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ORIGINAL ARTICLE

Long-term Safety and Efficacy of Etanercept in the Treatment of Psoriasis

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KEYWORDS

Etanercept;
Long-term treatment;
Safety;
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Abstract

Background: Clinical experience has shown that, in patients with psoriasis, suspending treatment with etanercept at week 24, as indicated in the prescribing information, may lead to a rebound effect. Several clinical trials support long-term use of etanercept, which was shown to have a good safety and efficacy profile.

Material and methods: This was a retrospective, observational study of 43 patients with moderate to severe plaque psoriasis, with and without joint involvement, who received continuous treatment with etanercept for more than 24 weeks.

Results: Etanercept was administered for a mean of 57 weeks. Overall, the Psoriasis Area and Severity Index (PASI) score decreased from a baseline value of 22.5 to 4.3 after treatment. In addition, with continuous treatment, most patients maintained decreases in PASI scores of 50% and even of 75%. Some patients without significant improvement in their PASI score in the first 24 weeks did manage to achieve significant results after prolonged treatment. These outcomes were achieved with a low incidence of adverse effects (reported in 13 patients [30.2%]), which were generally mild.

Conclusions: We present our clinical experience with long-term etanercept treatment in patients with moderate to severe psoriasis, with and without associated joint involvement. The efficacy and safety profiles were found to be favorable.

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PALABRAS CLAVE

Etanercept;
Tratamiento a largo
plazo;
Seguridad;
Eficacia

Seguridad y eficacia de etanercept a largo plazo en el tratamiento de la psoriasis

Resumen

Introducción: La experiencia clínica demuestra que la suspensión del tratamiento con etanercept en pacientes con psoriasis en la semana 24, como indica la ficha técnica del fármaco, produce en algunos casos rebrote de la enfermedad. Existen diversos ensayos que avalan el uso de etanercept a largo plazo con un buen perfil de seguridad y eficacia.

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Material y métodos: Estudio observacional, retrospectivo, en el que se recogió a 43 pacientes con psoriasis en placas de moderada a grave, con y sin artropatía, tratados con etanercept de forma continua durante más de 24 semanas.

Resultados: El etanercept se administró durante un tiempo promedio de 57 semanas, y disminuyó el PASI (Psoriasis Area Severity Index) de forma global de un valor basal de 22,5 a 4,3. Además, con el tratamiento continuo, la mayor parte de los pacientes mantuvieron puntuaciones PASI inferiores al 50% o incluso al 75%. Por otra parte, algunos pacientes que no alcanzaron mejorías significativas en su puntuación PASI en las primeras 24 semanas pueden conseguirlo prolongando el tratamiento. Todo ello con una baja incidencia de efectos adversos (13 pacientes [30,2%]) y de características leves.

Conclusiones: Exponemos nuestra experiencia clínica con el tratamiento con etanercept a largo plazo en pacientes con psoriasis de moderada a grave, con y sin artropatía asociada, y demostramos un perfil favorable de eficacia y seguridad.

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Introduction

Psoriasis is an immune-mediated chronic inflammatory disease that affects between 0.5% and 5% of the general population, depending on country. No differences have been found between sexes. In Spain, the prevalence is 1.4%,¹ meaning that approximately 600 000 persons have the disease. Symptoms are moderate or intense for between 25% and 30% of patients with psoriasis, which is a frequent complaint that accounts for between 5% and 15% of all visits to a dermatologist.² From 5% to 42% of patients have joint involvement, characterized by degenerative arthritis that is usually seronegative. This disease has evident negative repercussions on the physical, mental, emotional, and social domains of a patient's quality of life.³

Conventional systemic treatments (cyclosporin, methotrexate, acitretin, and psoralen plus ultraviolet A) are not free of cumulative toxicity and their usefulness over the long-term is therefore limited. Additionally, their clinical efficacy is unsatisfactory from the perspective of both patient and clinician. These problems have meant that drug development research continues in the hope of producing medications with better efficacy and long-term safety profiles.

Advances in our understanding of the immunopathology and molecular biology of psoriasis have led to so-called biological therapies. This new therapeutic arsenal is comprised of drugs that selectively block specific molecular pathways that play a role in the pathogenesis of psoriasis.

In this line, etanercept (under the brand name Enbrel), is a recombinant fusion protein containing the human tumor necrosis factor (TNF) receptor. It acts as a competitive antagonist of endogenous TNF by blocking the interaction with cell-surface receptors, thereby inhibiting its proinflammatory activity.

First used in humans in clinical trials in 1992, etanercept has been the object of further trials of efficacy and safety in inflammatory diseases for 16 years. In 2 Phase II trials^{4,5} and 2 placebo-controlled Phase III trials^{6,7} in patients with moderate-to-severe psoriasis, etanercept conferred

benefits and showed a good safety profile. The drug was approved by the European Medicines Evaluation Agency for treating psoriasis in 2004.

The dosage recommended in the summary of product characteristics is 25 mg twice weekly, although it is also possible to take 50 mg twice weekly, for up to 12 weeks, followed by a dosage of 25 mg twice weekly if required. The recommendation is to maintain etanercept therapy until remission is achieved, subject to a 24-week limit; therapy should be discontinued after 12 weeks if a patient is not responding. Contraindications are hypersensitivity to the drug or any excipients that might be present, sepsis or risk of sepsis, and infection.⁸

Safety issues must be taken into account before prescribing etanercept. The usual laboratory tests to rule out infections are recommended, but the other reasons for excluding a patient can be identified by taking a medical history. Contraindications are demyelinating neurologic diseases, malignant tumor in the last 5 years (with the exception of nonmelanoma skin cancer), chronic infection, and pregnancy.

As clinical experience with etanercept for the treatment of psoriasis has been gained with ever-increasing use of the drug in Europe, new ways of managing therapy to enhance efficacy have been suggested. Consensus guidelines⁹ based on clinical experience have attempted to clarify statements given in the package insert, always in the interest of improving both efficacy and safety. Aspects addressed include the establishment of an induction protocol for etanercept, higher dosages, and criteria for continuing or halting treatment.

One issue remains to be addressed, however. This is the product summary's indication that treatment for psoriasis should last no longer than 24 weeks. Routine practice in dermatology shows that patients often need to continue therapy and that temporarily or permanently suspending use leads to worsening of symptoms (rebound effect). Recent studies have attempted to investigate the safety and efficacy of long-term use of this drug. Papp et al¹⁰ treated patients for 48 weeks and Krueger et al¹¹

for 72 weeks. Treatment experiences lasting even up to 2.5 years have been reported on posters at international conferences.¹²⁻¹⁷

We analyzed our patients' long-term use of etanercept to treat moderate-to-severe plaque psoriasis in order to assess the drug's efficacy and safety in this setting.

Material and Methods

This was a retrospective study of information extracted from the medical records of 43 patients with moderate-to-severe plaque psoriasis with and without joint involvement. The patients' use of etanercept was uninterrupted for periods longer than 24 weeks.

The purpose was to assess the efficacy and safety of long-term use, defined as therapy extending beyond the period recommended in the prescribing information.

The decision to continue etanercept for a longer period was based on evidence of the drug's efficacy and safety in patients with psoriatic arthritis and on clinical experience with the worsening of skin lesions after withdrawal of etanercept at 24 weeks.

Before etanercept was prescribed, all patients had a complete blood workup, including biochemistry; a Mantoux test; and a chest x-ray. Conditions that would contraindicate etanercept therapy were thus ruled out.

Efficacy was assessed with the Psoriasis Area Severity Index (PASI), the severity scoring system most widely used internationally in spite of its limitations. PASI scores were recorded at the start of treatment and every 8 weeks thereafter as long as the patient was on etanercept. In addition, the PASI score was used to assess therapeutic response at the moment of maximum accumulated exposure at the study cut point, defined as the time when etanercept was withdrawn (in those patients who discontinued therapy) or the time of data collection (in patients who were still on the drug).

Likewise, the percentage of patients who achieved a PASI score reduction of 50% (PASI 50) and 75% (PASI 75) was determined at various points during treatment in order to analyze efficacy in more depth.

No standardized protocol was followed. Rather, dosing was tailored to each patient based on symptoms.

Follow-up laboratory tests (complete blood counts, liver function tests, and lipid profile) were performed bimonthly. To rule out adverse effects, blood pressure was also checked bimonthly and a clinical interview with physical examination took place.

Results

Patient characteristics and medication history are summarized in Table 1.

Twenty-eight men (65.1%) and 15 women (34.9%) were studied. Ages ranged from 20 to 76 years (mean, 47.1 years). The mean time since onset of psoriasis was 20.5 years and 19 patients (44.2%) had psoriatic arthritis.

The mean duration of etanercept therapy was 57 weeks; treatment duration ranged from 32 to 148 weeks (Figure 1).

No standardized protocol was followed, as dosages were tailored in response to each patient's condition. Clinical variables (weight, medical history, etc), degree of improvement in skin lesions or joint symptoms, and the eventual development of adverse effects influenced the decision to prescribe 50 or 100 mg of etanercept per week. Twenty-four patients (55.8%) started therapy at 100 mg and 19 patients (44.2%) started at 50 mg. The maintenance dose was 50 mg for 32 patients (74.4%) and 100 mg for 11 (25.6%). A decision to increase or decrease the dose was based on clinical response. An induction protocol was applied for 22 patients (51.2%) based on the 2006 recommendations for using etanercept in psoriasis.⁹ The protocol called for an initial dose of 100 mg for the first 3 months and a maintenance dose of 50 mg thereafter.

The mean PASI score for the group decreased overall from 22.5 (range, 7-42) at baseline to 4.3 (range, 0-32) after uninterrupted etanercept therapy (Figure 2). The graph of mean PASI scores during this period shows that patients maintained PASI 75 during prolonged treatment. However, a substantial increase in PASI scores occurred at week 96, when only 5 out of the total of 43 patients were still on the drug at this time. For this reason, any individual's variation in score had a strong statistical effect. When the study ended, 4 of these patients were still on treatment, given that their symptoms were well controlled in terms of skin lesions (maintenance of PASI 75, achieved at week 24) and joint involvement (present in 3 of these patients). Nevertheless, the PASI scores of 2 patients at week 96 revealed a self-limiting outbreak of skin lesions. In 1 patient, the rebound was attributed to temporary interruption of treatment for surgery. The other was explained by attempts to reduce the weekly maintenance dose from 50 mg to 25 mg. Another reason for the high mean at week 96 was the score of a patient who stopped taking etanercept at that time owing to poor control of skin lesions in spite of good control of joint symptoms. The patient was also on ultraviolet B therapy and later on methotrexate.

More detailed assessment of the efficacy of etanercept showed that 35 patients (81.4%) had achieved PASI 50 at week 24. Twenty-six of them had also achieved PASI 75.

Table Patient Characteristics and Medication History at Baseline

Characteristics	Patients, n=43
Women, n (%)	15 (34.9)
Men, n (%)	28 (65.1)
Age, mean (range), y	47 (20-76)
Mean time since diagnosis of psoriasis, y	20.5
Psoriatic arthritis, n (%)	19 (44.2)
<i>Prior systemic treatment, n (%)</i>	
Acitretin	26 (60.5)
Methotrexate	34 (79.1)
Cyclosporin	28 (65.1)
Phototherapy	14 (32.6)
Biologic agents	25 (58.1)

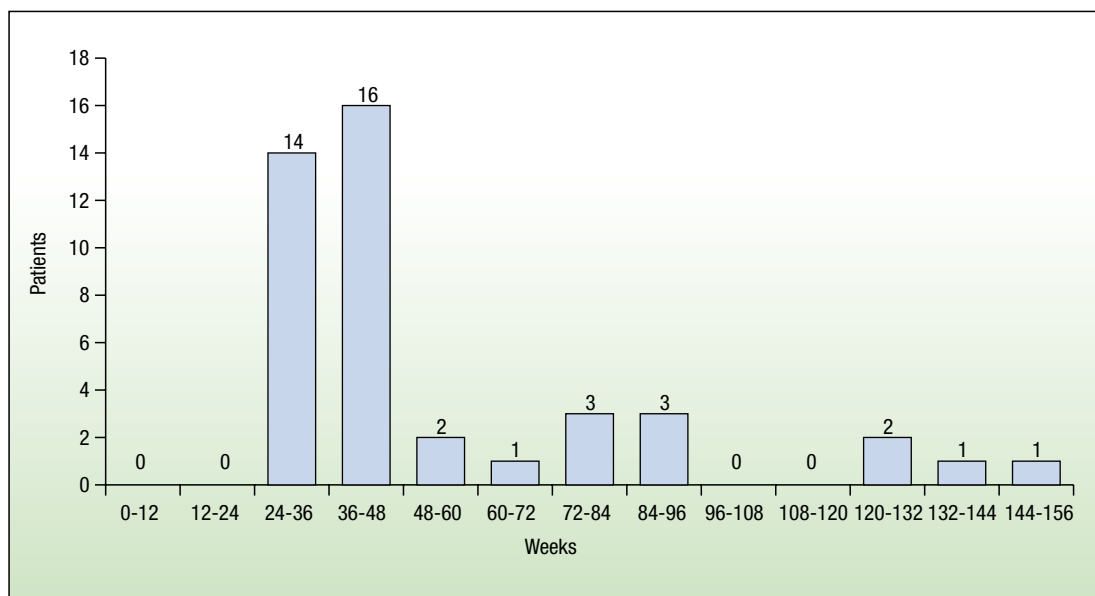


Figure 1 Duration of treatment.

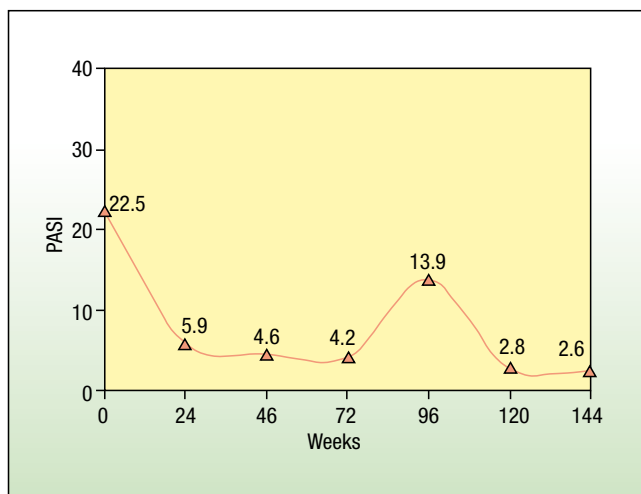


Figure 2 Changes in the Psoriasis Area Severity Index score during treatment.

Determining the PASI score at 24 weeks is an indication of efficacy within the therapeutic period assumed in the prescribing information. Given that one of the aims of the study was to evaluate long-term efficacy, we also assessed psoriasis severity at 48 weeks.

Of 21 patients who were still being treated at 48 weeks, 19 (90.5%) had achieved PASI 50. Fifteen patients had improved further, achieving PASI 75.

Besides the 21 out of 43 patients who were still being treated at 48 weeks or longer, 22 patients continued treatment until some point between 24 and 48 weeks. Of these 22 patients, 12 (54.5%) were still on treatment at the time of data collection. The exposure of these patients probably went

on even longer and their experience will allow us to further assess long-term continuous etanercept treatment. The 22 patients on etanercept when the study closed had been taking the drug for less than 48 weeks; 11 had achieved PASI 75 at week 24 and maintained that level of improvement, justifying continued treatment. However, 6 of these patients with less than 48 weeks of therapy had to suspend treatment because of whitening of skin lesions. For 3 patients, the drug was withdrawn because of lack of response. In 1 case, therapy was interrupted due to adverse effects. In the interest of assessing therapeutic response at the moment of maximum exposure to the drug, the PASI score was calculated at the moment etanercept was withdrawn (for those patients who stopped treatment) and at the moment data collection stopped (for those still on etanercept).

We found that 37 patients (86.0%) maintained PASI 50 scores and that 35 (81.4%) maintained PASI 75. These findings show that the majority of patients maintain PASI 50 and PASI 75 scores with prolonged etanercept use (mean duration, 57 weeks).

We also aimed to determine whether long-term etanercept therapy was influenced by certain variables, such as duration of treatment, dosage or regimen, and the presence of psoriatic arthritis or comorbidity. We observed better response with greater cumulative exposure to the drug (unrelated to dosage) in patients without joint involvement and associated diseases.

We also saw that long-term etanercept treatment not only ensured maintenance of the improvement gained at the start, but that some patients who did not achieve significant improvement in PASI score at week 24 were able to make gains with long-term treatment.

Thus, 24 of the 35 patients who achieved PASI 75 did so within 24 weeks. The remaining 11 patients achieved the same degree of reduction later: 1 patient in week 32, 3 in

week 36, 2 in week 40, 3 in week 48, 1 in week 88, and finally 1 in week 96 (Figure 3).

Another aim of this study was to analyze the safety of long-term etanercept use.

Adverse effects were described in 13 cases (30.2%). The remaining 30 patients (69.8%) experienced no complications (Figure 4). Adverse effects were classified as gastrointestinal complaints (4 patients [9.3%]), infections (3 [7%]), joint pain (3 [7%]), cardiovascular events (2 [4.6%]), tumor (1 [2.3%]), pain at the injection site (1 [2.3%]), and psychiatric symptoms (1 [2.3%]) (Figure 5).

Gastrointestinal symptoms, which were the most frequent complaint (9.3%), consisted mainly of diarrhea and short bouts of nausea and vomiting. These complications were self-limiting and led to no further complications.

Infection developed in 3 patients (7%). They included 1 case of tinea pedis, 1 of onychomycosis, and 1 of herpes zoster of the first trigeminal branch. All complications resolved with conventional treatment within normal time frames and without sequelae.

The adverse cardiovascular events that affected 2 patients (4.6%) were a hypertensive crisis in a patient with a history of hypertension and persistent chest pain in another patient with a history of unstable angina. The hypertension responded to treatment. The chest pain, however, led to withdrawal of etanercept after 8 months of uninterrupted treatment. It is noteworthy that this patient was the only one in the group who had to suspend treatment due to adverse effects.

One patient (2.3%) developed a basal cell carcinoma that was removed surgically without complications. One patient (2.3%) reported slight, transient pain at the injection site. Another patient (2.3%) showed signs of anxiety, which responded well to conventional treatment. It is noteworthy that the group of patients who experienced adverse effects had been taking etanercept for an average of 67 weeks, whereas the average duration was 48 weeks for patients without complications.

Finally, at the time data collection was completed, 23 patients (53.3%) were still on etanercept, whereas treatment had stopped for 20 patients (46.5%).

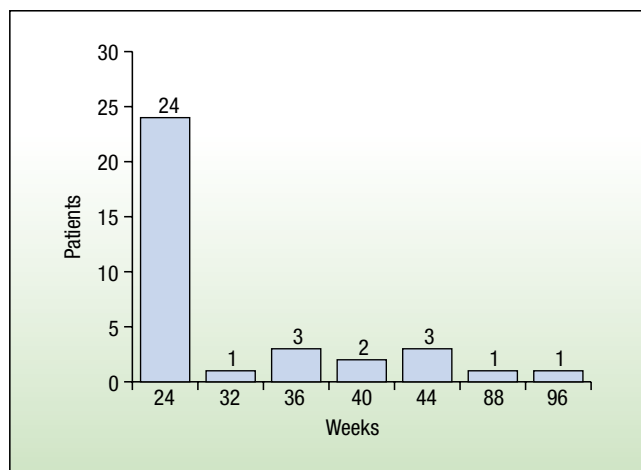


Figure 3 Moment during treatment when patients reached a Psoriasis Area Severity Index score reduction of 75%.

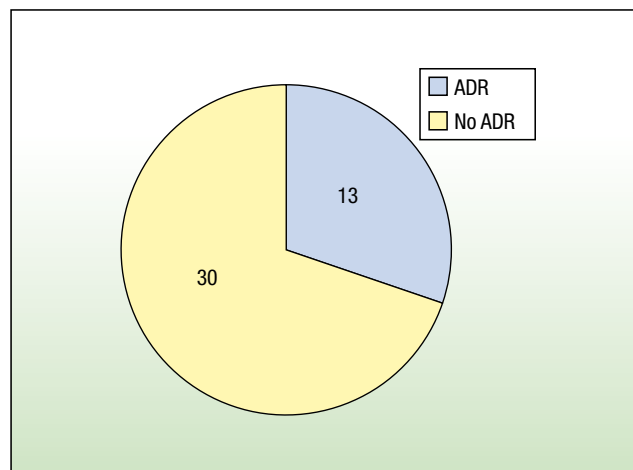


Figure 4 Adverse events during treatment. ADR indicates adverse drug reaction.

The most frequent reason for discontinuing the drug was whitening of skin lesions (13 patients [65%]) verified by the physician in week 44 on the average. Etanercept was stopped because of inefficacy in only 6 patients (30%). As mentioned in the paragraph on safety, treatment was withdrawn because of adverse effects in only 1 case (5%).

Discussion

The prescribing information for etanercept states that treatment is expected to last no longer than 24 weeks. This has led to successive interruptions and repetitions of treatment marked by rebound flare-ups that frustrate both patients and their dermatologists. Physicians feel obliged to halt treatment at week 24 when patients have shown sufficient improvement, yet symptoms often worsen after the drug is withdrawn. Clinical experience indicating that it is safe for patients with psoriatic arthritis to stay on etanercept therapy has suggested the possibility of long-term use. Moreover, many publications have reported on long-term etanercept therapy, mostly based on extensions of preliminary studies.

Our study shows that prolonged treatment supports the maintenance of improvements achieved in 24 weeks. Moreover, patients with a weak response within the therapeutic period foreseen by the summary of product characteristics can benefit from significant improvement if therapy continues beyond the assumed limit. Prolonged exposure does not increase the rate of adverse effects, and improved response rates have been observed in patients without joint involvement or associated comorbidity.

Our experience indicates that etanercept seems to be appropriate for long-term use in psoriasis, consistent with the findings of several trials of prolonged administration. When the treatment was extended from 24 weeks to 48 weeks for a group of patients in the study of Papp et al,¹⁰ the percentage of patients who achieved PASI 75 at

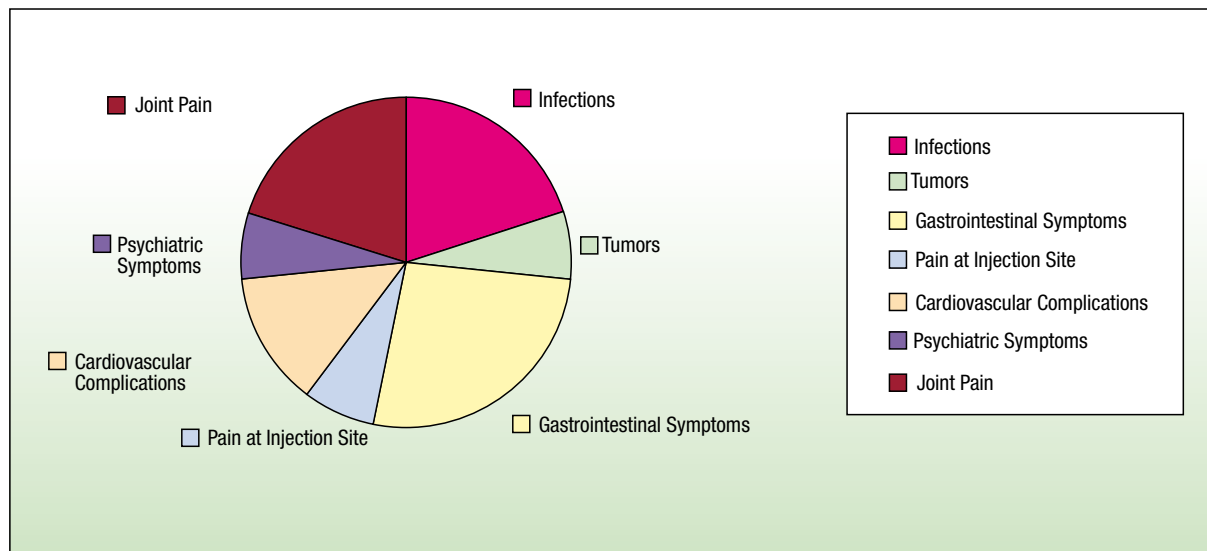


Figure 5 Types of adverse reactions.

48 weeks was similar to the proportion achieving that level of improvement at 24 weeks.

Krueger et al¹¹ also reported extending etanercept treatment (25 mg twice weekly for 48 weeks), continuing an earlier study by Leonardi et al⁶ with patients who had not reached PASI 50 scores at week 24. They concluded that regardless of the doses that had been received in the first 24 weeks, 23% of the 112 patients who had not yet responded were able to reach PASI 75 scores at 60 weeks while 55% improved to PASI 50. As in the earlier study, response rates were higher in patients receiving lower doses of etanercept (a weekly dose of 25 mg vs 25 mg twice weekly): 23% of those on the weekly regimen and 27% of those on the twice weekly regimen achieved PASI 75. Similar results for the safety and efficacy of etanercept treatment continuing up to 2.5 years were reported by Elewski et al¹⁴ after a study that extended the research of Papp et al,⁷ Leonardi et al,⁶ and Krueger et al.¹¹

Finally, the safety of long-term administration of etanercept has been demonstrated by several studies. Tying et al¹⁷ enrolled 591 patients on etanercept (50 mg twice weekly); 464 had completed 96 weeks and 147 had completed 144 weeks of treatment. The authors concluded that the rates of adverse events and infections (adjusted for exposure) were similar in patients with extended exposure to etanercept and patients treated with placebo. Numerous studies support the safety of etanercept therapy, confirming that the incidences of serious infections and tumors are not higher than in the general population.^{18,19}

Lebwohl et al²⁰ described the safety of subcutaneous injections of etanercept (25 mg twice weekly for over 7 consecutive years) in patients with rheumatoid arthritis. They concluded that the rates of serious infections and other adverse events continued to be low and stable over time, with no cumulative toxicity as a consequence of prolonged use.

The same conclusions were reached by Weinblatt et al²¹ after 9 years of uninterrupted etanercept use by patients with rheumatoid arthritis.

Our experience supports long-term use of etanercept by psoriasis patients, as the drug has an acceptable efficacy and safety profile.

Conflict of Interest

The authors declare they have no conflicts of interest.

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