquaphor cream, are more effective, but less acceptable to patients for cosmetic reasons, including the shininess and stickiness of treated skin.

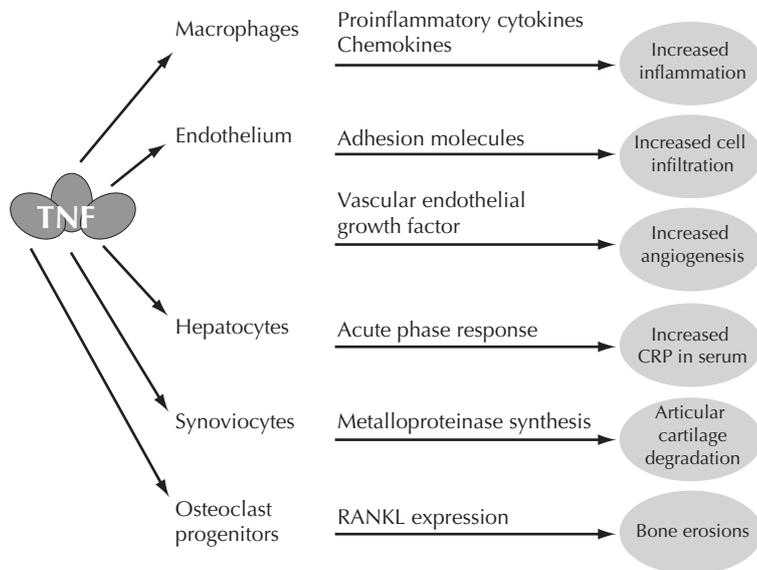
Keratolytic agents such as salicylic acid are used alone or in combination with coal tar or a topical corticosteroid. Salicylic acid softens the scaly layers of psoriatic plaques and eases their removal. It also enhances the efficacy of topical corticosteroids or coal tar by increasing their absorption.

The Role of Cytokines in the Pathogenesis of PsA

Several exciting discoveries regarding the pathogenesis of PsA have led to the development of new DMARDs more closely targeted to the mechanisms of rheumatic and skin inflammation of PsA.

Psoriasis and PsA: Pathogenic Parallels. There are a number of parallels between what happens pathologically in the skin and what can be seen in the rheumatoid and psoriatic joint. In the skin, there is infiltration of the dermis by

Figure 1. Key Actions Attributed to TNF



CRP = C-reactive protein; RANKL= receptor for activation of nuclear factor kappa B ligand; TNF = tumor necrosis factor.

mononuclear cells (predominantly T cells). The infiltration is accompanied by increased cytokine production by these T cells, which results in the hyperproliferation of keratinocytes and the abnormal plaque seen phenotypically. This is analogous to what is seen in the rheumatic joint in the sense that in the deep layers of sub-synovial tissue there is infiltration with mononuclear cells, release of cytokines, and a significant synovial proliferation of lining cells.

In the skin, infiltration by activated T cells precedes the development of the psoriatic plaque. CD4 cells are present in the dermis, and CD8 cells are noted in the epidermis.²¹ There is a distinctive cytokine profile in psoriatic plaque, with increased levels of interleukin-2 (IL-2) and interferon-gamma expressed.²² There is also an associated increase in the levels of IL-6, IL-8, and TNF.²³

In addition, the role of infection as a potential driver of the T-cell response has also been emphasized in the psoriasis and PsA literature. For example, guttate psoriasis occurs predominantly in children and

may be triggered by streptococcal infections of the respiratory tract.²⁴ Elevated antistreptococcal antibody titers and positive streptococcal throat cultures appear to be associated with acute disease.²⁵ Psoriatic plaques are often colonized by bacteria, and these bacteria are considered the potential source of ongoing stimulation entering through breaks in the skin, thereby leading to a chronic inflammatory response.

Key Actions Attributed to TNF. There has been an increased understanding of the role of cytokines, such as TNF, in the pathogenesis of both skin and joint disease in psoriasis and PsA. It is well documented that TNF production is increased in psoriatic skin, and the pathogenic role for TNF in the rheumatic inflammation of PsA has recently been elucidated, including observations of increased concentrations in synovial tissue and fluid.^{24,26,27}

In chronic inflammatory states, such as PsA, TNF plays a central role, as it stimulates the production of other inflammatory mediators in macrophages and other cells. TNF affects several mechanisms involved in inflammation, including cell proliferation and activation. TNF upregulates the expression of adhesion molecules on synoviocytes and endothelium, stimulates neovascularization, induces bone resorption, and leads to cartilage and bone destruction (**Figure 1**).²⁸⁻³¹ In the PsA synovial membrane, the synovial lining layer cells express increased amounts of osteoclast progenitors such as the TNF-family osteoclastogenesis-osteoblastogenesis coupling factor known as receptor for activation of nuclear factor kappa B ligand (RANKL).³²⁻³⁹ Synovial lining cells, in response to TNF and other mediators, upregulate the surface expression of RANKL, which then interacts with its receptor RANK on the surface of preosteoclasts, causing them to be transformed into activated osteoclasts, thereby resulting in bone resorption. In summary, the protean effects of TNF on a variety of immunologic cells and other cell types result in a proinflammatory state of increased inflammatory cell traffic and

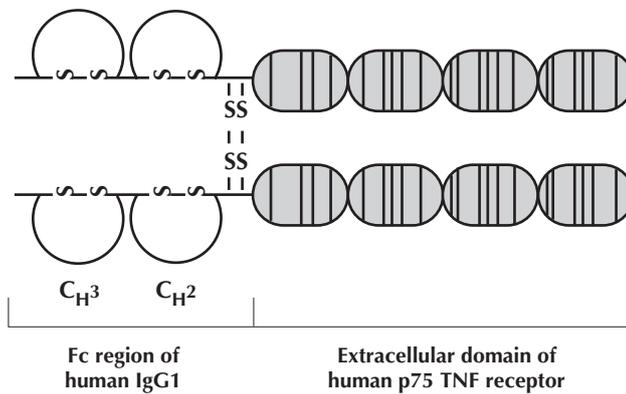
proliferation, as well as tissue inflammation and destruction. These observations provide a powerful impetus for the development of TNF inhibitors as a means of effectively treating both the skin and joint manifestations of PsA.

Etanercept

Description. Etanercept is a recently developed TNF inhibitor. It is a recombinant form of the human p75 soluble TNF receptor (TNFR) fused to the Fc fragment of human immunoglobulin G1. The resulting molecule, TNFR:Fc, is a dimer consisting of 2 soluble TNFR molecules per Fc molecule (Figure 2). TNFR:Fc is a potent antagonist of TNF biologic activity both in vitro and in vivo.⁴⁰⁻⁴² It has been effective in many models of inflammation, including animal models of RA, and in clinical RA trials. In addition, the serum half-life of TNFR:Fc fusion protein is increased dramatically in comparison with the monomer.⁴²

Clinical Trials of Etanercept in the Treatment of Psoriasis and PsA. We undertook a 3-month, randomized, double-blind, placebo-controlled phase 2 study to assess the efficacy and safety of etanercept (25-mg subcutaneous injections twice weekly) in 60 patients with PsA and psoriasis.⁴³ Thirty patients were randomized to each study arm. Eligible patients were adults between 18 and 70 years of age who had active PsA (defined as 3 or more swollen joints and 3 or more tender or painful joints) at the time of study enrollment. Patients must have had an inadequate response to NSAIDs. Patients taking methotrexate (less than or equal to 25 mg/week) were allowed to continue taking methotrexate if the dose was stable for 4 weeks before study initiation and remained stable throughout the study. Other DMARDs were discontinued at least 2 weeks before beginning the study drug, and were not allowed during the study. Corticosteroids were allowed if the dose was less than or equal to 10 mg/day of prednisone, stable for at least 2 weeks before the first dose of study drug, and maintained at a constant dose throughout

Figure 2. Structure of Etanercept



IgG = immunoglobulin G; TNF = tumor necrosis factor.

Table 1. Demographics and Disease History in Randomized, Double-Blind, Placebo-Controlled Study of Etanercept in Patients With Psoriatic Arthritis and Psoriasis

Characteristic	Placebo (n = 30)	Etanercept (n = 30)
Mean age (years)	43 (24 to 63)	48 (30 to 70)
Male	60%	53%
Arthritis duration (mean years)	10.5	11.6
Psoriasis duration (mean years)	18.9	20.5
Concomitant medications:		
Corticosteroids	40%	20%
NSAIDs	77%	67%
Methotrexate	47%	47%

NSAIDs = nonsteroidal anti-inflammatory drugs.

Source: 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;356:385-390. Adapted with permission.

the study. Patients with evidence of skin conditions other than psoriasis (such as eczema) were not allowed to enter the study. Topical therapies and oral retinoids for psoriasis were discontinued at least 2 weeks before the baseline evaluation, and phototherapy was discontinued at least 4

Table 2. Mean Baseline Arthritis Activity in Randomized, Double-Blind, Placebo-Controlled Study of Etanercept in Patients With Psoriatic Arthritis and Psoriasis

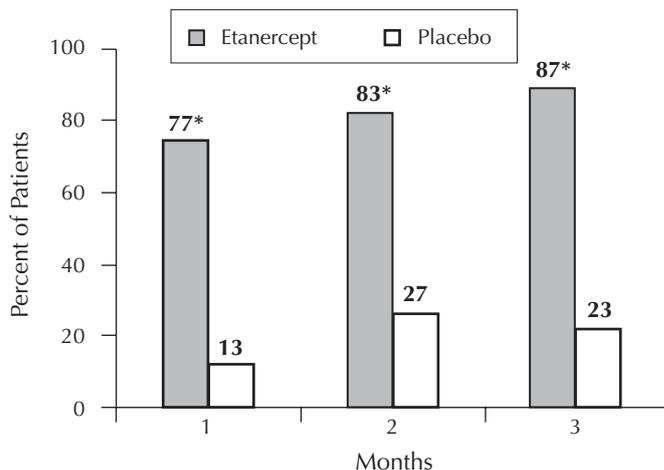
	Etanercept (n = 30)	Placebo (n = 30)
Tender joint count	23	25
Swollen joint count	16	18
Physician global (0 to 5)	3.3	3.4
Patient global (0 to 5)	3.3	2.9
Pain (0 to 5)	3.0	3.1
HAQ disability (0 to 3)	1.2	1.2
CRP (mg/dL)	2.3	1.6

HAQ = Health Assessment Questionnaire; CRP = C-reactive protein.
 Source: 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;356:385-390. Adapted with permission.

weeks before treatment. The 3-month controlled phase was followed by a 6-month open-label phase.⁴⁴

The demographics and disease history of enrolled patients are presented in **Table 1**.⁴³ Enrolled patients tended to have more polyarticular disease because of longer disease duration and increased severity. Among patients enrolled in the study, arthritis duration was slightly greater than 10 years, and the duration of psoriasis approached 20 years. There was a slight male predominance among enrollees. Concomitant medications included low-dose prednisone in 40% of placebo-treated patients and 20% of etanercept-treated patients. NSAIDs were used in roughly two thirds of the patients, and methotrexate was used in 47% of the patients in each group. A significant number of tender and swollen joints and other manifestations of disease activity were also well balanced between the 2 groups (**Table 2**).⁴³ All of the patients in the etanercept group and 87% of those in the placebo group completed the study. Most of the placebo-treated patients who dropped out of the study did so because of lack of efficacy.

Figure 3. Psoriatic Arthritis Response Criteria (PsARC) Response Over Time



*P <.001.
 Source: 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;356:385-390. Adapted with permission.

The primary endpoint with respect to efficacy in PsA was the proportion of patients who met the Psoriatic Arthritis Response Criteria (PsARC)⁴⁵ at 12 weeks. This composite measure requires improvement in 2 factors (with at least 1 being a joint score), with worsening in none of the following factors: patient and physician global assessments, tender joint score, and swollen joint score. A secondary endpoint for the assessment of PsA was the proportion of patients meeting the American College of Rheumatology-20 (ACR-20) response criteria (at least a 20% reduction in tender and swollen joint counts and improvement in at least 3 of the following: patient's assessment of pain, physician's global assessment, patient's assessment of disability, and C-reactive protein level).³⁶ ACR-50 and ACR-70 responses were also assessed.

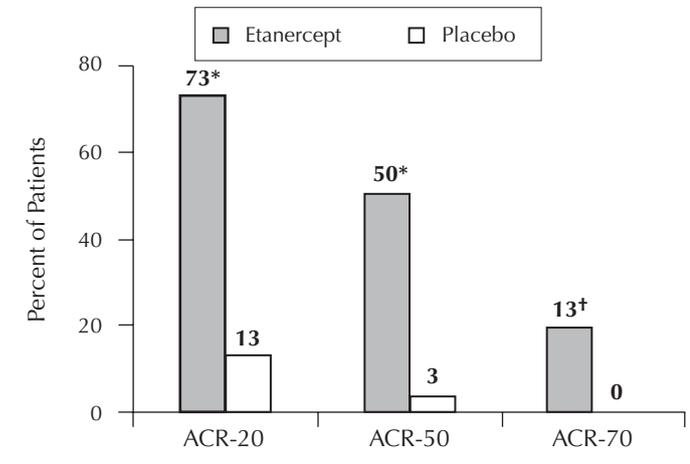
By 1 month, 77% of the patients in the etanercept arm achieved a PsARC response (**Figure 3**).⁴³ By 3 months, 87% achieved a

PsaARC response. The PsARC response among placebo-treated patients was no greater than 27% at any time point. The results achieved statistical significance ($P < .001$) at each monthly time point. Among patients who received concomitant methotrexate, 93% achieved a PsARC response, and it appeared that the effect of etanercept was at least additive to the effect of methotrexate in this group.

At 3 months, 73% of etanercept-treated patients achieved an ACR-20 response, 50% achieved an ACR-50 response, and 13% achieved an ACR-70 response (Figure 4).⁴³ There was no clear distinction in response between patients who received concomitant methotrexate and those who did not. Evaluation of several of the individual response criteria demonstrated a dramatic drop in the tender joint and swollen joint counts over time (Figure 5). Similar dramatic improvements were observed in etanercept-treated patients with regard to duration of morning stiffness and change in disability index scores (Figure 6). All of these responses attained impressive statistical significance at each time point.

At 3 months, etanercept-treated patients showed significant improvement ($P = .0002$) in all measures of disease activity. The median percentage improvements in

Figure 4. American College of Rheumatology (ACR) Response at 3 Months



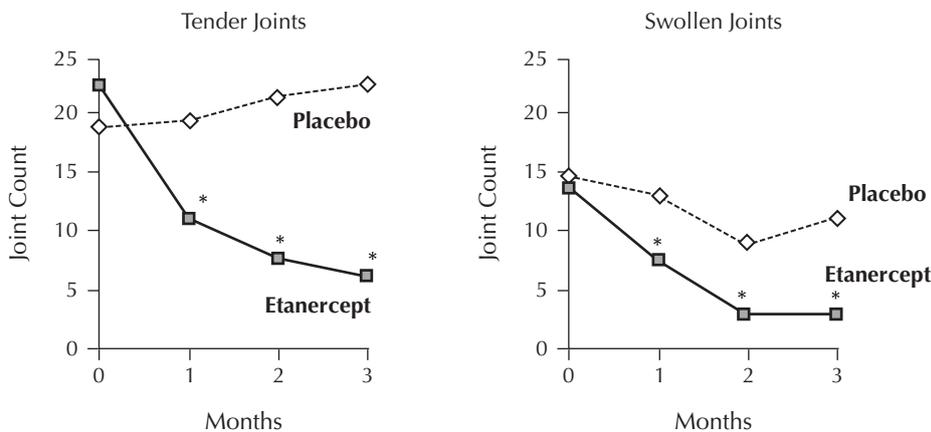
* $P < .001$.

[†] $P < .04$.

Source: 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;356:385-390. Adapted with permission.

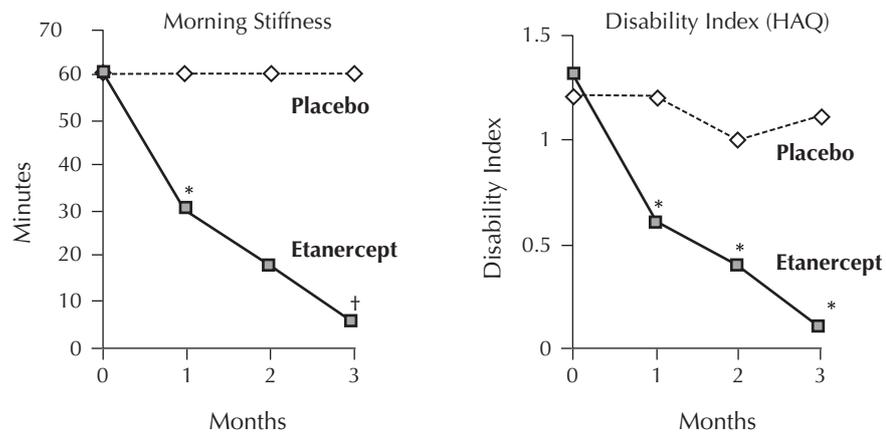
tender and swollen joint counts for etanercept-treated patients were 75% and 72%, respectively, compared with 5% worsening and 19% improvement in placebo-treated patients. Disability, as assessed by responses on the Health Assessment Questionnaire, was also significantly more improved in the etanercept group than in the placebo

Figure 5. Median Tender and Swollen Joint Counts Among Etanercept- and Placebo-Treated Patients at 1, 2, and 3 Months



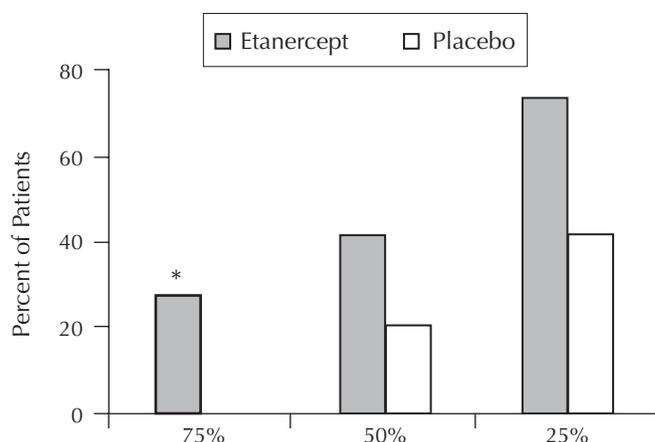
* $P < .001$.

Figure 6. Duration of Morning Stiffness and Change in Disability Index (as Assessed by Health Assessment Questionnaire [HAQ] Score) Among Etanercept- and Placebo-Treated Patients at 1, 2, and 3 Months



* $P < .01$; † $P < .001$.

Figure 7. Improvement in Psoriasis Area and Severity Index at 3 Months in Etanercept- and Placebo-Treated Patients



N = 38.

* $P < .05$.

Source: Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: A randomized trial. *Lancet* 2000;356:385-390. Adapted with permission.

group, with improvements from baseline of 83% and 3%, respectively ($P < .0001$).

Etanercept was also effective in improving the skin lesions of psoriasis (Figure 7).⁴³ Of the 19 patients in each treatment

group who were evaluable for psoriasis (defined by involvement of at least 3% of body surface area), 5 etanercept-treated patients (26%) and no placebo-treated patients achieved the primary psoriasis endpoint—a 75% improvement in psoriasis area and severity index (PASI) at 3 months ($P = .0154$). Similar differences between treatment groups were also seen at the 25% and 50% improvements in PASI scores; in fact, the median improvement in PASI score was 46.2% among etanercept-treated patients and 8.7% among patients who received placebo ($P = .0032$). Among etanercept-treated patients, 60% achieved a 50% improvement in target lesion (Figure 8).⁴³

The most common adverse events in the study were upper respiratory tract infections and injection-site reactions. Injection-site reactions were mild and well tolerated. The incidence of headache was relatively similar in etanercept- and placebo-treated patients (13% and 10%, respectively). Fatigue was seen more frequently in patients treated with etanercept (13% versus 0%).

Investigators of the initial 3-month randomized, double-blind, placebo-controlled study concluded that etanercept is well tolerated and appears to work dra-

matically well in patients with PsA, both in alleviating rheumatic signs and symptoms and in reducing skin disease.⁴⁴ All patients enrolled in the initial study were eligible to enter a 6-month, open-label trial for the purpose of ongoing surveillance of efficacy and safety.⁴⁴ During this phase of the study, patients were allowed to reduce or discontinue concomitant DMARDs.

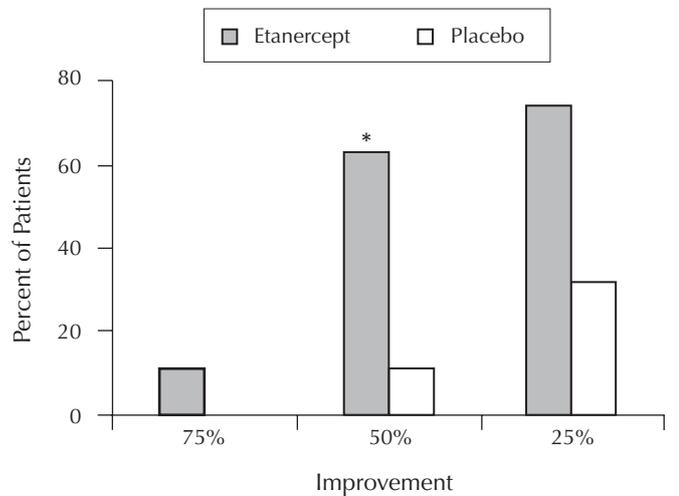
All etanercept-treated patients from the first phase of the study and 28 of 30 placebo-treated patients entered the open-label extension phase. Twenty-six of the 30 etanercept-treated patients (87%) and 24 of the 28 placebo-treated patients (86%) completed the open-label extension phase.

In the 6-month extension phase, all patients who received etanercept during the 3-month blinded phase demonstrated sustained efficacy with regard to PsARC response (Figure 9). Furthermore, patients who received placebo during the blinded phase rapidly attained a similar degree of efficacy during the open-label extension phase. Similarly, all patients who received etanercept during the 3-month blinded phase demonstrated sustained efficacy with regard to ACR responses. Patients who received placebo during the blinded phase rapidly attained a similar degree of ACR response during the open-label extension phase. At 6 months, of the 58 patients who entered the open-label extension phase, 74%, 56%, and 30% attained ACR-20, ACR-50, and ACR-70 responses, respectively. At 9 months, 28% of patients had zero tender joints, 42% had zero swollen joints, and 40% had a disability score of zero.

With regard to PASI, there was further improvement from the end of the 3-month phase through the 6-month, open-label phase among patients who were treated with etanercept initially. Overall, the median improvement in PASI was 62% at the end of the 6-month extension phase. The target-lesion score remained at 50%.⁴⁴

Of the 28 patients who were taking concomitant methotrexate at baseline, 12 (43%) decreased their methotrexate dose and 7 (25%) discontinued methotrexate

Figure 8. Improvement in Target Lesion at 3 Months in Etanercept- and Placebo-Treated Patients

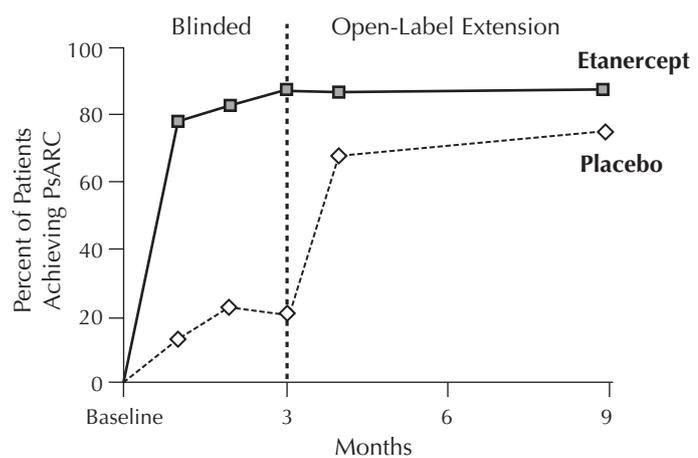


N = 38.

*P <.05.

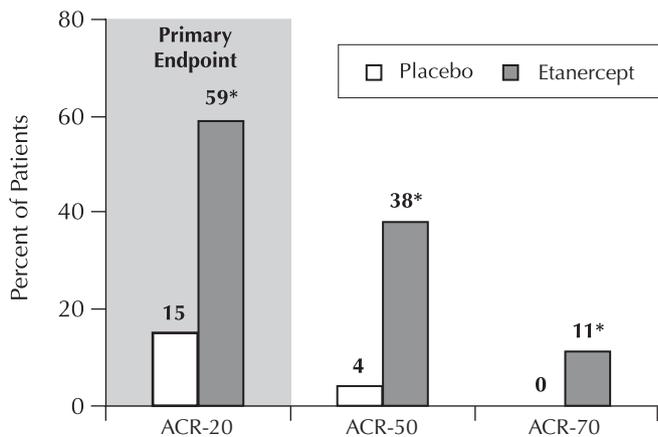
Source: Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: A randomised trial. *Lancet* 2000;356:385-390. Adapted with permission.

Figure 9. Percentage of Patients Treated With Etanercept or Placebo During 3-Month Blinded Phase Who Maintained Psoriatic Arthritis Response Criteria (PsARC) Response During Open-Label Extension Phase



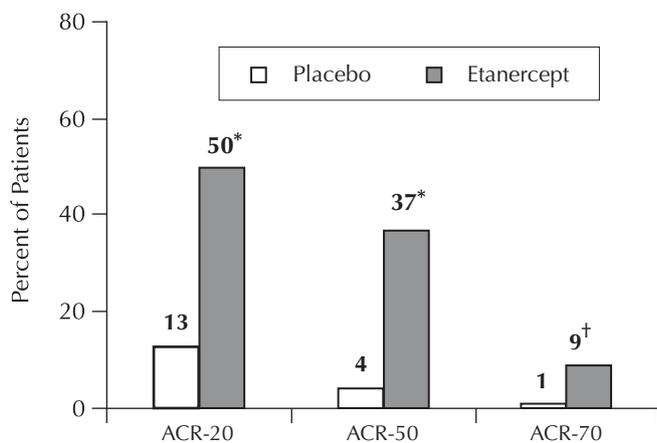
altogether. Similarly, of the 18 patients who were receiving concomitant corticosteroids at baseline, 12 (67%) decreased their corticosteroid dose and 8 (44%) discontinued corticosteroids altogether.⁴⁴

Figure 10. American College of Rheumatology (ACR) Response at 12 Weeks in Etanercept- and Placebo-Treated Patients



* $P \leq .001$.
Source: Reference 47.

Figure 11. American College of Rheumatology (ACR) Response at 24 Weeks in Etanercept- and Placebo-Treated Patients



* $P \leq .001$; [†] $P \leq .009$.
Source: Reference 47.

During the 6-month phase, no further injection-site reactions were seen among patients who had received etanercept in the initial 3-month phase. As predicted, injection-site reactions were

seen early and tended to fade over time, and no patient who received etanercept discontinued treatment because of an injection-site reaction. Among placebo-treated patients who went on to receive etanercept, 14% experienced injection-site reactions. Other adverse events were similar between patients originally treated with placebo who went on to receive etanercept, and those who received etanercept throughout the 9-month period.⁴⁴

These results have been confirmed by other studies evaluating the effectiveness of etanercept in the treatment of severe, treatment-resistant PsA.⁴⁶

We recently reported the results of a 24-week double-blind, placebo-controlled, multicenter phase 3 study evaluating the effectiveness of etanercept in 205 patients with psoriasis and PsA.⁴⁷ Etanercept-treated patients exhibited a significantly greater response than the patients in the placebo group in each of the parameters of disease activity measured, including ACR-20, PsARC, target lesion score, and PASI. At 12 weeks, 59% of the etanercept group had achieved an ACR-20 response, compared with 15% of the placebo group ($P < .001$) (Figure 10).⁴⁷ This benefit was sustained at 24 weeks as well (Figure 11).⁴⁷ A 50% improvement in the target lesions was achieved in 43% of the etanercept-treated patients and 17% of the placebo-treated patients (Table 3).⁴⁷ PsARC response and improvement in PASI are summarized in Figure 12 and Table 4, respectively.⁴⁷ Improvement in median tender and swollen joint counts is shown in Figure 13.⁴⁷

Etanercept was well tolerated, with no increase in the number of serious adverse events occurring in patients receiving etanercept as compared with those receiving placebo. Based on our results, patients with PsA treated with etanercept experience significant improvement in arthritis activity, psoriasis activity, and disability. Etanercept produces statistically significant improvement in the symptoms and signs of both PsA and psoriasis. The phase 3 trial represents the largest and longest

randomized, placebo-controlled trial of TNF antagonism in PsA.

Safety Profile. In all controlled trials, approximately 37% of patients treated with etanercept developed injection-site reactions.⁴⁸ Injection-site reactions were described as mild to moderate (erythema and/or itching, pain, or swelling) and virtually never necessitated drug discontinuation. Injection-site reactions generally occurred in the first month and subsequently decreased in frequency. The mean duration of injection-site reaction was 3 to 5 days. Seven percent of patients experienced redness at a previous injection site when subsequent injections were given. In postmarketing experience, injection-site bleeding and bruising have also been observed in conjunction with etanercept therapy.

In all controlled trials, there were no differences in rates of infection among patients treated with etanercept and those treated with placebo or methotrexate.⁴⁸ The most common type of infection was upper respiratory tract infection, which occurred in 16% of placebo-treated patients and 29% of patients treated with etanercept. When the longer observation of patients on etanercept was accounted for, the event rate was similar in both groups. In postmarketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving etanercept alone or in combination with immunosuppressive agents.

In all controlled trials, there were no differences in rates of demyelinating central nervous system disorders among patients treated with etanercept and those treated with placebo or methotrexate.⁴⁸

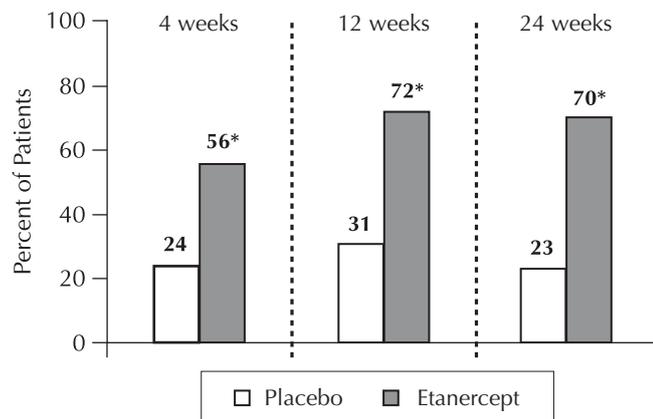
Seventeen malignancies of various types were observed in 1197 RA patients treated in clinical trials with etanercept for up to 36 months. The observed rates and incidences were similar to those expected for the populations studied. Other adverse events reported in at least 3% of etanercept-treated patients include

Table 3. Improvement in Target Lesion Score at 6 Months in Etanercept- and Placebo-Treated Patients

Parameter	Placebo n = 104	Etanercept n = 101	P value
Median % improvement in: Target lesion score	0	33	< .0001
Percent of patients who improved target lesion score by:			
50%	17	43	< .0001
75%	10	22	.0169

Source: Reference 47.

Figure 12. Psoriatic Arthritis Response Criteria Response at 4, 12, and 24 Weeks in Etanercept- and Placebo-Treated Patients



*P ≤ .001.

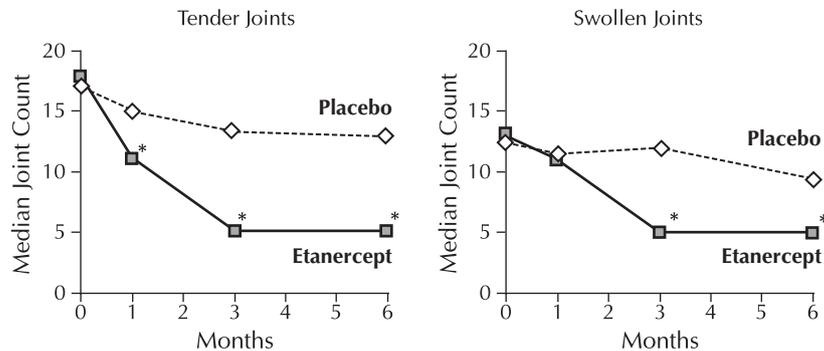
Source: Reference 47.

Table 4. Improvement in Psoriasis Area and Severity Index (PASI) at 6 Months in Etanercept- and Placebo-Treated Patients

Parameter	Placebo n = 62	Etanercept n = 66	P value
Median % improvement in: PASI score	0	47	< .0001
Percent of patients who improved PASI score by:			
50%	18	47	< .0005
75%	3	23	.0013

Source: Reference 47.

Figure 13. Median Tender and Swollen Joint Counts Among Etanercept- and Placebo-Treated Patients at 1, 3, and 6 Months



**P* < .0001.
 Source: Reference 47.

headache, nausea, vomiting, abdominal pain, dizziness, and rash.⁴⁸

The safety profile seen in PsA studies with etanercept has been similar to that seen in trials in RA.⁴⁸

Conclusion

Patients and clinicians alike are becoming increasingly aware of the severe physical and emotional devastation that PsA can produce. Furthermore, many who suffer from PsA or treat PsA patients are dissatisfied, predominantly because of the shortcomings of current therapeutic approaches. New compounds and recently introduced strategies, which have arisen in part from our evolving understanding of the inflammatory process and biotechnology tools, may offer new hope to a population that has long been without it.

Specifically, advances in our understanding of the role of cytokines, such as TNF in the pathogenesis of PsA, have led to the development of TNF inhibitors that directly target the mechanisms of cutaneous and articular inflammation. The availability of TNF-inhibiting drugs has been hailed as the first quantum leap in the pharmacotherapy of PsA in more than 2 decades.

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