Our Experience with Etanercept in the Treatment of Psoriasis

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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...
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, 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, para-neoplastic 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 anti-rheumatic 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.
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.

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

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

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.
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.

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

<table>
<thead>
<tr>
<th>Baseline T0</th>
<th>2 weeks T15</th>
<th>4 weeks T30</th>
<th>8 weeks T60</th>
<th>12 weeks T90</th>
<th>16 weeks T120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median RAI</td>
<td>22.7</td>
<td>16.8</td>
<td>13.5</td>
<td>8.8</td>
<td>6.0</td>
</tr>
<tr>
<td>RAI 50</td>
<td></td>
<td>6/29 (20.6%)</td>
<td>12/28 (42.8%)</td>
<td>16/24 (66.6%)</td>
<td>21/24 (87.5%)</td>
</tr>
<tr>
<td>RAI 75</td>
<td></td>
<td>3/29 (10.3%)</td>
<td>4/28 (14.2%)</td>
<td>9/24 (37.5%)</td>
<td>14/24 (58.3%)</td>
</tr>
<tr>
<td>RAI 90</td>
<td></td>
<td>1/29 (3.4%)</td>
<td>3/28 (10.7%)</td>
<td>6/24 (25%)</td>
<td>7/24 (29.1%)</td>
</tr>
<tr>
<td>% RAI improvement</td>
<td></td>
<td>25.9 %</td>
<td>40.5%</td>
<td>61.2%</td>
<td>73.6%</td>
</tr>
</tbody>
</table>

### References


