Acta Dermatovenerol Croat 2006;14(4):241-245 CLINICAL ARTICLE

Our Experience with Etanercept in the Treatment of Psoriasis

Franco Kokelj, Stanislava Miertusova Tothova, Mario Patamia, Giusto Trevisan

Institute of Dermatology, University of Trieste, Trieste, Italy

Corresponding author:
Franco Kokelj, MD
Institute of Dermatology
University of Trieste
Via Stock 2
34100 Trieste
Italy
franco.kokelj@libero.it

Received: June 20, 2006
Accepted: October 22, 2006.

SUMMARY Psoriasis is a chronic inflammatory disorder that usually requires long-term control. Etanercept has been shown to be effective in this disease. The efficacy and safety of etanercept were assessed in patients with psoriasis. In this 16-week open clinical trial, 29 patients with clinically stable psoriasis and psoriatic arthritis received etanercept (25 mg twice weekly) subcutaneously. All patients were evaluated for the psoriasis area, severity index (PASI) and Ritchie's articular index (RAI) which measures arthritis disease activity. Improvement by 75 percent in PASI, considered significant for psoriasis remission, was observed in nearly sixty percent of patients after 12-week etanercept therapy. The percentage of PASI improvement was nearly 25% at two weeks, 52.3% at four weeks and 78% at 12 weeks of etanercept treatment, and was maintained for the next four weeks. Comparable results were obtained in the improvement of psoriatic arthritis symptoms, as improvement of 75 percent in RAI was observed in 58.3 percent of patients after 12 weeks of etanercept therapy. The percentage of RAI improvement was nearly 26% at two weeks, 40.5% at four weeks and 73.6% at 12 weeks and 77.1% at 16 weeks of etanercept treatment. Etanercept was generally well tolerated, as most events were of mild severity. The treatment with etanercept led to significant improvement in patients with psoriasis over a period of 16 weeks.

KEY WORDS: psoriasis; etanercept; tumor necrosis factor; biologicals; therapy

INTRODUCTION

Psoriasis is a chronic inflammatory disorder that affects the skin and joints. The prevalence of the disease varies from 0.5% to 4.6%, with rates varying between countries and races. In Italy, it is approximately 2 percent of the population (1). The disease varies in severity; some patients have mild disease with isolated scaling erythematous plaques on the elbows, knees or scalp, whereas others can have up to 100% of their skin surface affected. Patients report substantial disease related impairment of health related quality of life, inability to work, and may face discrimination or depression (2,3).

Current therapies include topical and systemic treatments or phototherapy (4). Approximately 25% of patients have moderate to severe disease

Acta Dermatovenerol Croat
2006;14(4):241-245

and require phototherapy or systemic treatment (5). Many therapies are associated with cumulative toxicity that may limit their usefulness in this chronic disease (4,5).

For many years psoriasis was thought to be mainly epidermal disease, but the fact that immunosuppressive agents improve psoriasis has changed our knowledge about psoriasis. Although the pathogenesis of psoriasis is not fully understood, there is evidence to support the role of the immune system, particularly T cells and cytokines (6,7). The concentration of the inflammatory cytokine tumor necrosis factor (TNF) is higher in psoriatic lesions compared to the uninvolved skin and decreases after successive treatment of psoriasis, suggesting that TNF plays an important role in the pathogenesis of the disease (8,9). Based on these facts, a new class of agents, targeted biological therapies, have has been developed.

Etanercept is a soluble recombinant human TNF-α-receptor fusion protein that prevents TNF-α-mediated cellular response competitively inhibiting its interaction with cell-surface receptors. Etanercept has been shown to be effective in patients with psoriasis (10,11). Based on these results we conducted a study evaluating the efficacy and safety of etanercept in patients with psoriasis.

PATIENTS AND METHODS

It was an open clinical trial that evaluated the efficacy of etanercept in the treatment of psoriasis and psoriatic arthritis over a period of 16 weeks.

Patients

All patients enrolled in the study gave a written informed consent before entering the study. Patients were eligible for the study if they were at least 18 years of age, with active but stable chronic plaque psoriasis. Patients were required to have a minimum psoriasis area and severity index (PASI) of 10 (indicating moderate to severe psoriasis) and an active psoriatic arthritis (defined as >3 tender or painful joints and >3 swollen joints, or Ritchie's articular index /RAI/ >12) at the time of study enrolment. All patients had been previously treated with systemic treatments such as cyclosporine, retinoids or methotrexate, resulting in inadequate response or intolerance of respective therapy. Disease-modifying antirheumatic agents were discontinued for at least 2 weeks before the study and were not allowed during the study. Oral retinoids, corticosteroids and phototherapy were discontinued for at least 4 weeks before the study and were not allowed during the study. Exclusion criteria were as follows: patients with autoimmune disorders or positive autoantibodies, infectious diseases on screening, positive history of tuberculosis, neoplastic disorders, heart failure or other serious diseases, pregnancy, and breast feeding. Patients with active guttate, erythrodermic or pustular psoriasis were excluded from the study.

Study protocol

Screening laboratory studies included hematology, serum chemistry, urinalysis, blood culture and urinary culture tests, serum immunoglobulins, peripheral lymphocyte typing, Mantoux test, paraneoplastic markers (CEA, GICA, CA19.9, TPA and PSA), autoantibodies (ANA, ENA, nDNA), rheumatoid factor, anti-streptolysin O, serum concentration of C-reactive protein, and erythrocyte sedimentation rate. Instrumental tests included chest and hand x-rays.

The measures of psoriasis activity included PASI with the assessment of surface area involvement, infiltration, erythema and scaling of psoriatic plaques. The measures of arthritis disease activity included RAI. It is based on the summation of joint responses upon application of firm digital pressure. The sum of RAI is 78 and reflects disease exacerbations and improvement induced by antirheumatic agents.

Control testing was performed at 2, 4, 8, 12 and 16 weeks (T15, T30, T60, T90 and T120, respectively). This testing consisted of physical examination, vital signs, measures of disease activity (psoriasis and psoriatic arthritis), laboratory studies (hematology parameters, serum chemistry with kidney and liver function tests), and monitoring for adverse events.

Treatment

Patients received etanercept (Enbrel) at a dose of 25 mg twice weekly by subcutaneous route for 16 weeks. During the study the patients were allowed to use topical emollients only. No other systemic or topical treatments for psoriasis were allowed.

Statistical analysis

All patients who completed at least a 2-week study period were included in the analysis. Statistical analysis was performed by use of specific StataSE/8 software (Stata Corporation, TX, USA). Continuous efficacy variables (percentage change from baseline) were ranked using a nonparametric Wilcoxon signed rank test with a significance level of 0.05.

Acta Dermatovenerol Croat
2006;14(4):241-245

RESULTS

A total of 29 Caucasians with active, clinically stable psoriasis and psoriatic arthritis, 19 (65.5%) male and ten female, aged 30 to 81 (mean age 53.4) years, mean duration of psoriasis 23.7 years, were included in the study. All study patients had psoriatic arthritis, had previously received topical corticosteroids and/or topical vitamin D analogs and were non-responsive or intolerant to systemic treatments such as cyclosporine, retinoids or methotrexate. Of 29 study patients, 23 completed 16-week (T120), 24 completed 12-week (T90), 28 completed 4-week (T30) and all 29 patients completed 2-week (T15) study period.

All patients were evaluated for PASI and RAI measuring arthritis disease activity. An improvement in PASI by 50%, 75% and 90% percent was recorded (Table 1). An improvement in PASI by 75% (PASI 75) was considered significant for psoriasis remission. An improvement in RAI by 50%, 75% and 90% was recorded (Table 2).

Safety

Etanercept was generally well tolerated in our patient population. Most adverse events were of mild to moderate severity. No cases of tuberculosis or severe infections were reported during the study. Two patients presented acute urticaria after two weeks of treatment and they withdrew from the study. One patient withdrew for psoriasis reactivation and development of erythroderma. This patient, on the contrary, showed improvement in articular symptoms. Other side effects were of mild severity and they disappeared in the first two weeks of treatment. Two patients had injection-site reaction, two had nausea and headache, and two patients had transiently increased articular pain.

DISCUSSION

Our study demonstrated the efficacy and tolerability of etanercept, a TNF-α antagonist, in the treatment of psoriasis, underscoring the role of TNF-α in the pathogenesis of this disease. In our study, etanercept induced marked clearance of psoriatic skin lesions and improvement of psoriatic arthritis symptoms. Significant improvement by at least 50% in PASI was achieved by three quarters of patients within the first 8 weeks of treatment with etanercept. An improvement by 75% in PASI 75, considered significant for psoriasis remission, was observed in nearly sixty percent of patients after 12 weeks of therapy. The response to treatment with etanercept was rapid and effective. The mean percentage of PASI improvements from baseline as measured by this index was statistically significant. The rate of PASI improvement was nearly 25% after two weeks, 52.3% after four weeks and 78% after 12 weeks of etanercept treatment, and was maintained for the next four weeks. Comparable results were obtained in the improvement of psoriatic arthritis symptoms, as an improvement by 75% in RAI was observed in 58.3 percent of patients after 12 weeks of etanercept treatment. The rate of RAI improvement was nearly 26% after two weeks, 40.5% after four weeks, 73.6% after 12 weeks and 77.1% after 16 weeks of etanercept therapy. We found psoriatic arthritis response to be slightly slower than but as effective as the clearance of psoriatic skin lesions. Other studies have also shown the efficacy of etanercept in psoriasis (10-12). Few controlled clinical trials have been conducted in patients with psoriatic arthritis and have shown inconsistent results (13-15). Cyclosporine was compared with methotrexate in an open trial in psoriatic arthritis showing greater responses in arthritis measures with methotrexate,

Table 1. Clinical improvement of psoriasis area and severity index (PASI) after 2, 4, 8, 12 and 16 weeks of treatment with etanercept

	Baseline T0	2 weeks T15	4 weeks T30	8 weeks 60	12 weeks T90	16 weeks T120
Median PASI	15.5	11.5	7.4	4.9	3.5	3.3
PASI 50	-	6/29 (20.6%)	15/28 (53.5%)	18/24 (75%)	22/24 (91.7%)	22/23 (95.6%)
PASI 75	-	2/29 (6.8%)	4/28 (14.2%)	12/24 (50%)	14/24 (58.3%)	14/23 (60.8%)
PASI 90	-	0/29	0/28	4/24 (16.6%)	8/24 (33.3%)	8/23 (34.7%)
% PASI improvement	-	25.8 %	52.3%	68.4%	77.4%	78.7%

Table 2. Clinical improvement of Ritchie's articular index (RAI) after 2, 4, 8, 12 and 16 weeks of treatment with etanercept

	Baseline T0	2 weeks T15	4 weeks T30	8 weeks T60	12 weeks T90	16 weeks 120
Median RAI	22.7	16.8	13.5	8.8	6.0	5.2
RAI 50	-	6/29 (20.6%)	12/28 (42.8%)	16/24 (66.6%)	21/24 (87.5%)	21/23 (89.4%)
RAI 75	-	3/29 (10.3%)	4/28 (14.2%)	9/24 (37.5%)	14/24 (58.3%)	14/23 (60.8%)
RAI 90	-	1/29 (3.4%)	3/28 (10.7%)	6/24 (25%)	7/24 (29.1%)	10/23 (43.4%)
% RAI improvement	-	25.9 %	40.5%	61.2%	73.6%	77.1%

whereas PASI improved more with cyclosporine (16). However, the cumulating toxicity of these agents was a limiting factor (15,17), posing the need of a therapy treating both psoriasis and psoriatic arthritis.

Health-related quality of life is impaired in patients with psoriasis; it strongly depends on its severity and may be improved with treatment (3,18,19). Increased levels of TNF-α are associated with major depression and it has been speculated that inflammatory cytokines such as TNF-α may form a link between fatigue and depression (20-22). Etanercept treatment may relieve fatigue, sleepiness and depression associated with this debilitating disease (23). Rapid clearance of skin lesions is an important aspect of effective psoriasis management and may correlate with patient satisfaction with the treatment.

Etanercept has been approved for the treatment of rheumatoid arthritis since 1998. Long-term clinical safety studies in more than 2000 patients have shown continued efficacy and favorable risk-benefit profile of etanercept (24). In our study including 29 patients, etanercept was generally well tolerated, as most events were of mild severity. Adverse events included two cases of acute urticaria, one case of erythroderma, injection-site reactions, nausea, headache, and transiently increased articular pain.

Although long-time safety studies in psoriasis patients treated with etanercept are not available, data from patients with rheumatoid arthritis suggest that the treatment with etanercept may be considered a viable option in the treatment of selected patients with psoriasis. Future studies will reveal how this therapy will expand previously established psoriasis treatment protocols.

References

1. Koo J. Population-based epidemiologic study of psoriasis with emphasis on quality of life assessment. Dermatol Clin 1996;14:485-96.
2. Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. Br J Dermatol 1995;132:236-44.
3. de Arruda LH, De Moraes AP. The impact of psoriasis on quality of life. Br J Dermatol 2001;144 Suppl 58:33-6.
4. Ashcroft DM, Li Wan Po A, Griffiths CE. Therapeutic strategies for psoriasis. J Clin Pharm Ther 2000;25:1-10.
5. Boehnicke WH. Immunomodulatory drugs for psoriasis. BMJ 2003;327:634-5.
6. Bonifati C, Ameglio F. Cytokines in psoriasis. Int J Dermatol 1999;38:241-51.
7. Prinz JC. The role of T cells in psoriasis. J Eur Acad Dermatol Venereol 2003;17:257-70.
8. Ettehadi P, Greaves MW, Wallach D, Aderka D, Camp RD. Elevated tumour necrosis factor-alpha (TNF-alpha) biological activity in psoriatic skin lesions. Clin Exp Immunol 1994;96: 146-51.
9. Mussi A, Bonifati C, Carducci M, D'Agosto G, Pimpinelli F, D'Urso D, *et al.* Serum TNF-alpha levels correlate with disease severity and are reduced by effective therapy in plaque-type psoriasis. J Biol Regul Homeost Agents 1997;11:115-8.
10. 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.
11. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, *et al.* Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003;349:2014-22.

12. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, *et al.* A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 2005;152:1304-12.
13. Palit J, Hill J, Capell HA, Carey J, Daunt SO, Cawley MI, *et al.* A multicentre double-blind comparison of auranofin, intramuscular gold thiomalate and placebo in patients with psoriatic arthritis. Br J Rheumatol 1990;29:280-3.
14. Farr M, Kitas GD, Waterhouse L, Jubb R, Felix-Davies D, Bacon PA. Sulphasalazine in psoriatic arthritis: a double-blind placebo-controlled study. Br J Rheumatol 1990;29:46-9.
15. Cuellar ML, Espinoza LR. Methotrexate use in psoriasis and psoriatic arthritis. Rheum Dis Clin North Am 1997;23:797-809.
16. Spadaro A, Taccari E, Mohtadi B, Riccieri V, Sensi F, Zoppini A. Life-table analysis of cyclosporin A treatment in psoriatic arthritis: comparison with other disease-modifying antirheumatic drugs. Clin Exp Rheumatol 1997;15:609-14.
17. Lebwohl M, Ellis C, Gottlieb A, Koo J, Krueger G, Linden K, *et al.* Cyclosporine consensus conference: with emphasis on the treatment of psoriasis. J Am Acad Dermatol 1998;39: 464-75.
18. de Korte J, Sprangers MA, Mombers FM, Bos JD. Quality of life in patients with psoriasis: a systematic literature review. J Invest Dermatol Symp Proc 2004;9:140-7.
19. Prins M, Krabbe PF, Swinkels QO, de Boo T, van de Kerkhof PC, van der Valk PG. The effect of treatment on quality of life in psoriasis patients. Acta Derm Venereol 2005;85: 304-10.
20. O'Brien SM, Scott LV, Dinan TG. Cytokines: abnormalities in major depression and implications for pharmacological treatment. Hum Psychopharmacol 2004;19:397-403.
21. Patarca R, Klimas NG, Lugtendorf S, Antoni M, Fletcher MA. Dysregulated expression of tumor necrosis factor in chronic fatigue syndrome: interrelations with cellular sources and patterns of soluble immune mediator expression. Clin Infect Dis 1994;18 Suppl 1:S147-53.
22. Vgontzas AN, Chrousos GP. Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. Endocrinol Metab Clin North Am 2002;31:15-36.
23. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, *et al.* Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006;367: 29-35.
24. Moreland LW CS, Klareskog J, Sanda M, Wajdula J, Burge DJ. Global safety and efficacy of more than 5 years of etanercept (ENBREL) therapy in rheumatoid arthritis. Arthritis Rheum 2002;46:S53.