

ORIGINAL ARTICLE

## Clinical Experience With Etanercept in the Treatment of Psoriasis

B. Martín, J.L. Sánchez-Carazo, A. Pérez-Ferriols, C. Laguna, V. Oliver, and V. Alegre

Servicio de Dermatología, Consorcio Hospital General Universitario de Valencia, Valencia, Spain

**Abstract.** *Background.* Etanercept is one of the new biologic agents available for treating psoriasis. It has proved an effective option in a high percentage of patients, leading to sustained improvements in the psoriasis area severity index (PASI). Likewise, it is effective at controlling psoriatic arthritis, and its safety profile is excellent, with a much lower specific organ toxicity than traditional drugs and few side effects. Many of the data published to date are derived from clinical trials with this medication, but further studies are needed on the use of this therapy to manage patients in daily clinical practice.

*Methods.* This was a retrospective observational study of 36 patients with psoriasis who received etanercept between March 2004 and March 2006. We describe the experience of using this agent at our hospital, with the clinical outcomes and the problems we have faced.

*Results.* The PASI score was assessed before treatment and at 3 and 6 months of patient follow-up. After 3 months of treatment, 13 patients (36.11 %) had achieved a 50 % improvement in PASI score (PASI50), and 16 patients (44 %) had achieved a 75 % improvement (PASI75). Two of the patients (5.56 %) experienced an improvement in their disease without reaching PASI50 and only 4 patients (11.11 %) did not show clinical improvement or deteriorated. After 6 months, efficacy improved, with 27 patients (75 %) achieving PASI75, 6 patients (16.67 %) achieving PASI50, and 2 patients (5.56 %) showing no benefit from treatment. After 6 months, 13 of the patients (36.1 %) had achieved a 90 % improvement in PASI score. No adverse events of sufficient significance to warrant discontinuation of treatment were reported. At present, 11 of the patients remain on etanercept treatment as efficacy has been sustained and they have not experienced any adverse events of note.

*Conclusions.* Our clinical experience with the use of etanercept for treating plaque psoriasis shows a favorable efficacy and safety profile. We propose a standardized procedure for consultations with psoriasis patients involving extensive data collection on each visit and the creation of a national surveillance system for patients under treatment with biologic agents.

**Key words:** psoriasis, systemic therapy, biologic therapy, etanercept.

### ETANERCEPT EN LA PSORIASIS. EXPERIENCIA CLÍNICA

**Resumen.** *Introducción.* Etanercept es uno de los nuevos fármacos biológicos surgidos para el tratamiento de la psoriasis. Ha demostrado ser una opción eficaz en un alto porcentaje de pacientes, provocando mejoras en el PASI (*Psoriasis Assessment and Severity Index*) que se mantienen en el tiempo. Además, resulta igualmente adecuado para el control de la artritis psoriásica. Por otra parte, el perfil de seguridad es excelente, con una toxicidad órgano específica mucho menor que los fármacos clásicos y la aparición de escasos efectos secundarios. Muchos de los datos publicados hasta el momento proceden de los distintos estudios clínicos que se han realizado con esta medicación, pero se necesitan trabajos que reflejen la experiencia en la práctica clínica diaria con el manejo de esta terapia en condiciones normales.

*Métodos.* Estudio observacional, retrospectivo, en el que se recogen los 36 pacientes con psoriasis a los que administramos etanercept durante el período de tiempo comprendido entre marzo de 2004 y marzo de 2006. Exponemos la experiencia de nuestro centro en la utilización de este fármaco, con la evolución clínica y los problemas a los que nos hemos enfrentado.

---

Correspondence:  
Blanca Martín González  
Consorcio Hospital General Universitario de Valencia  
C/ Tres Cruces, 2  
46014 Valencia, Spain  
blancamartin@hotmail.com

Manuscript accepted for publication February 27, 2008.

*Resultados.* El PASI se evaluó antes de comenzar el tratamiento y a los tres y seis meses de seguimiento de los pacientes. A los tres meses de tratamiento 13 de los pacientes (36,11 %) habían alcanzado el PASI 50, y 16 pacientes (44,44 %) habían alcanzado el PASI 75. Dos de los pacientes (5,56 %) experimentaron una mejora de su psoriasis, sin alcanzar el PASI 50, y sólo 4 pacientes (11,11 %) no mostraron mejoría clínica o incluso empeoraron. A los 6 meses se observó un aumento de la eficacia, con 27 pacientes (75 %) que alcanzaron el PASI 75 y 6 pacientes (16,67 %) que llegaron a obtener el PASI 50, 2 pacientes (5,56 %) no mostraron ningún beneficio tras la terapia. A los 6 meses 13 de los pacientes (36,1 %) habían alcanzado el PASI 90. En ninguno de los casos se presentaron acontecimientos adversos de importancia que obligaran a suspender el tratamiento. Once de los pacientes siguen en tratamiento con etanercept en el momento actual, ya que se ha mantenido la eficacia y no han presentado efectos adversos importantes.

*Conclusiones.* Exponemos nuestra experiencia clínica con la utilización de etanercept para el tratamiento de la psoriasis en placas, con un perfil muy favorable de eficacia y seguridad. Proponemos la estandarización de la visita clínica al paciente con psoriasis, con recogida exhaustiva de datos en cada visita y la creación de un sistema nacional de registro de datos de pacientes con tratamientos biológicos.

**Palabras clave:** psoriasis, tratamiento sistémico, terapia biológica, etanercept.

## Introduction

Psoriasis is a chronic inflammatory disease that affects patients throughout the world.<sup>1</sup> The number of patients in Spain is calculated to be 600 000, of whom approximately a quarter suffer from moderate-severe psoriasis,<sup>2</sup> with a score of 10 or more on the Psoriasis Area Severity Index (PASI). Patients with such scores have been shown to suffer important psychological consequences, physical discomfort, and interference in their private and professional life.<sup>3</sup>

Furthermore, in 5% to 42% of patients, skin involvement is accompanied by joint involvement, with destructive arthritis affecting mainly the interphalangeal and sacroiliac joints.<sup>4</sup>

Conventional treatments (methotrexate, cyclosporine, phototherapy, etretinate) are not free from side effects or toxicity, and they have not proven to be completely satisfactory in the long-term control of the disease. Therefore, patients are obliged to rotate their therapies, that is, follow sequential treatments aimed at minimizing the toxic effects of these drugs. Furthermore, patients must be closely monitored because of cumulative specific organ toxicity and side effects.

In recent years, we have seen how advances in molecular biology and immunology and better understanding of the immunopathogenesis of psoriasis have led to the addition of a new group of drugs to the traditional therapeutic arsenal. These are the so-called biologic agents, which act more selectively than traditional drugs on the molecules that cause the disease.<sup>5</sup>

Tumor necrosis factor (TNF) is a proinflammatory glycoprotein that has been shown to play an important role in activating the inflammatory cascade and in the onset and perpetuation of several chronic inflammatory conditions, including psoriasis.<sup>6</sup> This molecule is involved in the proliferation of keratinocytes, inflammation of the dermis, expression of molecules in endothelial cells that facilitate adhesion and extravasation of activated T cells, and angiogenesis.<sup>7</sup> High levels of TNF- $\alpha$  have also been detected in psoriatic plaques and in the serum of patients with psoriasis. These levels correlate with those of disease activity.<sup>8</sup>

Etanercept is a human recombinant protein formed by fusing 2 human soluble TNF receptors with the constant region of human immunoglobulin (Ig) G1. This molecule binds competitively to TNF- $\alpha$  and TNF- $\beta$ , preventing them from interacting with their membrane receptors and, therefore, from exercising their proinflammatory effects.<sup>5</sup> It is currently indicated for the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis.

Various studies have been performed throughout the world to evaluate the efficacy and safety of etanercept, and the results have been extremely positive. After 24 weeks' treatment, 44% and 59% of patients treated, respectively, with etanercept at 25 mg and 50 mg twice weekly achieved a 75% improvement in their PASI score. Studies involving treatment lasting more than 1 year did not show a loss in efficacy over time, even when treatment was stopped and reintroduced later.<sup>5,9</sup>

As for safety, etanercept has proven to have a favorable profile, with good tolerance and scant adverse effects. The most common adverse effect is local injection site reaction, which has been reported in 16% of patients and tends to disappear from the second month of treatment onward.<sup>10</sup>

However, as we know, clinical trial results do not always reflect reality, since they very often involve ideal patients analyzed under very specific conditions. Therefore, we present our clinical experience with this drug in patients with moderate-severe psoriasis for whom other systemic treatments were contraindicated or had little effect. We evaluate the efficacy of the drug in our patients and the problems we faced while using the drug in daily clinical practice.

## Material and Methods

We performed a retrospective review of the clinical histories of 36 adult patients (26 men and 10 women) who received treatment with etanercept in our department from March 2004 through March 2006. Of these, 24 patients had been studied previously.<sup>11</sup> We recorded the time since diagnosis of psoriasis and the type of psoriasis, in addition to disease severity measured by the PASI. We evaluated the clinical efficacy of the drug using the PASI, as it is the most commonly used index internationally, despite its limitations. The clinical efficacy of the drug was evaluated using PASI50, that is, a 50% improvement in the baseline PASI score, and PASI75, which reflects a 75% improvement in the baseline PASI score.

All the patients had previously received 1 or several so-called conventional treatments, without achieving satisfactory control of the skin disease or joint disease.

Patients were informed of the possible side effects of the medication. Those patients whose therapy was started before September 2004—when the drug was approved for use against moderate or severe psoriasis that was refractory to other treatments—provided signed informed consent.

Before the study, patients underwent the following tests: a complete blood count (including lymphocyte subpopulations), biochemistry, Mantoux test followed by a booster test in those patients with a negative result, and a radiographic examination of the chest. The degree of skin involvement was also assessed using the PASI.

None of the patients studied had heart failure, active infections, neoplasms, a history of demyelinating disease or connective tissue disease, or the possibility of becoming pregnant. One patient with a positive Mantoux test result underwent tuberculosis chemoprophylaxis before starting therapy.

Until September 2004, etanercept was administered subcutaneously at 25 mg twice weekly from the start of treatment. Thereafter, the regimen followed was 50 mg of subcutaneous etanercept twice weekly for the first 3 months

and 25 mg subcutaneously twice weekly for the remainder of the treatment period. The small number of patients in our series led us to evaluate both groups as a whole, regardless of whether they had received 25 mg or 50 mg during the first months, since the statistical differences obtained would not be significant. The drug was administered as monotherapy in all cases. The only other therapeutic options permitted during the treatment period were emollients, class I and II topical corticosteroids, and heliotherapy.

The duration of treatment varied, and 11 patients are still receiving treatment due to their good response and the absence of severe adverse events. The disease-free period after suspension of etanercept was analyzed, as was the existence, or not, of a rebound effect. Adverse effects (including infections and neoplasms) were also recorded.

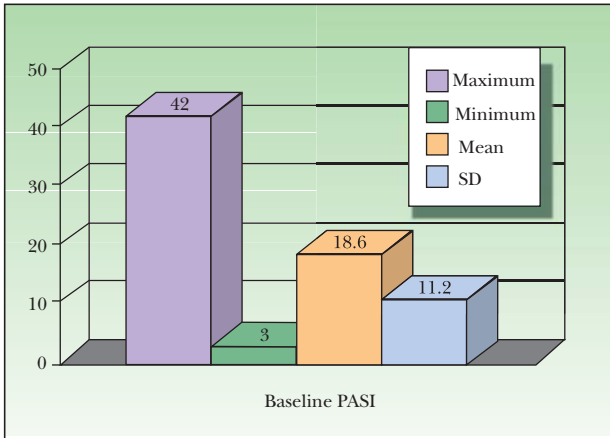
This was an observational study based on the retrospective review of patients' clinical histories, which were not recorded according to a specific protocol. Given that the study was intended to be no more than a report of our clinical experience with the drug at a given time, it was subject to several limitations.

## Results

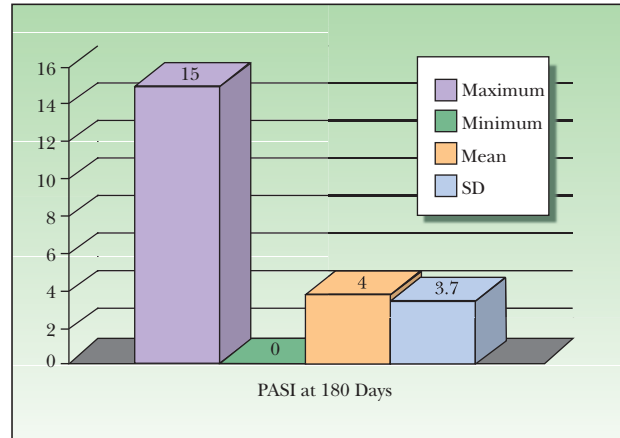
The study patients were aged between 19 and 72 years (mean 46.1 years), and 26 were men (72%) and 10 were women (28%). Time since the diagnosis of psoriasis varied from 3 to 61 years (mean [SD] 20 [12.9] years).

Most patients (29) had moderate-severe plaque psoriasis (PASI > 10). The PASI score was not recorded in the clinical history in 2 cases. However, there were large variations in the baseline PASI ranging from 3 to 42 (mean 18.6 [11.2]) (Figure 1). Five patients had a PASI score of less than 10 before starting treatment with etanercept. Treatment was justified in these cases because the psoriatic lesions, although scant in terms of area covered, were very debilitating. Such was the case of palmoplantar psoriasis or well established lesions that were refractory to several previous attempts at treatment.

The PASI was evaluated before treatment started and at 3 and 6 months. Comparison of the 3 measurements confirmed an excellent efficacy for etanercept. Thus, at 3 months, 13 of the patients (36.11%) had achieved PASI50, that is, their baseline PASI had improved by 50%, and 16 patients (44.44%) had reached PASI75 during the same period. Two patients (5.56%) experienced an improvement, but they did not reach PASI50, and only 4 patients (11.11%) did not improve clinically, and even deteriorated. The evaluation at 6 months revealed an increase in efficacy, with 27 patients (75%) reaching PASI75 and 6 (16.67%) reaching PASI50, whereas 2 patients (5.56%) showed no benefit after therapy. At 6 months, 13 patients (36.1%) had reached a PASI90 (Figure 2).



**Figure 1.** Maximum, minimum, and mean values of the Psoriasis Area Severity Index before starting treatment. The statistical analysis shows the wide range in the clinical status of the study patients.



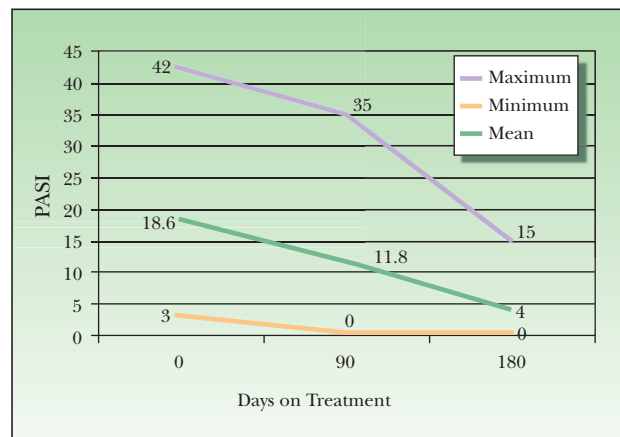
**Figure 2.** Maximum, minimum, and mean values of the Psoriasis Area Severity Index (PASI) at 6 months of treatment. Notice how the values decrease considerably after therapy and how the sample becomes more homogeneous, with the PASI scores converging and falling.

As for outcome, 11 patients are currently taking etanercept, since it is still effective and there have been no adverse effects worthy of note. The mean disease-free period for patients in whom the drug was withdrawn, defined as the time taken to reach a PASI equal to baseline, was 4.22 months. There were no cases of rebound, defined as reaching a PASI equal to or greater than 12.5 during the 3 months after treatment was stopped (Figure 3).

Only 7 adverse events were recorded during treatment. They were all mild and did not require the drug to be withdrawn. Curiously, injection site reaction, the most common effect according to the clinical studies carried out, was not recorded, probably due to its frequency and harmlessness. The undesirable effects recorded were 2 urinary tract infections, 2 episodes of fever, 1 case of herpes zoster, and 1 injection site reaction.

## Discussion

Psoriasis is a chronic condition that can only develop when infiltration of the epidermis by T lymphocytes occurs. These cells overexpress proinflammatory cytokines—such as TNF—and contribute to the anomalous proliferation of keratinocytes and perpetuation of inflammation. Several studies have shown that its concentration is much higher in psoriatic lesions than in the healthy skin of the same patient or in the skin of healthy individuals. The levels of these inflammatory cytokines also increase in joints affected by psoriatic arthritis.<sup>9</sup> Etanercept acts by antagonizing the effects of TNF through competitive inhibition of its binding to receptors on the cell surface, thus preventing triggering of the cell responses mediated by this molecule.<sup>4,5,12</sup>



**Figure 3.** Mean values of the Psoriasis Area Severity Index during treatment with etanercept.

The relatively recent incorporation of biologic agents to the therapeutic arsenal used by dermatologists up until the present for the treatment of psoriasis means that some physicians are still reticent about using them. Several clinical studies covering large populations have evaluated these agents, although they only analyzed ideal patients under very specific conditions. Therefore, we believe it is very important to carry out prospective studies that enable professionals to report their clinical experience in unselected patients. Such studies should reflect both the efficacy of biologic agents and the daily problems encountered in their management. The publication of reports of this type would help to standardize the use of drugs such as etanercept, and



provide the dermatologist with a certain level of confidence in the product.

Our clinical experience supports previous results on the efficacy, outcome, and safety of etanercept. In our opinion, it is a good, safe, and efficacious alternative for the treatment of psoriasis refractory to other approaches.

As for efficacy, the results of several phase II trials and 2 randomized phase III trials including more than 1000 patients revealed that 34% of patients who had received 25 mg twice weekly achieved PASI75 at 12 weeks. If the dose was 50 mg twice weekly, this proportion increased to 49%. When treatment was extended to 24 weeks, 44% and 59% of patients who had received etanercept at 25 mg and 50 mg twice weekly, respectively, achieved PASI75.<sup>9</sup>

Our results were even better than those of the clinical trials, since 44.44% of the patients treated reached PASI75 after 12 weeks of treatment. This percentage increased to 75% when the patients were re-evaluated at 24 weeks.

However, we must remember that although PASI is the standard and most widely used index in clinical trials and studies, it is imperfect. PASI75 is an arbitrary cutoff that does not reflect the patient's clinical status, but only patient outcome over time with respect to baseline. Furthermore, it is of little use when comparing different patients, especially—as in our study—when patients with very disparate PASI scores are included. In such cases, perhaps the most reliable way to reflect clinical reality is by analyzing the mean PASI values.

In our experience, the adverse effects recorded with etanercept were mild, to such an extent that they were sometimes not recorded in the clinical history. We found no signs of tuberculous infection in our patients, partly due to the screening process they underwent, which, as is well known, reduces the incidence of granulomatous processes.<sup>13</sup>

No increased incidence of severe infection or malignancy was detected in patients taking etanercept compared to the general population. In patients with underlying rheumatoid arthritis receiving this therapy, we did observe a greater incidence than expected in the development of lymphoma; nevertheless, we must remember that the appearance of this type of hematologic cancer is greater than in the reference population, even if they have not received etanercept.<sup>10</sup> Malignancy was not observed in the patients we treated with etanercept, although follow-up may not have been long enough for cancer to develop.

As mentioned above, the retrospective nature of the study and the not-so-rigorous recording of information in clinical histories in daily practice give rise to certain limitations when analyzing and comparing the results. Therefore, we wish to stress the need to draw up a protocol to follow during visits from patients with psoriasis. This should include parameters such as the PASI or quality-of-life indices, and potentially noteworthy events during treatment should be carefully recorded. The resulting information

would therefore be available in a concise and ordered form—with the corresponding benefits for health care, follow-up, and outcome—and enable us to extrapolate and compare results.

We consider that there is a clear need for a central database for reporting information about patients treated with biologic agents through the Spanish national health system. This would increase our understanding of the safety profiles and management of these patients and help us analyze data globally and in the long term. Such is the reasoning behind the creation of BIOBADADERM, a national adverse event registry supported by the Spanish Academy of Dermatology and Venereology and presented at the last National Congress in Granada, Spain. This registry aims to help us evaluate the long-term safety of biologic agents in dermatologic diseases.

### Conflict of Interests

The authors declare no conflicts of interest.

### References

1. Krueger G, Koo J, Lebwohl L, Menter A, Stern RS, Rolstad T. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. *Arch Dermatol.* 2001;137:280-4.
2. Ferrándiz C, Bordas X, García-Patos V, Puig S, Pujol R, Smandiá A, et al. Prevalence of psoriasis in Spain (Epiderma Project: phase I). *J Eur Acad Dermatol Venereol.* 2001;15:20-3.
3. Finlay AY, Coles, BC. The effects of severe psoriasis on the quality of life of 369 patients. *Br J Dermatol.* 1995;132:236-44.
4. Kormeili T, Lowe NJ, Yamauchi PS. Psoriasis: immunopathogenesis and evolving immunomodulators and systemic therapies. US experiences. *Br J Dermatol.* 2004;151:3-15.
5. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler D, et al. British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. *Br J Dermatol.* 2005;153:486-97.
6. Mehls SL, Gordon KB. The immunology of psoriasis and biologic immunotherapy. *J Am Acad Dermatol.* 2003;49:S44-50.
7. López Estebanz JL. Etanercept. Estructura química, farmacocinética y mecanismo de acción. *Actas Dermosifiliogr.* 2005;96 Suppl 3:2-9.
8. Bonifati C, Carducci M, Cordiali Fei P, Trento E, Sacerdoti G, Fazio M, et al. Correlated increases of tumor necrosis factor- $\alpha$ , interleukin-6 and granulocyte monocyte-colony stimulating factor levels in suction blister fluids and sera of psoriatic patients: relationships with disease severity. *Clin Exp Dermatol.* 1994;19:383-7.
9. Herrera Ceballos E, Habicheyn S. Eficacia clínica del etanercept en psoriasis y artritis psoriásica. *Actas Dermosifiliogr.* 2005;96 Suppl 3:10-24.
10. García-Patos Briones V. Seguridad de etanercept. *Actas Dermosifiliogr.* 2005;96:S25-32.

11. Mahiques Santos L, Martínez Menchón T, Sánchez Carazo JL, Pérez-Ferriols A, Soriano Navarro CJ, Fortea Baixauli JM, et al. Tratamiento de la psoriasis refractaria con etanercept. *Med Clin (Barc)*. 2005;125:371-3.
12. Gamo R, López-Estebanz JL. Terapia biológica y psoriasis. *Actas Dermosifiliogr*. 2006;97:1-17.
13. Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum*. 2003;48:2122-7.