Actas Dermosifiliogr. 2010;**101(5)**:421–427

ACTAS
Dermo-Sifiliográficas

Full English text available at
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ORIGINAL ARTICLE

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

Manuscript received September 7, 2009; accepted for publication December 16, 2009

KEYWORDS
Efalizumab;
Progressive multifocal leukoencephalopathy;
Psoriasis;
Rebound;
Relapse;
Treatment discontinuation

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).

PALABRAS CLAVE
Efalizumab;
Leucoencefalopatía multifocal progresiva;
Psoriasis;
Rebote;
Recaída;
Suspensión

Evolución clínica de los pacientes psoriásicos tratados con efalizumab al suspender el fármaco

Resumen

Introducción: En febrero de 2009 la Agencia Europea de Evaluación de Medicamentos (EMEA) suspendió la comercialización de efalizumab por la notificación de tres casos confirmados de leucoencefalopatía multifocal progresiva (LMP). Nos planteamos realizar un estudio prospectivo de seguimiento de los pacientes tratados en nuestro Servicio con efalizumab en el momento de la suspensión y comparar la evolución con las perspectivas publicadas en la literatura.

Pacientes y métodos: Se incluyeron 32 pacientes (28 con psoriasis en placas y 4 con psoriasis palmoplantar) entre febrero y marzo de 2009. Se recogió el Psoriasis Area and Severity Index (PASI) previo al comienzo del tratamiento con efalizumab, en el momento de la suspensión, a las 6 semanas y posteriormente cada tres meses. En el caso de los pacientes que presentaron brotes generalizados se recogió el tiempo transcurrido desde la suspensión y el manejo terapéutico que se realizó.

Resultados: A pesar de que el 92,8% de los pacientes correspondían a buenos respondedores (mejoría PASI > 75), presentaron rebote un 25% de los sujetos (8/32) y recaídas un 15,7% (5/32). Con respecto a la terapia de transición presentaron rebote un 18% de los pacientes (2/11) con ciclosporina, un 50% (1/2) con metotrexato, un 50% (1/2) con adalimumab, un 50% (1/2) con etanercept y un 27% (3/11) de los que recibieron tratamiento tópico.

Conclusiones: Hemos encontrado un porcentaje muy alto de rebote y formas generalizadas inflamatorias en pacientes que habían conseguido un buen control de la psoriasis durante varios años.

Introduction

Efalizumab 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 efalizumab to be well tolerated,[1-4] and studies that followed patients that took the drug continuously for up to 3 years reported a favorable safety profile.[5,6] The situation for users of efalizumab, 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 efalizumab 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 efalizumab and natalizumab, which are selective adhesion molecule inhibitors, appear to alter T-cell trafficking to the central nervous system.[7]

It is well known that the abrupt withdrawal of efalizumab 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%,[8] but higher figures have been reported from smaller studies (22.5% in a series of 31 patients[9] and 17.8% in a series of 49 patients[10]). 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 efalizumab has been reported to be 1.3% in a group of 1316 patients[11] and 0% in a group of 130 patients.[12]

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

Patients and Methods

We studied a group of patients being treated with efalizumab 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 efalizumab 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

Table 1 Data Collected for the Sample

Age
Type of psoriasis
Previous treatments
Psoriatic arthritis
History of pustular or erythrodermic psoriasis
Hospital admissions due to psoriasis
Baseline PASI score
PASI score at the moment of efalizumab discontinuation
PASI score at 6 weeks post-discontinuation
PASI score at 3 months post-discontinuation
Transition therapy
Rebound (time since discontinuation)

Abbreviation: PASI, Psoriasis Area and Severity Index.

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.

Table 2 Clinical Characteristics of the 32 Patients

Characteristics	
Sex	
Men[a]	16 (50)
Women[a]	16 (50)
Age, mean (range), y	41.5 (65-19)
Age at diagnosis, mean, y	22.7 (6-59)
Type of psoriasis	
Plaque psoriasis[b]	28
Palmoplantar psoriasis[b]	4
Hospital admissions due to psoriasis[b]	3
Erythrodermic/pustular psoriasis[b]	2 (erythroderma)
Previous treatments[a]	
Phototherapy	19 (59.3)
Acitretin	14 (43.7)
Methotrexate	14 (43.7)
Ciclosporin	15 (46.8)
Etanercept	9 (28.1)
Infliximab	1 (3)
Baseline[c] PASI (plaque psoriasis)	
Mean score	13.4
Median score	12.9
Range	8-29
Baseline[c] sPGA score (palmoplantar psoriasis)	
5 (moderate to severe)[a]	2 (50)
6 (severe)[a]	2 (50)
Exposure time to efalizumab, mean (range), mo	26.1 (4-41)
Response to efalizumab	
Plaque psoriasis, % reduction in PASI[d]	
≥90%	18/28 (64.3)
≥75%	26/28 (92.8)
≥50% to <75%	1/28 (3.6)
<50%	1/28 (3.6)
Palmoplantar psoriasis[e]	
1 - Almost cleared	1/4 (25)
2 - Mild	1/4 (25)
3 - Mild to moderate	2/4 (50)

Abbreviations: PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment.
[a]No. (%) of patients.
[b]No. of patients.
[c]Before treatment with efalizumab.
[d]No./Total No. (%) of patients with plaque psoriasis.
[e]No./Total No. (%) of patients with palmoplantar psoriasis.

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

Table 3 Transition Therapy By Risk of Rebound[a]

	Ciclosporin	Methotrexate	Adalimumab	Etanercept	NB-UVB	Topical Treatment Only	Total
High risk	11	2	3	0	0	0	16
Moderate risk	0	0	0	2	5	0	7
Low risk	0	0	0	0	0	5	5
Palmoplantar psoriasis	0	0	0	0	0	4	4

Abbreviation: NB-UVB, narrowband ultraviolet B phototherapy.
[a]Data are presented as No. of Patients.

Table 4 Clinical Outcomes During Transition Period

	Ciclosporin[a]	Methotrexate[a]	Etanercept[a]	Adalimumab[a]	NB-UVB[a]	Topical Treatment Only[a]	Total[b]
Rebound	2/11 (18)	1/2 (50)	1/2 (50)	1/2 (50)	0/4 (0)	3/11 (27)	8 (25)
Relapse	2/11 (18)	0/2 (0)	0/2 (0)	1/2 (50)	1/4 (25)	1/11 (9)	5 (15.7)
Maintenance of PASI 75[c]	7/11 (64)	1/2 (50)	1/2 (50)		3/4 (75)	7/11 (64)	19 (59.3)

Abbreviations: PASI, NB-UVB, narrowband ultraviolet B phototherapy; Psoriasis Area and Severity Index.
[a]No. of patients/Total No. (%) of patients per subgroup.
[b]Total No. (%) of patients.
[c]75% improvement in PASI from baseline.

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 psoriasis or highly localized lesions. 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

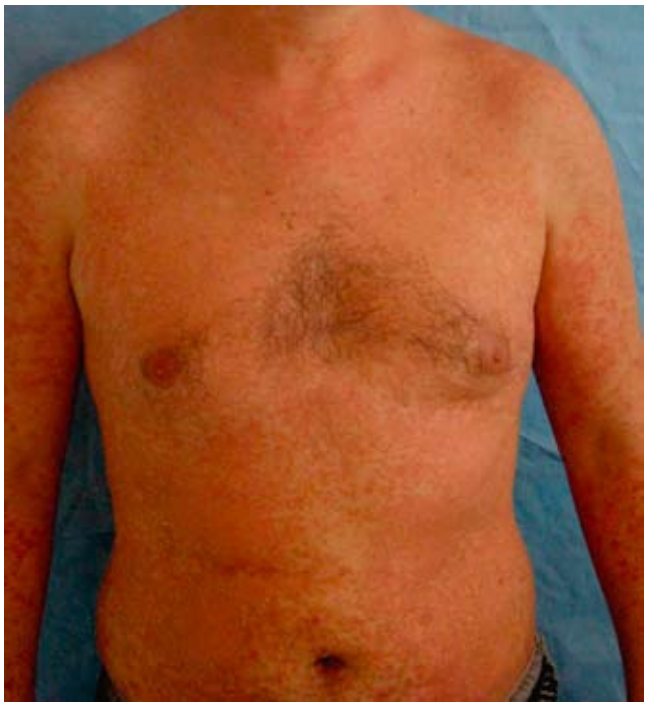

Figure 1 Generalized inflammatory flare reaction in patient no. 8, who had previously had palmoplantar psoriasis only.

Table 5 Patients Who Experienced Rebound

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

Abbreviations: PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment.

Figure 2 Severe facial erythema in patient no. 4 at day 21 following discontinuation of efalizumab and initiation of etanercept therapy.

coincided with the gradual withdrawal of efalizumab over 4 weeks) improved their PASI score. Table 5 shows the clinical course of the 8 patients who experienced rebound; the mean length of time between efalizumab discontinuation and the appearance of the rebound flare was 47 days. Three of these patients were prescribed infliximab as rescue medication to treat intense inflammation and lesion spread, with very fast control achieved after the second infusion (Figure 2). Adequate control was achieved in the other patients in the 3-month follow-up period, although the improvement with ciclosporin and methotrexate was more gradual.

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

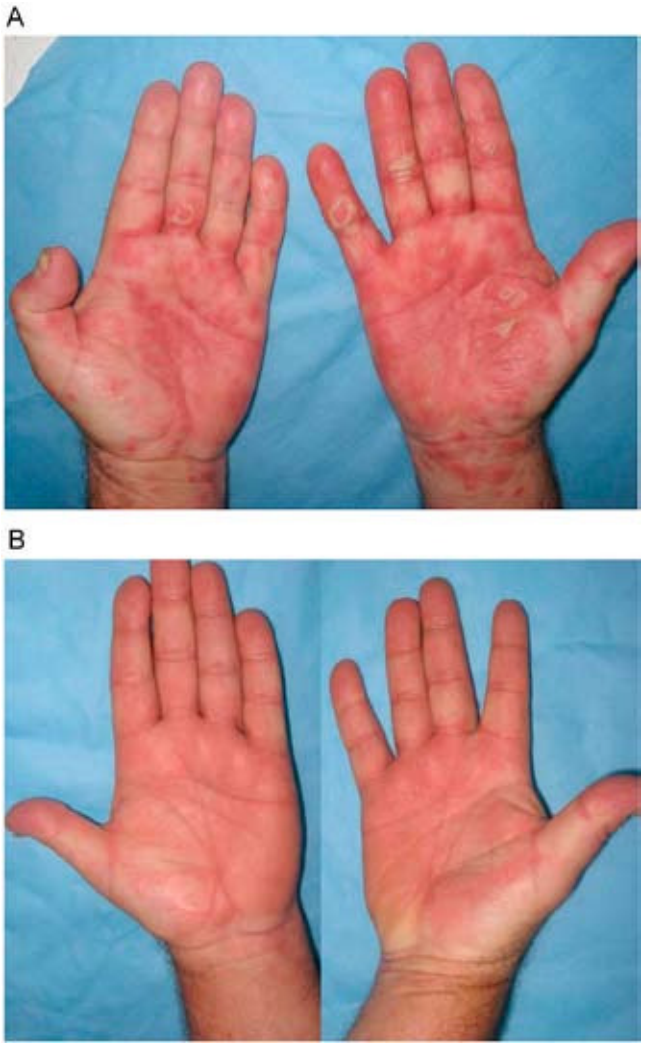

Figure 3 A, Intense erythema and edema on palms (previously unaffected) in patient no. 1, despite a treatment overlap period of 4 weeks with efalizumab and ciclosporin. B, Control of lesions after second infusion of infliximab.

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

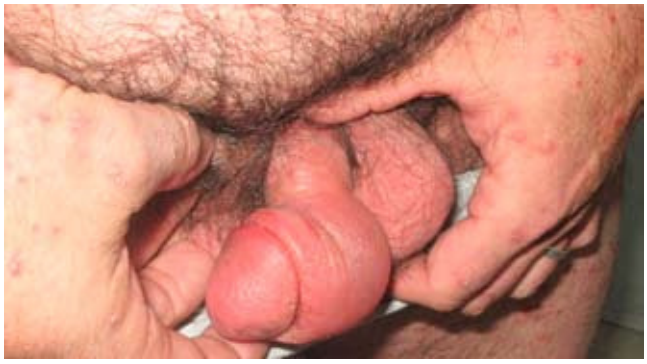

Figure 4 Severe genital psoriasis 30 days after efalizumab discontinuation and initiation of adalimumab in patient no. 5.

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.[11,12,14,15] 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,[16] although not all authors have found this to be beneficial in preventing rebounds.[14]

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[9] or pustular[17] forms of psoriasis or in whom neither UVB therapy[18] nor etanercept[19] 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[20-22] 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[23] 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

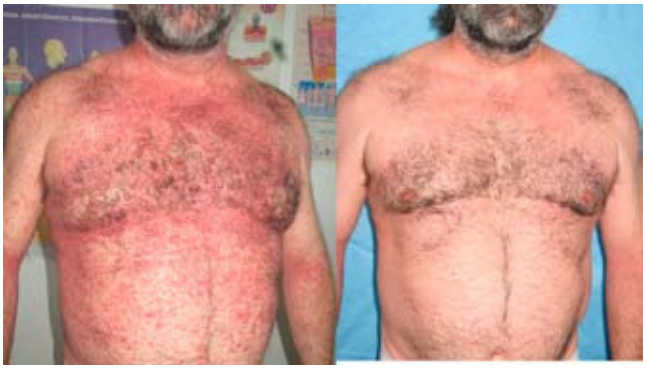

Figure 5 Good control of generalized inflammatory flare after 2 months' treatment with adalimumab and ciclosporin in patient no. 5.

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.

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