Efficacy of etanercept in an integrated multistudy database of patients with psoriasis

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Background: The tumor necrosis factor (TNF) inhibitor etanercept has been demonstrated to be safe and effective for treating chronic plaque psoriasis in 3 clinical trials.

Objectives: To refine efficacy results for etanercept on the basis of a larger population size through the integration of the 3 studies, and to determine if the efficacy profile across all 3 studies is consistent with efficacy profiles observed for individual trials.

Methods: In these integrated analyses, data for 1187 patients from 3 blinded treatment groups were pooled to compare efficacy at 12 weeks: etanercept 50 mg weekly (equivalent to 25 mg twice weekly) subcutaneously, etanercept 50 mg twice weekly subcutaneously, and placebo. The primary efficacy end point in all 3 studies was at least a 75% improvement in the Psoriasis Area and Severity Index (PASI 75). Other measurements included PASI 50, PASI 90, patient's and dermatologist's global assessments, and Dermatology Life Quality Index.

Results: In the integrated analyses, statistically significant, dose-dependent improvements in PASI 75 at 12 weeks were observed in patients treated with etanercept 50 mg weekly (33%) and 50 mg twice weekly (49%), compared with the placebo group (3%; $P < .05$). Significant improvements also were seen in all secondary end points (PASI 50 and PASI 90 responses, patient's and dermatologist's global assessments, and Dermatology Life Quality Index) at 12 weeks. Subgroup analyses of baseline patient characteristics demonstrated that there were no statistically significant treatment-by-covariate interactions.

Limitations: A limitation of these integrated analyses is the relatively short (12-week) time frame.

Conclusion: The efficacy profile of etanercept in patients with psoriasis was consistent across multiple studies as shown in the integrated analyses of the primary and secondary end points. Etanercept demonstrated rapid, dose-dependent improvements in disease severity and quality of life consistently over all studies. (J Am Acad Dermatol 2006;54:S101-11.)

Psoriasis is a chronic, debilitating, inflammatory disease characterized by erythrosquamous scaly skin lesions.[1,2] The disease is associated with many physical and mental disabilities, including work-related discrimination, financial distress, depression, and suicidal ideation.[3-7] The pathogenesis of psoriasis is quite complex, but there is compelling evidence that overproduction of proinflammatory cytokines by T cells and keratinocytes, including tumor necrosis factor (TNF), plays a very important role.[1,2,8,9] TNF levels are increased in psoriatic lesions, compared with levels in uninvolved

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Abbreviations used:

BSA:	body surface area
CI:	confidence interval
DLQI:	Dermatology Life Quality Index
DSGAP:	Dermatologist's Static Global Assessment of Psoriasis
MTX:	methotrexate
OR:	odds ratio
PASI:	Psoriasis Area and Severity Index
PGA:	Patient's Global Assessment
PUVA:	psoralen plus ultraviolet A
SC:	subcutaneous
TNF:	tumor necrosis factor

skin in psoriatic patients and in the healthy skin of individuals who do not have psoriasis. Serum and lesional TNF levels decrease after effective psoriasis therapy, correlating with clinical improvement in the disease.[10] These observations suggest that interfering with the proinflammatory effects of TNF may reduce the characteristic inflammation seen in psoriatic lesions.

Until recently, treatments for psoriasis usually have not been satisfactory with respect to either safety or efficacy.[4] Treatment options ranged from topical products for mild to moderate forms of psoriasis to phototherapy and systemic therapies, such as methotrexate (MTX) and cyclosporine, for moderate to severe disease.[11-13] Because psoriasis usually is a chronic disease, long-term therapy is indicated. However, long-term treatment with psoralen plus ultraviolet A (PUVA) therapy can result in cutaneous malignancies, while long-term therapy with MTX and cyclosporine can lead to hepatotoxicity and nephrotoxicity, respectively. In addition, other commonly used therapies such as phototherapy or topical therapies are inconvenient, time consuming, or have limited effect in moderate to severe psoriasis.

Newer biologic agents targeting T cells such as alefacept (Amevive, an anti-CD2 fusion protein, Biogen Idec, Inc, Cambridge, Mass) and efalizumab (Raptiva, an anti-CD11a antibody, Genetech, Inc, South San Francisco, Calif) have been approved in the United States and provide additional therapeutic options for patients with psoriasis.[14,15] The recognition that TNF plays a central role in the pathogenesis of T-cell–mediated autoimmune diseases, coupled with the recent clinical successes of the TNF inhibitor etanercept in treating patients with other inflammatory disorders (adult and juvenile rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis), has provided an impetus for examining etanercept in patients with psoriasis.[1,16-25] Etanercept (Enbrel, Immunex Corp, Thousand Oaks, Calif) is a fully human, soluble TNF receptor immunoglobulin GI fusion protein that antagonizes the biologic activity of endogenous TNF by competitively inhibiting its interaction with cell-surface receptors. In April 2004, etanercept was approved in the United States for use in adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

In 3, randomized, double-blind, placebo-controlled trials, it was demonstrated that etanercept, administered either at 50 mg weekly (equivalent to 25 mg twice weekly) or 50 mg twice weekly, can improve signs and symptoms of psoriasis significantly.[26-28] In these integrated analyses, data from a phase 2 and two phase 3 trials are combined to refine efficacy results for etanercept on the basis of a larger population size and to determine if the efficacy profile for etanercept across multiple studies is consistent with efficacy profiles observed for individual trials. We also explore the impact of various patient characteristics (eg, age, gender, race, and baseline weight), different prior antipsoriatic therapies, and regional differences (eg, North America, South America, Europe) on clinical response.

METHODS

Patient population

The institutional review boards of the participating medical centers approved the protocols. All patients gave written informed consent before initiation of the clinical trials. Patients included in the integrated analyses were eligible if they were 18 years of age or older; had active, stable plaque psoriasis involving at least 10% of body surface area (BSA); and were candidates for or had received previous phototherapy or systemic therapy for psoriasis. Patients in the phase 2 study required 10% BSA involvement for their psoriasis,[26] and patients in the United States and multinational phase 3 trials required a minimum Psoriasis Area and Severity Index (PASI) score of 10 at screening in addition to 10% BSA involvement.[27,28] Patients were permitted to receive stable doses of topical corticosteroids on the scalp, axilla, and groin during the study if these preparations were of low or moderate potency.

Exclusion criteria included the following: guttate, erythrodermic, or pustular psoriasis at the time of screening or another active skin condition that would interfere with evaluations; previous treatment with etanercept or antibody to TNF; treatment with anti-CD4 antibodies or interleukin-2-diptheria-toxin fusion protein within the previous 6 months; treatment with any biologic or investigational drug, PUVA, systemic corticosteroids, or systemic psoriasis therapy within the previous 4 weeks; treatment with ultraviolet B phototherapy, topical corticosteroids,