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-Estebaranz,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 Clinic 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

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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.

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**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.3,4 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.

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.4,5 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.4,5 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 \( \chi^2 \) 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. 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 \( \chi^2 \) test and the Mann-Whitney test.

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

The differences in terms of developing transient papular eruption and recurrence were analyzed using the \( \chi^2 \) 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 [13%]), 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>147</td>
</tr>
<tr>
<td>Mean age</td>
<td>46 y</td>
</tr>
<tr>
<td>Mean weight</td>
<td>76 kg</td>
</tr>
<tr>
<td>Family history</td>
<td>53 (36%)</td>
</tr>
<tr>
<td>Form of psoriasis</td>
<td></td>
</tr>
<tr>
<td>Plaques</td>
<td>135 (91%)</td>
</tr>
<tr>
<td>Palmoplantar</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Guttate</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Inverse</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Admission to hospital</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Prior systemic treatments</td>
<td></td>
</tr>
<tr>
<td>≥ 1: 135 (91.8%) ≥ 2: 101 (68.7%)</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>89 (60.5%)</td>
</tr>
<tr>
<td>Retinoids</td>
<td>85 (57.8%)</td>
</tr>
<tr>
<td>Ciclosporin A</td>
<td>75 (51%)</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>67 (45.5%)</td>
</tr>
<tr>
<td>Biologics</td>
<td>14 (9.5%)</td>
</tr>
</tbody>
</table>
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 ciclosporin (Table 2). The mean duration of overlap was 7 weeks (range, 1-20 weeks).
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.
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]).

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.
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.6,21,23 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.4,24,25

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 discontinue 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, PASI decreased once again at 24 weeks, presumably due to newly prescribed drugs. The PASI 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 PASI50 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 suggest 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.

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

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