Clinical Outcomes in Patients With Psoriasis Following Discontinuation of Efalizumab Due to Suspension of Marketing Authorization

O. Baniandrés,* A. Pulido, C. Silvente, R. Suárez, and P. Lázaro

Servicio de Dermatología, Hospital General Universitario Gregorio Marañón, Madrid, Spain

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Abstract

Introduction: In February 2009, the European Medicines Agency suspended the marketing authorization for efalizumab after 3 confirmed cases of progressive multifocal leukoencephalopathy were reported. To assess the consequences of this decision, we performed a prospective follow-up study of patients in our department who were being treated with efalizumab at the time and compared clinical outcomes with data from the literature.

Patients and methods: Thirty-two patients (28 with plaque psoriasis and 4 with palmoplantar psoriasis) were enrolled between February and March 2009. We recorded psoriasis area and severity index (PASI) scores at the moment of efalizumab discontinuation, at 6 weeks post-discontinuation, and at 3-monthly intervals thereafter. PASI scores prior to treatment with efalizumab were also noted. For patients who experienced rebounds with generalized psoriasis, we noted the time that had elapsed since efalizumab discontinuation and the treatment they were receiving.

Results: Even though 92.8% of the patients were considered good responders (>75% reduction in PASI score), 25% of the group (8/32) experienced rebound and 15.7% (5/32) experienced relapse. The percentage of patients in whom rebound was observed on transition therapy was 18% (2/11) for cyclosporin, 50% (1/2) for methotrexate, 50% (1/2) for adalimumab, 50% (1/2) for etanercept, and 27% (3/11) for topical treatment.

Conclusions: We observed a very high rate of rebound and generalized inflammation in patients whose disease had previously been well controlled for several years.

*Corresponding author.
E-mail address: ofelia_baniandres@yahoo.es (O. Baniandrés).

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Introduction
Efailizumab is a humanized monoclonal antibody that binds to the adhesion molecule CD11a and blocks the activation, adhesion, and migration of T cells. In October 2004, the European Medicines Agency (EMA) approved its use for the treatment of moderate and severe psoriasis in patients who did not respond to other systemic therapies or in whom such treatments were contraindicated or poorly tolerated. Numerous short-term clinical trials (lasting 6 months) found efailizumab to be well tolerated, and studies that followed patients that took the drug continuously for up to 3 years reported a favorable safety profile. The situation for users of efailizumab, however, changed suddenly in February 2009, when the EMEA suspended the marketing authorization for the drug after the report of 3 confirmed cases of progressive multifocal leukoencephalopathy (PML) in patients who had been receiving efailizumab for more than 3 years. PML is a progressive demyelinating disease caused by the reactivation of the JC virus. It tends to occur in severely immunocompromised patients and generally leads to severe incapacity and even death. There is no effective treatment. It generally develops in patients with severe lymphopenia secondary to human immunodeficiency virus infection, chemotherapy, or immunosuppressive treatment. The mechanism underlying the unexpected association between PML and the use of certain monoclonal antibodies that modulate the immune response remains unclear. Both efailizumab and natalizumab, which are selective adhesion molecule inhibitors, appear to alter T-cell trafficking to the central nervous system.

It is well known that the abrupt withdrawal of efailizumab in patients with psoriasis can cause rebound. Based on data from clinical trials, the incidence of rebound in such cases has been estimated at between 5% and 14%, but higher figures have been reported from smaller studies (22.5% in a series of 31 patients and 17.8% in a series of 49 patients). The risk of rebound has been considered to be inversely proportional to treatment response, with disease worsening estimated to be much more common in nonresponders than in good responders; the frequency of rebound in patients who had responded well to efailizumab has been reported to be 1.3% in a group of 1316 patients and 0% in a group of 130 patients.

We followed the clinical course of a group of patients with psoriasis in whom efailizumab was discontinued following the suspension of the marketing authorization for the drug.

Patients and Methods
We studied a group of patients being treated with efailizumab at the Dermatology Department of Hospital General Universitario Gregorio Marañón in Madrid, Spain when the marketing authorization for this drug was suspended. The clinical data analyzed are shown in Table 1. All of the patients were called in between February and March 2009 to initiate discontinuation of the drug. The Psoriasis Area and Severity Index (PASI) was used to assess disease severity at the moment of efailizumab discontinuation and again at 6 weeks and 3 months. The patients were asked to return if they developed generalized inflammation between these visits. The transition therapy administered was recorded in all cases and for patients who developed rebounds with generalized
inflammation, we noted the number of weeks that had elapsed since treatment discontinuation and the treatment used. Response to treatment with efalizumab was assessed prior to discontinuation of the drug and patients were classified according to the improvement in PASI from baseline (≥90%, ≥75%, ≥50% to <75%, or <50%). Response to treatment in patients with palmoplantar psoriasis was classified according to the static Physician’s Global Assessment system.

Ciclosporin was the transition therapy of choice for patients with plaque psoriasis because of its efficacy and fast action. Alternative treatments included methotrexate, adalimumab, etanercept, narrowband ultraviolet B (NB-UVB) phototherapy, and topical treatment only. In the case of patients scheduled to receive conventional systemic treatment, an overlap period of 4 weeks was used in which efalizumab was discontinued and the new drug introduced. The choice of transition therapy was decided on a case-by-case basis depending on baseline PASI, the effectiveness of previous treatments, the level of response to efalizumab, and the presence of concomitant disease. Topical treatment only (corticosteroids, vitamin D derivatives, or emollients) was used following the withdrawal of efalizumab in patients with palmoplantar psoriasis.

Rebound was defined as a 125% worsening of psoriasis from baseline or the development of a more inflammatory, erythrodermic, or pustular form of the disease within 3 months of discontinuation of efalizumab, as described by the US National Psoriasis Foundation.\(^{13}\) Relapse was defined as a 50% reduction in the PASI improvement achieved with efalizumab.

### Results

Thirty-three patients from our department were being treated with efalizumab when the marketing authorization for this drug was suspended. We were able to follow the clinical course of 32 of these (28 with plaque psoriasis and 4 with palmoplantar psoriasis) following efalizumab discontinuation. Table 2 shows the clinical characteristics of the patients analyzed.

The mean time since onset of disease was 19 years. All of the patients had been previously treated with systemic drugs or phototherapy. Nine patients had required treatment with etanercept and 1 with infliximab prior to efalizumab therapy. Three patients had required hospital admission due to the severity of their condition and 2 patients had had erythrodermic psoriasis. At the time of efalizumab discontinuation, 92.8% of the patients had achieved at least a 75% reduction in PASI, and of these, 64.3% had achieved at least a 90% reduction. Of the 32 patients analyzed, there was only 1 partial responder (≥50%-<75% reduction in PASI) and 1 nonresponder (<50% reduction). The mean length
of time to which a patient was exposed continuously to efalizumab was 26.1 months (range, 4–41 months).

We considered that the risk of rebound with transition therapy (Table 3) was higher in patients who had not achieved a 75% reduction in PASI and in those with unstable psoriasis (defined by very rapid relapse after the discontinuation of systemic or biologic therapy, the presence of highly erythematous or guttate lesions, episodes of erythroderma, or admission to hospital). The main treatment used in these higher-risk patients was ciclosporin at a dose of 3 to 5 mg/kg (administered to 11 patients [39.3% of patients with plaque psoriasis]). In patients with contraindications or who did not respond to ciclosporin, we administered adalimumab (3 patients, 10.7%) or methotrexate at a dose of 15 or 20 mg/wk (2 patients, 7.1%). In patients with a moderate risk of rebound, we prescribed etanercept 50 mg twice weekly (2 patients, 7.1%) or NB-UVB therapy (5 patients, 17.8%). Topical treatment only was administered to 9 patients: 4 with palmoplantar psoriasis and 5 (17.8%) with very stable lesions, which were completely white at the time of efalizumab discontinuation. Two patients (one receiving adalimumab and the other receiving NB-UVB therapy) decided to discontinue treatment. As mentioned previously, a 4-week treatment overlap period was used for patients in whom efalizumab was replaced by conventional systemic treatment. Biologic treatments were initiated immediately on discontinuation of efalizumab.

Table 4 shows the response of patients to transition therapy: 25% (8/32) experienced rebound, 15.7% (5/32) experienced relapse, and 59.3% (19/32) maintained good disease control. Rebound was most common in patients on methotrexate, etanercept, or adalimumab (50%, 1/2 patients in all 3 cases), although it also occurred in 18% (2/11) of patients on ciclosporin. Only 3 patients (27%) on topical treatment experienced rebound. These included 1 patient who had decided to discontinue treatment with ciclosporin, 1 patient with palmoplantar psoriasis (Figure 1), and 1 patient with very stable lesions, which were completely white at the time of efalizumab discontinuation. It is noteworthy that neither the partial responder nor the nonresponder to efalizumab experienced rebound. Indeed, the administration of ciclosporin (which

### Table 3  Transition Therapy By Risk of Rebound

<table>
<thead>
<tr>
<th></th>
<th>Ciclosporin</th>
<th>Methotrexate</th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>NB-UVB</th>
<th>Topical Treatment Only</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>11</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Low risk</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Palmoplantar psoriasis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviation: NB-UVB, narrowband ultraviolet B phototherapy.

*Data are presented as No. of Patients.

### Table 4  Clinical Outcomes During Transition Period

<table>
<thead>
<tr>
<th></th>
<th>Ciclosporin</th>
<th>Methotrexate</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>NB-UVB</th>
<th>Topical Treatment Only</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebound</td>
<td>2/11 (18)</td>
<td>1/2 (50)</td>
<td>1/2 (50)</td>
<td>1/2 (50)</td>
<td>0/4 (0)</td>
<td>3/11 (27)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Relapse</td>
<td>2/11 (18)</td>
<td>0/2 (0)</td>
<td>0/2 (0)</td>
<td>1/2 (50)</td>
<td>1/4 (25)</td>
<td>1/11 (9)</td>
<td>5 (15.7)</td>
</tr>
<tr>
<td>Maintenance</td>
<td>7/11 (64)</td>
<td>1/2 (50)</td>
<td>1/2 (50)</td>
<td>3/4 (75)</td>
<td>7/11 (64)</td>
<td>19 (59.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PASI, NB-UVB, narrowband ultraviolet B phototherapy; Psoriasis Area and Severity Index.

*No. of patients/Total No. (%) of patients per subgroup.

Total No. (%) of patients.

*75% improvement in PASI from baseline.

Figure 1  Generalized inflammatory flare reaction in patient no. 8, who had previously had palmoplantar psoriasis only.
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Discussion

The patients in our series can be described as good responders who had shown excellent response to the continuous use of efalizumab over a mean of 26.1 months (range 4-41 months). Those with plaque psoriasis (the vast majority) had had the disease for many years (mean of 19

Figure 2

Severe facial erythema in patient no. 4 at day 21 following discontinuation of efalizumab and initiation of etanercept therapy.

Table 5

<table>
<thead>
<tr>
<th>Patients</th>
<th>Baseline PASI</th>
<th>PASI on Discontinuation</th>
<th>Transition Therapy</th>
<th>Rebound PASI</th>
<th>Time to Rebound, d</th>
<th>Hospital Admission</th>
<th>Symptoms</th>
<th>Rescue Treatment</th>
<th>PASI at 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>3</td>
<td>Ciclosporin (discontinued treatment)</td>
<td>20</td>
<td>40</td>
<td>No</td>
<td>Generalized inflammatory papules, palmoplantar edema</td>
<td>Infliximab</td>
<td>2.6</td>
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<tr>
<td>2</td>
<td>19</td>
<td>2</td>
<td>Ciclosporin</td>
<td>24</td>
<td>58</td>
<td>No</td>
<td>Large plaques and generalized inflammatory papules</td>
<td>Increased dose of ciclosporin (5 mg/kg) and topical corticosteroids</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>0</td>
<td>Ciclosporin</td>
<td>13</td>
<td>50</td>
<td>No</td>
<td>Generalized inflammatory papules</td>
<td>Ciclosporin (5 mg/kg)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>2</td>
<td>Etanercept</td>
<td>25</td>
<td>21</td>
<td>Yes</td>
<td>Generalized inflammatory papules</td>
<td>Infliximab</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>4</td>
<td>Adalimumab</td>
<td>24</td>
<td>30</td>
<td>Yes</td>
<td>Generalized inflammatory papules</td>
<td>Adalimumab+ciclosporin</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>15.2</td>
<td>1</td>
<td>Methotrexate</td>
<td>20</td>
<td>70</td>
<td>No</td>
<td>Erythroderma</td>
<td>Infliximab</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>0</td>
<td>Topical</td>
<td>13</td>
<td>64</td>
<td>No</td>
<td>Plaque psoriasis</td>
<td>Methotrexate</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>Palmoplantar</td>
<td>sPGA 0</td>
<td>Topical</td>
<td>14.4</td>
<td>43</td>
<td>No</td>
<td>Erythema and widespread flaking</td>
<td>Ciclosporin</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: PASI, Psoriasis Area and Severity Index; sPGA, static Physician’s Global Assessment.
years) with very few cases of instability (only 3 patients had required hospital admission because of their condition and 2 had developed erythrodermic psoriasis). Despite the fact that the patients had a low risk of rebound and that most of them were prescribed transition therapy (mostly ciclosporin), 25% experienced rebound and 15.6% experienced relapse. These figures are markedly higher than those reported in the literature for good responders. Also in contrast with previous reports, we found that the morphology of lesions changed in the majority of the patients who experienced rebound in our series (7/8). These changes were characterized by the abrupt onset of highly pruritic lesions with confluent inflammatory papules and edematous lesions that spread to previously unaffected areas such as the face, the palms, and the genitals (Figures 2-4). One of these patients developed erythrodermic psoriasis and 2 required admission to hospital because of the severity of their lesions. The mean time from efalizumab withdrawal to rebound has been estimated at approximately 6 weeks (range, 4-9 weeks), which is similar to our figure (mean, 47 days; range, 4-10 weeks).

Ciclosporin was successful in controlling disease in 64% of the patients that we considered to be at greatest risk of rebound. The drug’s efficacy and fast action makes it the transition therapy of choice for numerous authors. Other drugs recommended in such cases, namely methotrexate, adalimumab, and etanercept, were less successful at preventing rebound in our series, but we are unable to draw any firm conclusions because of the small number of patients who received each of these drugs and differences in clinical history and disease severity. We followed the recommendation of gradually withdrawing efalizumab while replacing it with a conventional systemic drug for 4 weeks, although not all authors have found this to be beneficial in preventing rebounds.

Infliximab provided the fastest means with which to control intense flare-ups (generalized inflammation) in our group. There have been reports of the high efficacy of this drug in isolated cases of patients who, following efalizumab withdrawal, developed erythrodermic or pustular forms of psoriasis or in whom neither UVB therapy nor etanercept had been successful in controlling flare-ups. Other treatment regimens such as ciclosporin alone or in combination with adalimumab (Figure 5) were also efficient in controlling rebounds in our group, but the improvements were more gradual.

Reports of highly acute forms of erythrodermic or pustular psoriasis and widespread inflammation during treatment with or discontinuation of efalizumab should serve as a reminder that the abrupt withdrawal of oral corticosteroids can lead to the development of pustular psoriasis. The mechanisms by which efalizumab alters the course of psoriasis are not well known. An immunohistochemical study by Lowes et al of inflammatory papules from patients on efalizumab therapy who developed these lesions in previously unaffected areas (a condition known as localized papular eruption) revealed increased numbers of CD11b⁺, CD11c⁺, and iNOS⁺ cells. The authors suggested that this inflammatory reaction occurred only during CD11a blockade by efalizumab and not during the natural disease process. They also hypothesized that the localized papular eruption and widespread inflammation that occur following...
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Figure 5  Good control of generalized inflammatory flare after 2 months’ treatment with adalimumab and ciclosporin in patient no. 5.

the discontinuation of efalizumab are part of the same phenomenon.

The higher rate of rebound detected in our series might be due to the fact that the patients had been receiving continuous treatment with efalizumab for several years, contrasting with earlier series, in which the drug had been administered for just a few months.14 It is clear that evidence from clinical trials is insufficient to predict long-term effects of efalizumab and that such information only comes to light with time and experience.

To conclude, although efalizumab has been withdrawn from the market, we believe that it is noteworthy that such a high proportion of patients who had achieved good disease control over several years with efalizumab experienced rebound and widespread inflammation following discontinuation of this drug.

Conflicts of Interest

Dr Baniandrés participated as an advisor in meetings organized by Shering-Plough. The other authors declare that they have no conflicts of interest.

References