

ACTAS Derma-Sifiliográficas

Full English text available at
www.elsevier.es/ad



ORIGINAL ARTICLE

Clinical Characteristics and Disease Course in Patients Treated With Efalizumab Following Suspension of Marketing Authorization by the European Medicines Agency: A Multicenter Observational Study

L. Morell,^{a,*} J.M. Carrascosa,^a C. Ferrándiz,^a M. García-Bustinduy,^b E. Fonseca,^c G. Carretero,^d E. Daudén,^e S.E. Marrón,^f J.L. López-Estebarez,^g M. Ferrán,^h M. Sánchez-Regaña,ⁱ C. Muñoz-Santos,^j I. Belinchón,^k Luis Puig,^l
on behalf of the Spanish Psoriasis Group

^aServicio de Dermatología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain

^bServicio de Dermatología, Hospital Universitario de Canarias, Islas Canarias, Spain

^cServicio de Dermatología, Hospital Juan Canalejo, La Coruña, Spain

^dServicio de Dermatología, Hospital Universitario de Canarias Dr. Negrín, Islas Canarias, Spain

^eServicio de Dermatología, Hospital Universitario de la Princesa, Madrid, Spain

^fServicio de Dermatología, Hospital de Calatayud, Instituto Aragonés de Ciencias de la Salud, Zaragoza, Spain

^gServicio de Dermatología, Hospital de Alcorcón, Madrid, Spain

^hServicio de Dermatología, Hospital del Mar, Barcelona, Spain

ⁱServicio de Dermatología, Hospital del Sagrat Cor, Barcelona, Spain

^jServicio de Dermatología, Hospital Clínic i Provincial, Barcelona, Spain

^kServicio de Dermatología, Hospital General de Alicante, Alicante, Spain

^lServicio de Dermatología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Manuscript received October 22, 2010; accepted for publication December 20, 2010

KEYWORDS

Efalizumab;
European Medicines
Agency;
Rebound;
Generalized
inflammatory flare

Abstract

Background and objectives: The withdrawal of marketing authorization for efalizumab by the European Medicines Agency in February, 2009 provided a unique opportunity to assess the course of disease in patients who were not subject to the selection criteria and biases that were common in the pivotal trials. The aim of this study was to evaluate the course of psoriasis following forced suspension of efalizumab in a group of patients treated in normal clinical practice. As secondary objectives, we sought to assess the relationships between clinical characteristics, treatment response, and disease course during efalizumab treatment and 12 and 24 weeks after suspension.

*Corresponding author.

E-mail address: laiamorell@hotmail.com (L. Morell).

Patients and methods: Information on the epidemiological profile and disease course during treatment and following suspension of the drug was collected from a group of patients treated with efalizumab. Statistical analyses were performed to identify predictive factors. **Results:** One hundred forty-seven patients from 12 Spanish hospitals were included in the study. During treatment, 4% of patients were diagnosed with generalized inflammatory flares. Most patients could be classified as having a good (55%) or moderate (18%) response to treatment. Rebound following withdrawal of efalizumab was observed in 30% of patients. The likelihood of rebound was independent of clinical characteristics, treatment response, or therapeutic approach used by the dermatologist following suspension.

Conclusions: There was a high frequency of rebound following suspension of efalizumab, exceeding the rate reported in pivotal trials. This is particularly noteworthy given the large proportion of patients with a good response to treatment and therefore believed to have a better prognosis. Other significant findings were the higher frequency of positive treatment response than observed in previous studies (possibly influenced by the mean treatment duration) and the high frequency of generalized inflammatory flares.

© 2010 Elsevier España, S.L. and AEDV. All rights reserved.

PALABRAS CLAVE

Efalizumab;
 EMEA;
 Rebote;
 Exacerbación
 inflamatoria
 generalizada

Perfil clínico y curso evolutivo de los pacientes tratados con efalizumab tras la suspensión de su autorización por la EMEA. Estudio observacional y multicéntrico

Introducción: La reciente resolución de la EMEA con respecto a la suspensión de efalizumab, ocurrida en febrero del año 2009, ha proporcionado una oportunidad única para comprobar la evolución de un grupo de pacientes en cuya selección no intervinieron los filtros ni los sesgos habituales de los estudios pivotales. El objetivo planteado fue evaluar el curso de la psoriasis tras la suspensión forzosa de efalizumab en un grupo de pacientes tratados en el ámbito clínico. Como objetivos secundarios se planteó investigar su perfil clínico, la respuesta y evolución durante el tratamiento y el curso evolutivo a las 12 y 24 semanas tras la suspensión.

Pacientes y métodos: Se recogió información procedente de un grupo de pacientes tratados con efalizumab referida al perfil epidemiológico, al curso de la dermatosis durante el tratamiento y a su evolución al suspenderlo. Se llevaron a cabo estudios estadísticos con vistas a identificar variables predictivas de los distintos objetivos investigados.

Resultados: Se incluyeron 147 pacientes procedentes de 12 centros hospitalarios nacionales. Durante el tratamiento un 4% de los pacientes fue diagnosticado de exacerbación inflamatoria generalizada. La mayor parte de los pacientes pudieron ser clasificados como buenos respondedores (55%) o respondedores moderados (18%). Un 30% de los pacientes presentaron rebote tras la suspensión de efalizumab. La probabilidad de rebote fue independiente del perfil clínico, la respuesta al tratamiento o la actitud terapéutica del dermatólogo al suspenderlo.

Discusión y conclusiones: Se comprobó una elevada ocurrencia de fenómeno de rebote tras la suspensión de efalizumab, superior a la descrita en los ensayos clínicos pivotales y especialmente significativa si se tiene en cuenta la elevada incidencia de buenos respondedores durante el tratamiento, considerados de mejor pronóstico. Otros datos significativos son la superior perspectiva de respuesta clínica —presumiblemente condicionada por el tiempo medio de tratamiento—, y la elevada incidencia de episodios de exacerbación inflamatoria generalizada.

© 2010 Elsevier España, S.L. y AEDV. Todos los derechos reservados.

Introduction

When biologics were introduced for the treatment of psoriasis, great effort went into conducting research with these new agents and publishing the findings. Dermatologists therefore have at their disposal extensive high-quality information from multicenter pivotal trials.^{1,2} This information is subject to regular reviews and metaanalyses, with the corresponding increase in the level of evidence.³⁻⁵ However, although the clinical trials reported were subject to strict

requirements, a general problem with such trials is that the clinical-trial setting and its associated limitations do not always reflect everyday clinical practice. The decision in February 2009 by the European Medicines Agency (EMA) to withdraw marketing authorization for efalizumab created an exceptional circumstance. The forced discontinuation of this drug in a short period of time for reasons not related to therapeutic response and regardless of the clinical situation of the patient provided a unique opportunity to compare the disease course in a group of patients who

were not subject to the selection criteria and biases that were common in the pivotal trials. The assessment of their clinical characteristics and outcomes during treatment and after discontinuation should not only provide information on the characteristics of patients with moderate and severe psoriasis in treatment with biologics in Spain but also on the disease course after discontinuing efalizumab with regard to the different therapeutic strategies adopted. Thus, comparison is possible with that expected according to the pivotal clinical trials.

The primary objective of this study consisted of assessing the course of psoriasis after discontinuing treatment with efalizumab, with particular focus on recurrences and rebound, and of studying a possible association of these outcomes with the treatment and the approach adopted after discontinuation.

Secondary objectives included investigation of the clinical and epidemiological profile of patients treated with efalizumab in Spain in order to identify factors predictive of therapeutic response and side effects related to psoriasis. In addition, the clinical course of psoriasis in the short and medium term was investigated after discontinuation of efalizumab with respect to different clinical variables and outcomes during treatment. Finally, the possibility of epidemiological and clinical or prognostic differences according to efalizumab treatment duration was investigated.

Materials and Methods

This was a retrospective, multicenter observational study. Data were collected with a questionnaire distributed to the members of the Spanish Psoriasis Group. The questionnaire included a table that was filled out with data on the epidemiological profile of the patients, the clinical course during and after treatment with efalizumab, and psoriasis outcome at 12 and 24 weeks after discontinuation of treatment. Information was collected on the approaches taken by dermatologists to minimize the impact of discontinuation of efalizumab.

The percentage improvement in the Psoriasis Area and Severity Index (PASI) at the time of discontinuation compared to the PASI on initiation of treatment was used to assess the response to efalizumab. Patients were classified into 3 categories according to the response to efalizumab: good responders, moderate responders, and nonresponders. Patients with a 75% improvement in the PASI (PASI75) were classed as good responders, those with an improvement between 50% (PASI50) and 75% as moderate responders, and those with an improvement no better than 50% as nonresponders. In some parts of the results and discussion, those patients with good and moderate response have been pooled and described as having "satisfactory response," to reflect the definition used in some of the pivotal trials. With regard to adverse effects that occurred during treatment, particular attention was paid to those defined as *psoriasis-related*: transient papular eruption and generalized inflammatory flares.⁶

The therapeutic actions of the dermatologists on discontinuing treatment were classed as: a) sudden

discontinuation of efalizumab and clinical follow-up (watchful waiting) or b) sudden discontinuation of efalizumab and immediate initiation of another systemic treatment without any transition or overlap of efalizumab with another drug prior to discontinuation.

The outcomes assessed after discontinuation of treatment were presence of rebound or recurrence, as well as the mean PASI at 12 and 24 weeks. Recurrence has been defined by the National Psoriasis Foundation as loss of PASI50 in responders. In the pivotal clinical trials, recurrences were defined as occurring only when this decrease occurred in the first 12 weeks after discontinuation of efalizumab.⁶⁻⁸ Given the difficulty of standardizing this concept among different authors, and the retrospective nature of the study, the first definition was used. Rebound was defined as when the PASI reached a value 125% greater than the baseline one, a change occurred in the morphology of psoriasis, or onset of arthritis occurred in patients who did not previously have the condition within 3 months of discontinuation of efalizumab.^{6,9} The therapeutic approaches for dealing with efalizumab-related adverse effects and with recurrences or rebound were also recorded.

To assess the course of psoriasis at 12 and 24 weeks, the PASI and percentage body surface area (BSA) involvement were recorded at these 2 times. These results were compared with the PASI at the start and finish of efalizumab treatment.

Statistical Analysis

A possible statistically significant relation between the different study outcomes and data evaluated was studied.

To determine whether there were differences between the baseline PASI or BSA according to response to treatment, a nonparametric analysis of variance was employed (Kruskal-Wallis test).

To assess whether there was an association between treatment response and psoriasis-related adverse effects (generalized inflammatory flare and transient papular eruption), the Mann-Whitney test was used.

To determine whether there were differences in the baseline PASI among the different groups according to the approach followed after treatment discontinuation, the Kruskal-Wallis test was used. The same test was used to assess treatment response according to approach followed.

For the analysis of rebound effects and recurrence, and the possible association with other descriptive data, the χ^2 test was used. The association of these events with treatment response and with the PASI on discontinuation of treatment was analyzed using the Mann-Whitney test.

To assess whether there were differences in the PASI on discontinuation of treatment and the 3 strategies followed after discontinuation, nonparametric analysis of variance was used (Kruskal-Wallis test) as well as a parametric analysis of variance with log-transformed data (to ensure a closer approximation to a normal distribution).

To analyze whether there were statistically significant differences in the PASI at 12 and 24 weeks according to approach followed, the Kruskal-Wallis test was used.

Given that the long average treatment duration could have positively selected for good responders in our series, for certain analyses, patients were stratified into 2 groups according to treatment duration. The cut-off was 6 months, the duration used for the peak response to the drug in clinical trials.¹⁰ The analysis of possible group differences in the baseline PASI or BSA was performed using the Mann-Whitney test.

The analysis of possible group differences in therapeutic response was performed using the χ^2 test and the Mann-Whitney test.

For differences between the 2 groups in terms of generalized inflammatory flare and rebound, the χ^2 test and Fisher exact test were used.

The differences in terms of developing transient papular eruption and recurrence were analyzed using the χ^2 test.

Results

Disease History and Epidemiological Characteristics

In total, 147 patients were included from 12 Spanish hospitals. The mean (SD) age on initiating treatment with efalizumab was 46 (14) years (range, 17-83 years) and the mean weight was 76 (14) kg (range, 46-118 kg). The patients' sex was not reported. A family history of psoriasis was reported for 36% (53 patients). The most common clinical form of psoriasis was plaque psoriasis (135 [91%]), followed by palmoplantar psoriasis whether or not accompanied by plaques (9 [6%]), guttate psoriasis (2 [1.3%]), and finally inverse psoriasis associated with a plaque morphology (1 [0.6%]). Only 2 patients (1.3%) had shown clinical signs and symptoms of psoriatic arthritis prior to initiation of treatment. Most patients (135 [91.8%]) had previously received systemic treatments for psoriasis, although only 6% (9 patients) had required admission to

hospital (Table 1). The prior treatments administered most frequently were, in descending order, methotrexate, retinoids, ciclosporin A, and phototherapy, followed by different biological treatments (Figure 1). Two or more systemic treatments had been administered to 68% prior to efalizumab (Figure 2).

History of Efalizumab Treatment

The mean cumulative duration of efalizumab treatment was 18 (13.6) months (range, 1-46 months). Prior to treatment, the mean PASI (data available for 119 patients) was 12.38 (8.25) (range, 0.2-50.7), and the mean BSA (data available for 94 patients) was 17.6 (range, 1-74.4). While the patients were on treatment, none had signs of psoriatic arthritis attributable to the drug. With regard to psoriasis-related side effects, 4% of the patients (6/147) had a generalized inflammatory flare, and the development of clinical signs and symptoms compatible with transient papular eruption was reported in 12% (18/147). The generalized inflammatory flares were controlled largely with systemic treatment, in particular, methotrexate (4/6 patients), whereas topical treatment was used in 2 patients. Transient papular eruption required treatment in 77% of the cases (14/18). Topical corticoids were the treatment most frequently used (12 cases), followed by acitretin (1 case), and oral antihistamine treatment (1 case).

At the time of forced treatment discontinuation, the mean PASI was 3.7 (4.79) (range, 0-30; n=113) and the mean BSA was 6.7 (range, 0-55; n=89). The mean percentage improvement in the PASI and BSA between start and end of treatment was 70% and 62% respectively. According to the difference between the PASI at start and end of treatment, for the 100 patients with data available, most were classified as good responders (55%) or moderate responders (18%). In contrast, 27% were considered as nonresponders (Figure 3).

Table 1 Summary of Clinical and Epidemiological Characteristics of the Patients Included in the Study

Variable	Value
No. of patients	147
Mean age	46 y
Mean weight	76 kg
Family history	53 (36%)
Form of psoriasis	Plaques: 135 (91%) Palmoplantar: 9 (6%) Guttate: 2 (1.3%) Inverse: 1 (0.6%)
Psoriatic arthritis	2 (1.3%)
Admission to hospital	9 (6%)
Prior systemic treatments	≥ 1: 135 (91.8%) ≥ 2: 101 (68.7%) Methotrexate: 89 (60.5%) Retinoids: 85 (57.8%) Ciclosporin A: 75 (51%) Phototherapy: 67 (45.5%) Biologics: 14 (9.5%)

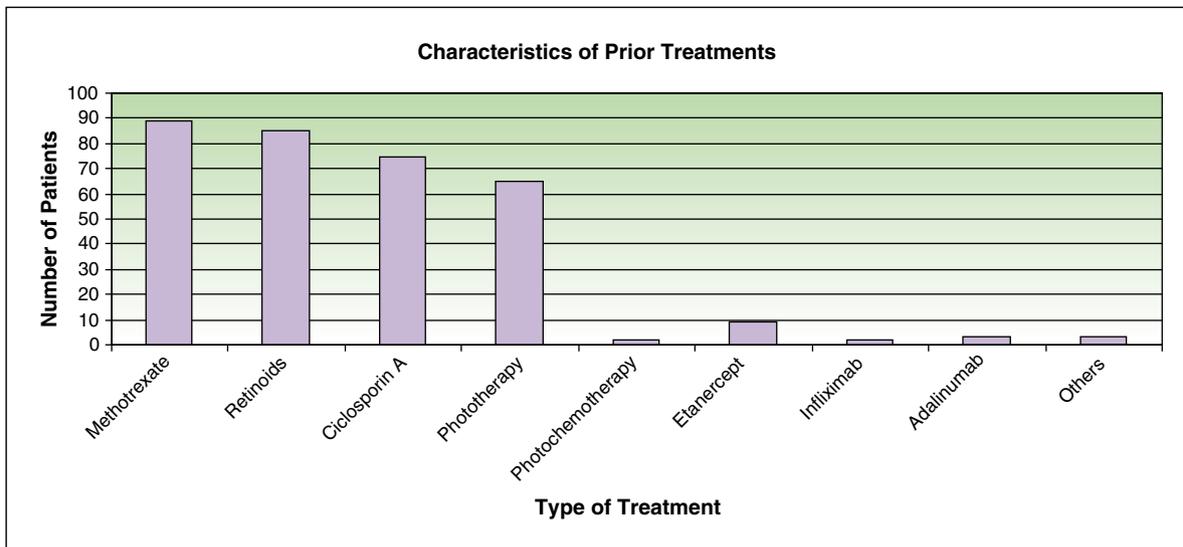


Figure 1 Prior systemic treatments before initiation of efalizumab.

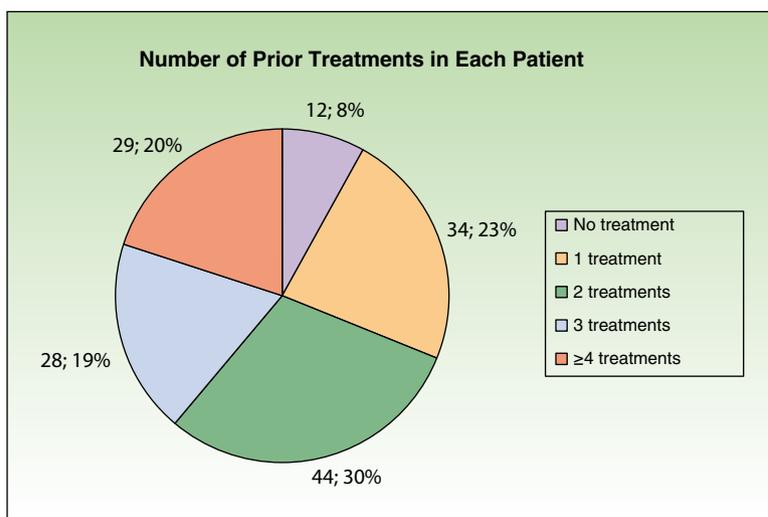


Figure 2 Number of systemic treatments administered prior to efalizumab in each patient.

Clinical Factors Predictive of Therapeutic Response

In the statistical analysis, a significant relationship ($P < .01$) between the baseline PASI and response to treatment was found. Thus, the baseline PASI was higher in good responders (mean, 12.3) and moderate responders (mean, 12.9) than in nonresponders (mean, 6.1). This relationship between baseline disease and treatment response was also observed when BSA was used as a measure of initial disease severity ($P < .05$).

In contrast, those patients who had a generalized inflammatory flare (6/ 147) had a worse response compared to those who did not experience this adverse effect ($P < .05$). In fact, of the 4 patients who presented this adverse effect and for whom information on response to efalizumab was

available, 3 were classed as nonresponders. However, a statistically significant relationship between treatment response and development of transient papular eruption was not found.

Approach After Suspension of Efalizumab

In 39% of the patients (57/ 145), the dermatologists decided to discontinue treatment and maintain a watchful waiting approach. In the remaining patients, the physicians chose to overlap treatments (44/ 145 patients [30%]) or discontinue efalizumab and immediately start another treatment (44/ 145 patients [30%]). The most common treatments used for overlap and switching were methotrexate, etanercept, and cyclosporin (Table 2). The mean duration of overlap was 7 weeks (range, 1-20 weeks).

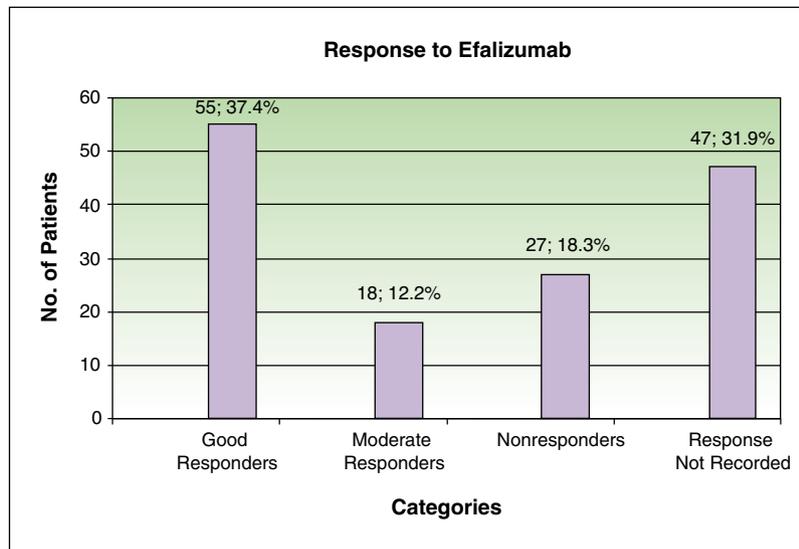


Figure 3 Groups of response to efalizumab according to improvement in PASI.

Association Between Epidemiological Characteristics and Clinical Course of Treatment By Approach

The baseline PASI was significantly greater ($P < .01$) in patients submitted to watchful waiting (mean, 14.48) and in those in whom efalizumab overlapped with another treatment (mean, 13.29), compared to those with the decision to discontinue efalizumab and start another treatment immediately (mean, 8.80).

There was no significant relationship between approach and epidemiological variables, treatment response, or psoriasis-related adverse effects (generalized inflammatory flare and transient papular eruption).

The PASI at the end of treatment did not show any significant differences for any of the 3 approaches.

Course of Psoriasis on Discontinuing Treatment

A rebound effect was reported in 30% of the patients (44/ 142) after a mean of 6 weeks (range, 1-

12 weeks; median, 6). This was usually in the form of a morphological change with respect to the prior psoriasis, with generalized appearance of guttate psoriasis or small plaques (66% 29/ 44 patients) or of pustular psoriasis (16% 7/ 44). Other clinical variants included in the definition of rebound are shown in Figure 4.

In the established follow-up period of 24 weeks, a further 45% (62/ 137) had a recurrence after a mean of 8 weeks (range, 1-20 weeks).

Twenty-seven patients required another drug to manage rebound or recurrence. In such cases, biologics were the most widely used. Of these, etanercept was the most popular, used in 62% of the patients. The different drugs used are shown in Figures 5 and 6.

The mean PASI and BSA at 12 weeks after discontinuation of efalizumab were 6.87 (range, 0-33.6; $n=114$) and 12.64 (range, 0-80; $n=87$), respectively. At 24 weeks, the values were 2.90 (range, 0-14.6; $n=63$) and 5.24 (range, 0-43; $n=87$), respectively.

Association Between Clinical Variables and Dermatological Approach and the Risk of Rebound or Recurrence

None of the clinical variables assessed were identified as predictive of rebound or recurrence. Likewise, the approach taken by the dermatologist after discontinuation of the drug had no effect on the subsequent risk of reappearance of dermatosis in the form of rebound or recurrence.

Association Between Clinical Variables and Dermatological Approach and Response at 12 and 24 Weeks

There was no statistically significant association between approach taken and response at 12 or 24 weeks.

Table 2 List of Different Treatments Used for Transition or Switching When Efalizumab Was Discontinued

Drug Used	Approach		Total
	Overlap	Switch	
Methotrexate	17	7	24
Ciclosporin	15	4	19
Acitretin	6	4	10
UV-B NB	1	0	1
PUVA	1	1	2
Etanercept	2	19	21
Adalimumab	1	9	10

Abbreviations: PUVA: psoralen-UV-A; UV-B NB: narrow band UV-B light.

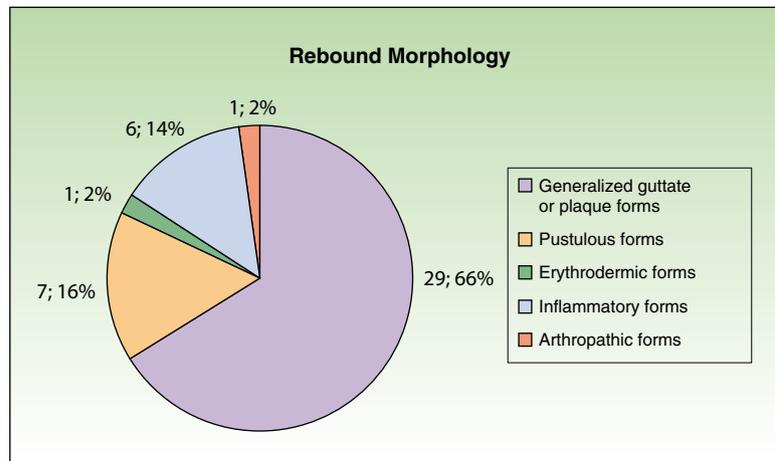


Figure 4 Clinical variants of rebound phenomena after discontinuation of efalizumab.

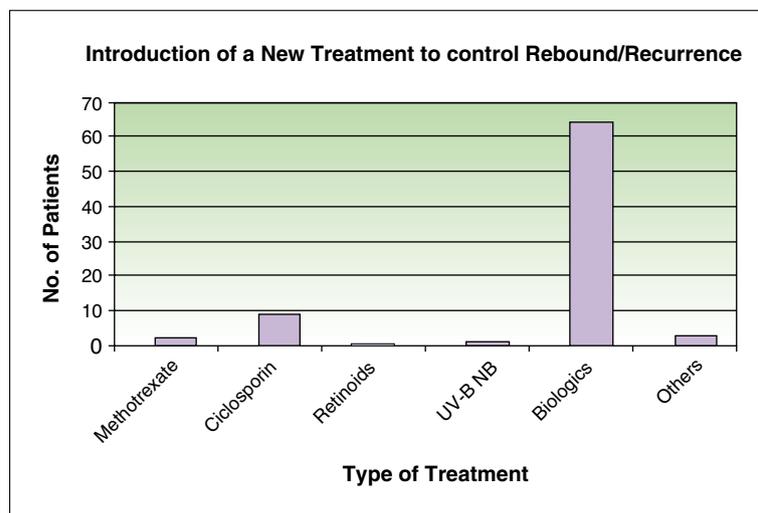


Figure 5 Drugs used to control psoriasis after discontinuation of efalizumab.

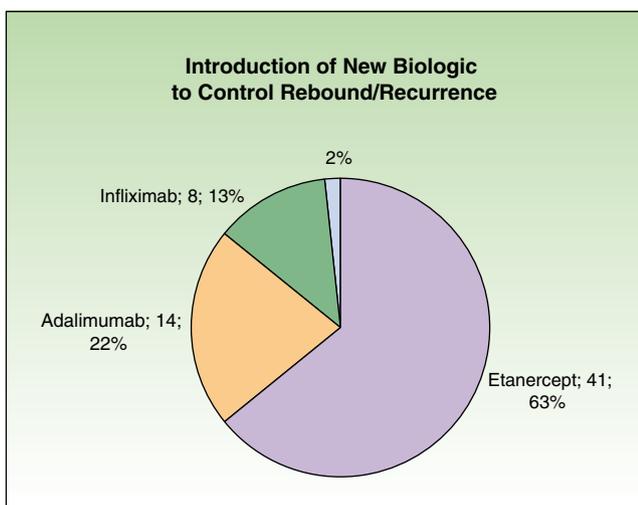


Figure 6 Detail of biologics used to control psoriasis after discontinuation of efalizumab.

Relationship Between Type of Drug Used for Switching/Overlap and PASI at 12 Weeks and 24 Weeks Compared to PASI at the End of Efalizumab Treatment

There were no statistically significant differences between PASI response at 12 weeks or 24 weeks (compared to PASI at the end of efalizumab treatment) according to type of treatment initiated after suspension of efalizumab.

However, differences were observed, although not significant ones, in PASI response at 12 weeks according to treatment chosen. Thus, 20.7% of the patients who received biologics were responders (moderate and good) compared to 6.3% of those who were given conventional drugs. For this analysis, a 2-tailed test (Fisher exact test) was applied, with $P=0.14$ and a statistical power of just 38.3%. The reason why these differences were not significant was attributed to the sample size, which needed to be 3 times larger than the actual sample size available.

Relationship Between Medium-term Psoriasis Outcome and PASI on Initiating and Discontinuing Treatment

The mean PASI at 12 and 24 weeks improved compared to the mean PASI at baseline (45% and 80% lower, respectively). The mean PASI at 12 weeks after discontinuation was greater than that obtained when efalizumab was discontinued (mean worsening of 83%). However, 12 weeks later, the mean PASI recovered to 35% lower than the value observed at the end of treatment. No differences were found according to whether or not patients were responders or nonresponders to efalizumab (PASI of 7.41 and 7.50, respectively, at 12 weeks and of 2.73 and 2.26, respectively, at 24 weeks).

Taking into account only patients for whom data at 12 and 24 weeks after discontinuation of efalizumab were available (57 patients), and assuming improvement of at least PASI50, it was found that 43.85% (25 patients) could have been considered as having satisfactory response (good or moderate responders). Of these, only 31% (18 patients) achieved PASI75 (good response). On analysis of the same variable at 24 weeks, satisfactory responders accounted for 82.45% (47 patients), most of whom attained PASI75 (68.42% [39 patients]).

Relationship Between Treatment Duration and Clinical Variables and Outcomes

Overall, patients receiving long-term efalizumab treatment (more than 6 months) had significantly higher baseline BSA values than the other patients. However, differences in terms of baseline PASI were not significant. Patients treated for more than 6 months did, however, show a trend towards greater therapeutic response ($P=.07$) and a lower incidence of generalized inflammatory flares ($P=.06$).

No statistically significant relationship was found between treatment duration and subsequent rebound or recurrence.

Study Limitations

This was a descriptive, retrospective study in which the recruiting centers applied their own follow-up protocols. There are therefore certain intrinsic design limitations such as biased patient selection. Probably as a result of retrospective data collection, the PASI and BSA at the start and end of treatment were not available for some patients. Although the statistical analysis has addressed the impact of these missing data, this should be taken into account when interpreting the results.

Of note regarding duration of efalizumab treatment is that all patients finished treatment at the same time, as the end date was taken to be February 2009, without taking into account other aspects (transition in medication, delay until the patient attended the clinic, etc.).

Discussion

The arrival of biologics has had a big impact on the management of patients with moderate to severe psoriasis in dermatology clinics.

The present retrospective analysis of a sizeable sample of patients from 12 Spanish hospitals is illustrative not only for the description of the outcomes of psoriasis treatment, but also because it allows comparison of the profile of patients with moderate and severe psoriasis who received biologic therapy in Spain—at least over the study period. We found statistically significant differences between the findings from pivotal clinical trials and behavior in clinical practice, in particular with regard to the safety profile.

From an epidemiological point of view, of note was the mean weight of the patients, which was significantly lower than that of other series.^{1,11} Biases may have arisen because the sex of the patients was not recorded. For the most part, the patients had guttate psoriasis, an observation which can largely be explained by the indication given in the prescribing information.¹ It was noteworthy, however, that 6% of the patients were treated for the indication of palmoplantar psoriasis. The presence of such patients in the sample is probably due to a number of articles on effectiveness of efalizumab in case reports and reports of small series of patients with this variant; indeed a specific clinical trial was ongoing at the time when the product was withdrawn.¹²⁻¹⁵ Other variables, such as the mean baseline PASI, the high number of prior systemic therapies, or the low prevalence of psoriatic arthritis strongly reflected the indication for the drug, which is restricted to skin manifestations without involvement of the joints, and also the requirements laid down by the EMA for prescription of the drug.¹ The prior systemic drugs reported were those that are commonplace in Spain, as recorded in the BIOBADADERM database.¹⁶ The lack of other biologics in the medical history of the patients can be readily explained by the fact that efalizumab was the first of the new group of biologics to become available.

The mean treatment duration in the group studied was 18 months, although some patients received treatment for several years. Given that peak response was expected after 6 months of treatment, there was clearly a risk of selection bias, as most patients recruited were good responders, whereas most moderate responders and, in particular, nonresponders, would have switched to alternative therapies after a few months on efalizumab. This probably explains why the percentage of responders in our series was higher than that observed in several clinical series and in pivotal clinical trials.^{1,17-20} In the statistical analysis, a higher baseline PASI was associated with a higher probability of satisfactory response. This apparently paradoxical observation can be explained if we remember that the target for satisfactory response (PASI75) is harder to attain with limited baseline disease.

In order to limit the impact of this bias, the patients were stratified according to duration of treatment. As expected, response was lower in the subgroup of patients treated for less than 6 months, although the differences were not statistically significant.

One of the features of efalizumab treatment in this study was the development of psoriasis-related side effects.²¹ The most common, and also the least clinically

significant, was transient papular eruption. Typically, the onset of this event occurs within the first 4 to 8 weeks of starting efalizumab. A papular lesion, usually affecting areas of previously healthy skin, forms with a preference for the neck, torso, or flexures.^{6,22,23} In the current series, transient papular eruption was diagnosed in 11% of the patients. The percentage was lower than expected from pivotal clinical trials, in which this event was reported in 25% to 33%. The outcome, as reflected in the literature, is benign in most patients and, if treated at all, topical corticosteroids are usually used.^{6,22,23} In fact, the benign nature of the process probably means that some of the mildest cases are not recorded in the everyday medical histories, which are not subject to the strict reporting requirements of clinical trials. Less common, though much more serious, is generalized inflammatory flare. This was reported in 4% of our patients (6/147), almost always in the form of inflammatory exacerbation of existing psoriatic plaques, at times accompanied by the appearance of lesions in previously unaffected areas. This percentage contrasts with that reported in pivotal clinical trials (1%–3%).⁶ Unlike transient papular eruption, generalized inflammatory flare is a serious adverse effect that has been considered more common in patients who do not respond to efalizumab.^{6,24,25} Often, systemic drugs are needed to control the event, and it often also leads to discontinuation of efalizumab.⁶ Of note is the high incidence of generalized inflammatory flare in our series. Given that good responders were overrepresented, the incidence could have been higher still if our sample had included all patients who received efalizumab at some time during their disease. In fact, it was observed in 9.5% of the patients with a treatment duration greater than 6 months compared to 1.9% of those with a shorter treatment duration. However, the differences in the incidence of this adverse effect with regard to treatment duration were not quite significant ($P=.06$), probably because of the low absolute number of reported episodes. The development of generalized inflammatory flare was, however, associated with a lower likelihood of satisfactory response, in line with previous studies.^{6,24,25}

The description of the therapeutic approach of the dermatologist on discontinuing the drug and the subsequent development of rebound or recurrence is one of the most interesting aspects of the study, as it is an anomalous situation in every day clinical practice and simulates the conditions imposed in clinical trials.^{25–27}

When treatment was discontinued, the majority of the physicians decided to start some other treatment, either overlapping with efalizumab while this was phased out or immediately discontinuing efalizumab then initiating a new treatment. The initiation of a different treatment is reasonable in view of the chronic course of moderate to severe psoriasis in most patients. Regimens with overlap and the suggested replacement drugs were chosen according to the personal experience of experts or small open-label studies with a low level of evidence.^{25,26,28} Both the number of weeks of overlap and the drugs employed overall corresponded with those reported in these articles and were consistent with the likelihood of initiating a response for the different drugs.

It should, however, be noted that the dermatologists decided to discontinue treatment and observe the natural course of the disease in up to 39% of the patients. Such an approach can be justified in a number of ways. First, the findings of clinical trials suggest that the natural disease course was, in most cases, benign in patients classed as good responders—most of the present group—with a latency period until recurrence of more than 60 days and a very low incidence of rebound episodes.^{6,22} In addition, and taking into account the high variability in baseline PASI, it might be supposed that a non-negligible percentage of patients had moderate psoriasis with a stable course. In such cases, watchful waiting or complementary use of topical treatments would be considered sufficient initially.

In those patients in whom the physician decided to replace efalizumab with another biologic, the most widely used approach was immediate discontinuation and initiation with the new drug. This is a reasonable approach bearing in mind the limited evidence for the safety of concomitant treatment with different biologics.

In the statistical analysis, it is perhaps surprising that the approach of overlap or therapeutic replacement was more frequent in those patients with a lower baseline PASI. However, it may be that a lower baseline PASI does not necessarily reflect less severe disease, as these patients could have been in active treatment with other established drugs before receiving efalizumab, and have decided to switch to the biologic because of poor tolerance, insufficient response, or risk of cumulative toxicity.

No other statistically significant relationship was found between the approach adopted and the different clinical variables assessed. This makes it difficult to determine the priorities of the dermatologists responsible for taking the decision.

The most relevant finding of our study is the high incidence of rebound and recurrence after discontinuing treatment.

One out of every 3 patients had rebound after suspending treatment. For the most part, rebound manifested as a change in disease morphology, as reported in another recently published series,²⁹ as well as a greater extent of psoriasis compared with baseline. Rebound is reported as a possible but infrequent complication of discontinuation with efalizumab, with an overall incidence of 14% in pivotal trials.^{6,22} However, the risk was reported as higher in poor responders, with an incidence of 25%.⁶ The high incidence of rebound in our group (33%) is therefore particularly noteworthy, given the high proportion of good responders in our sample. Measures to minimize the risk of rebound were taken in 60% of these good responders. This is consistent with the statistical analysis performed, according to which none of the clinical variables assessed or the therapeutic approach chosen by the dermatologist could help predict this adverse effect, although it was more frequent when the approach was watchful waiting after discontinuing treatment. Likewise, there were no statistically significant differences in terms of rebound or recurrence according to treatment duration.

While the 12-week assessment indicated a loss of response with respect to PASI on discontinuation of

treatment with efalizumab, PAS decreased once again at 24 weeks, presumably due to newly prescribed drugs. The PAS on starting treatment with efalizumab was not a factor that influenced the subsequent psoriasis outcome at 12 and 24 weeks after discontinuation of efalizumab. Overall, response or lack of response to efalizumab did not have an impact on outcome either. The variety of drugs used and the heterogeneous nature of the regimens prevented an evaluation of whether some drugs in particular achieved better outcomes than the others, although the short-term results at 12 weeks were somewhat better when biologics were used.

Regardless of drug and approach used, control of psoriasis at 24 weeks after discontinuation of efalizumab was comparable or even better than the control obtained with this drug (percentage of patients with PAS50 was 82.45% vs 73%). This provides evidence for the effectiveness of the different therapeutic resources available for dermatologists for control of moderate and severe psoriasis.

A finding of particular note is the higher than expected incidence of psoriasis-related adverse events during treatment with efalizumab and the development of rebound after discontinuation.

Our findings suggests that the pivotal clinical trials, although clearly of great value and scientific weight, are not always predictive of the results obtained in clinical practice, whether because of the profile of patients included, the study design, or limited follow-up.

Conflict of Interest

Abbott Laboratories contributed to the study through funding of the statistical analysis. This analysis was, however, performed by an independent company. Abbott had no knowledge of the content of this manuscript prior to publishing and did not participate in its publication.

José M. Carrascosa, Carlos Ferrándiz, Eduardo Fonseca, Isabel Belinchón, José L. López Estebanz, Gregorio Carretero, Marta Ferrán, Manuel Sánchez-Pegaña, Esteban Daudén, and Lluís Puig have received fees as conference speakers, consultants, or as investigators in clinical trials sponsored by some of the following companies: Merck-Serono, Wyeth Pharmaceuticals (Pfizer), Schering-Plough, Abbott, Janssen, Novartis, Leo Pharma, Amgen, Astellas, Biogen, Centocor Ortho Biotech Inc., Galderma, Glaxo, Stiefel, 3M, and Celgene.

The remaining authors declare they have no potential conflict of interest with the content of the present manuscript.

Acknowledgments

We thank ALCE Ingeniería for their support with the statistical analysis, Abbott Laboratories for their financial support of the statistical analysis, and all study centers for their collaboration in data collection.

References

- Dubertret L, Sterry W, Bos JD, Chimenti S, Shumack S, Larsen CG, et al. Clinical experience acquired with the efalizumab (Raptiva®) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from a phase III international randomized, placebo-controlled trial. *Br J Dermatol.* 2006;155:170-81.
- Hamilton T, Menter A, Caro I, Compton P, Sobell J, Papp KA. Safety of efalizumab therapy in patients with moderate to severe psoriasis: an open label extension of a phase IIIb trial. *Drug Saf.* 2008;31:715-26.
- Brimhall AK, King LN, Licciardone JC, Jacobe H, Menter A. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. *Br J Dermatol.* 2008;159:274-85.
- Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. *Br J Dermatol.* 2008;159:513-26.
- Zhang Z, Schmitt J, Wozel G, Kirch W. Treatment of plaque psoriasis with biologics. A meta-analysis of randomized controlled trials. *Med Klin.* 2009;104:125-36.
- Carey W, Glazer S, Gottlieb A, Lebwohl M, Leonardi G, Menter A, et al. Relapse, rebound and psoriasis adverse events: An advisory group report. *J Am Acad Dermatol.* 2006;54:S171-181.
- Gordon KB, Feldman SR, Koo JY, Menter A, Rblstad T, Krueger G. Definitions of measures of effect duration for psoriasis treatments. *Arch Dermatol.* 2005;141:82-4.
- Papp K, Miller B, Gordon KB, Caro I, Kwon P, Compton PG, et al. Efalizumab retreatment in patients with moderate to severe chronic plaque psoriasis. *J Am Acad Dermatol.* 2006;54:S164-170.
- Selenko-Gebauer N, Karlhofer F, Singl G. Efalizumab in routine use: a clinical experience. *Br J Dermatol.* 2007;156(Suppl 2):1-6.
- Sengel FM, Petri V, Campbell GA, Dorantes GL, López M, Galimberti RL, et al. Control of moderate-to-severe plaque psoriasis with efalizumab: 24-week, open label, phase IIIb/IV Latin American study results. *Arch Drug Inf.* 2009;2:71-8.
- Pincelli C, Henninger E, Casset-Semanaz F. The incidence of arthropathy adverse events in efalizumab-treated patients is low and similar to placebo and does not increase with long term treatment: pooled analysis of data from Phase III clinical trials of efalizumab. *Arch Dermatol Res.* 2006;298:329-38.
- Estudio TRUST. Available from: <http://clinicaltrials.gov/ct2/show/NCT00972543>.
- Colsmán A, Carrascosa JM, Ferrándiz C, Smon JC. Successful treatment of recalcitrant palmoplantar psoriasis with efalizumab. *J Eur Acad Dermatol Venereol.* 2008;22:1131-4.
- Wozel G, Vitéz L, Meurer M. Palmoplantar pustular psoriasis: successful therapy with efalizumab after non-response to infliximab. *Actas Dermatovenereol Alp Panonica Adriat.* 2008;17:133-6.
- Ferrándiz C, Carrascosa JM. Managing moderate-to-severe psoriasis with efalizumab: experience at a single Spanish institute. *Br J Dermatol.* 2007;156(Suppl 2):24-9.
- Biobadaderm Database (Spanish Academy for Dermatology and Venereology).
- Gordon KB, Papp KA, Hamilton TK, Walicke PA, Drummer W, Li N, et al. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA.* 2003;290:3073-80.
- Lebwohl M, Trying SK, Hamilton TK, Toth D, Glazer S, Tawfik NH, et al. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med.* 2003;349:2004-13.

19. Leonardi CL, Papp KA, Gordon KB, Menter A, Feldman SR, Caro I, et al. Extended efalizumab therapy improves chronic plaque psoriasis: results from a randomized phase III trial. *J Am Acad Dermatol.* 2005;52:425-33.
20. Sánchez-Peña M, Dílmé E, Puig LI, Bordas X, Carrascosa JM, Ferran M, et al. Efectos adversos observados durante la terapia biológica en la psoriasis. Resultados de una encuesta al Grupo Español de Psoriasis. *Actas Dermosifilogr.* 2010;101:156-63.
21. Puig L, Carrascosa JM, Daudén E, Sánchez-Carazo JL, Ferrándiz C, Sánchez-Peña M, et al. Directrices españolas basadas en la evidencia para el tratamiento de la psoriasis moderada a grave con agentes biológicos. *Actas Dermosifilogr.* 2009;100:386-413.
22. Menter A, Leonardi CL, Sterry W, Bos JD, Papp K. Long term management of plaque psoriasis with continuous efalizumab therapy. *J Am Acad Dermatol.* 2006;54(Suppl 1):S182-8.
23. Hamilton TK. Clinical considerations of efalizumab therapy. *Semin Cutan Med Surg.* 2005;24:19-27.
24. Gottlieb AB, Hamilton T, Caro I, Kwon P, Compton PG, Leonardi CL. Long-term continuous efalizumab therapy in patients with moderate to severe chronic plaque psoriasis: Updated results from an ongoing trial. *J Am Acad Dermatol.* 2006;54:S154-163.
25. Papp KA, Toth D, Folsoph L. Approaches to discontinuing efalizumab: an open-label study of therapies for managing inflammatory recurrence. *BMC Dermatology.* 2006;6:9.
26. Menter A, Hamilton TK, Toth DP, Leung HM, Wetherill G, Hennessey B, et al. Transitioning patients from efalizumab to alternative psoriasis therapies: findings from an open-label, multicenter, Phase IIIb study. *Int J Dermatol.* 2007;46:637-48.
27. Antoniou C, Dessinoti C, Vergou T, Stratigos AJ, Avgerinou G, Kostaki M, et al. Sequential treatment with biologics: switching from efalizumab to etanercept in 35 patients with high-need psoriasis. *J Eur Acad Dermatol Venereol.* 2010;24:1413-20.
28. Lebwohl M, Feldman SR, Walther R, Shelk J, Morgan P, Gutkin SW. Clinical management of psoriasis: principles and practice. *Cutis.* 2001;67:1-15.
29. Baniandrés O, Pulido A, Silvente C, Suárez R, Lázaro P. Evolución clínica de los pacientes psoriásicos tratados con efalizumab al suspender el fármaco. *Actas Dermosifilogr.* 2010;101:421-7.