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## ORIGINAL ARTICLE

### Adverse Reactions During Biological Therapy for Psoriasis: Results of a Survey of the Spanish Psoriasis Group

M. Sánchez-Regaña,<sup>a</sup> E. Dilmé,<sup>a</sup> Ll. Puig,<sup>b</sup> X. Bordas,<sup>c</sup> J.M. Carrascos,<sup>a,d</sup> M. Ferran,<sup>e</sup> P. Herranz,<sup>f</sup> M. García-Bustinduy,<sup>g</sup> J.L. López Estebaranz,<sup>h</sup> M. Alsina,<sup>i</sup> M.A. Rodríguez,<sup>j</sup> M. Ribera,<sup>d</sup> E. Fernández-López,<sup>k</sup> J.C. Moreno,<sup>l</sup> I. Belinchón Romero,<sup>m</sup> and D. Vidal<sup>n</sup>

<sup>a</sup>Hospital Universitari Sagrat Cor, Barcelona, Spain

<sup>b</sup>Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

<sup>c</sup>Hospital Universitari de Bellvitge, Barcelona, Spain

<sup>d</sup>Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain

<sup>e</sup>Hospital del Mar, Barcelona, Spain

<sup>f</sup>Hospital Universitario la Paz, Madrid, Spain

<sup>g</sup>Hospital Universitario de Canarias, La Laguna, Tenerife, Spain

<sup>h</sup>Fundación Hospital Alcorcón, Madrid, Spain

<sup>i</sup>Hospital Clínic, Barcelona, Spain

<sup>j</sup>Hospital de León, León, Spain

<sup>k</sup>Hospital Universitario de Salamanca, Salamanca, Spain

<sup>l</sup>Hospital Universitario Reina Sofía, Córdoba, Spain

<sup>m</sup>Hospital General Universitario de Alicante, Alicante, Spain

<sup>n</sup>Hospital Dos de Maig, Barcelona, Spain

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#### KEYWORDS

Psoriasis;  
Biologic agents;  
Survey;  
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Adverse reactions

#### Abstract

**Background:** Biologic therapies have been a major breakthrough in the treatment of psoriasis because they are more selective and have a better short-term and medium-term safety profile. There are reliable data to support both the efficacy and the safety of these drugs. However, it is always useful to report the clinical experience of dermatologists who are experts in the use of biologic agents to treat psoriasis, particularly with regard to their safety.

**Material and methods:** We present the results of a survey administered to the members of Spanish Psoriasis Group and based on a series of questions referring to the clinical

\*Corresponding author.

E-mail address: [ez.reg@terra.es](mailto:ez.reg@terra.es)

**PALABRAS CLAVE**

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safety of these agents. A total of 988 patients treated with efalizumab, infliximab, etanercept, and adalimumab were reported by 15 members of the group.

**Results:** There was a particularly high proportion of reactions (34%) to infliximab infusions. Blood test abnormalities were detected in 13.25% of patients and infections in 12.24%, with one case of pulmonary tuberculosis. Attention is drawn to the adverse effects profile of efalizumab: *de novo* arthritis in 5.8% and rebound in 20.9% of patients.

**Conclusion:** The safety data provided by our study should be taken into account in view of the large number of patients recruited by dermatologists experienced in the use of this type of therapy.

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### Efectos Adversos Observados Durante la Terapia Biológica en la Psoriasis. Resultados de una Encuesta al Grupo Español de Psoriasis

#### Resumen

**Introducción:** La terapia biológica ha representado un avance muy importante en el tratamiento de la psoriasis, al tratarse de una generación de fármacos más selectivos y con mejor perfil de seguridad a corto y medio plazo. Existen datos sólidos a favor de la eficacia de cada uno de estos fármacos, así como de su seguridad. A pesar de ello, siempre es útil aportar la experiencia clínica de dermatólogos expertos en el tratamiento de la psoriasis con biológicos, en especial en lo referente a su seguridad.

**Material y métodos:** Se realizó una encuesta a los miembros del Grupo Español de Psoriasis (GEP) basada en una serie de ítems relativos a aspectos referentes a la seguridad clínica de estos fármacos, cuyos resultados se presentan en este artículo. Un total de 988 pacientes tratados con efalizumab, etanercept, infliximab y adalimumab fueron recogidos por parte de 15 miembros del GEP.

**Resultados:** Entre los resultados obtenidos destaca la elevada proporción de reacciones a infliximab (34%). Se observaron alteraciones analíticas en el 13,25% de los pacientes e infecciones en el 12,24%, con un único caso de tuberculosis pulmonar. Es de destacar el perfil de efectos secundarios de efalizumab: *arthritis de novo* en el 5,8% y rebote en el 20,9%.

**Conclusión:** Los datos de seguridad aportados por nuestro trabajo deben tenerse en consideración, habida cuenta del importante número de pacientes reclutados por un grupo de dermatólogos expertos en el manejo de este tipo de fármacos.

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## Introduction

Psoriasis is a chronic inflammatory immune disease mediated by T lymphocytes and affects 1.4% of the Spanish population.<sup>1</sup> Up to 30% of patients with psoriasis also suffer from arthritis. The physical and emotional impact on the quality of life of affected individuals is similar to that associated with other diseases such as depression, diabetes mellitus, rheumatoid arthritis, hypertension, congestive heart failure, or cancer.<sup>2</sup>

Between 20% and 30% of patients with psoriasis require systemic treatment.<sup>3</sup> The treatments that have traditionally been most widely used in Spain are phototherapy, acitretin, ciclosporin, and methotrexate. During the last 5 years, however, the following so-called biologic therapies have gradually been added to the range of available treatment options: efalizumab, etanercept, infliximab, adalimumab, and ustekinumab. Biologic therapies act by selectively inhibiting the activation and maturation of antigen-presenting cells, by blocking the secretion of cytokines, and by inhibiting the activation and proliferation

of T lymphocytes, their migration to the skin, their effector function, or their reactivation.<sup>4</sup> All of these new molecules are effective, well-tolerated, and have a rapid onset of action. However, given their recent inclusion in the therapeutic arsenal, post-marketing studies are still required to confirm their safety.

Here we describe the first survey carried out in Spain to assess adverse events observed during biologic therapy for the treatment of psoriasis. This survey was performed among members of the Spanish Psoriasis Group (SPG), a working group of the Spanish Academy of Dermatology and Venereology made up of 50 hospital dermatologists who specialize in the treatment of psoriasis.

## Material and Methods

Members of the SPG completed a survey containing a series of items designed to assess adverse events or effects observed during treatment with the following biologics: efalizumab, etanercept, infliximab, and adalimumab.

The survey was designed by the first author of this article and sent to other members by e-mail between February and May, 2008.

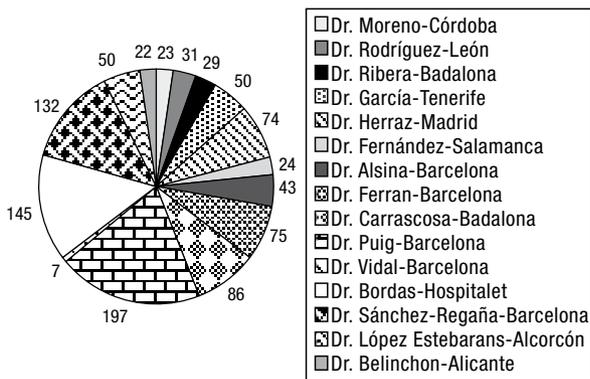
The survey assessed, on a member-by-member basis, the number of years each biologic had been prescribed, the number of patients treated with that drug, and the adverse events that were observed. It addressed injection-site reactions for subcutaneously administered drugs and infusion reactions (acute and delayed) associated with infliximab therapy. In the case of efalizumab, the adverse-events profile characteristic of the drug was assessed by

quantifying the number of transient papular eruptions, inflammatory exacerbations, headaches, cases of new onset arthritis, and rebounds. In all cases, the survey took into account the number of influenza-like syndromes, laboratory abnormalities, infections, tumors, heart failure, demyelinating diseases, and others.

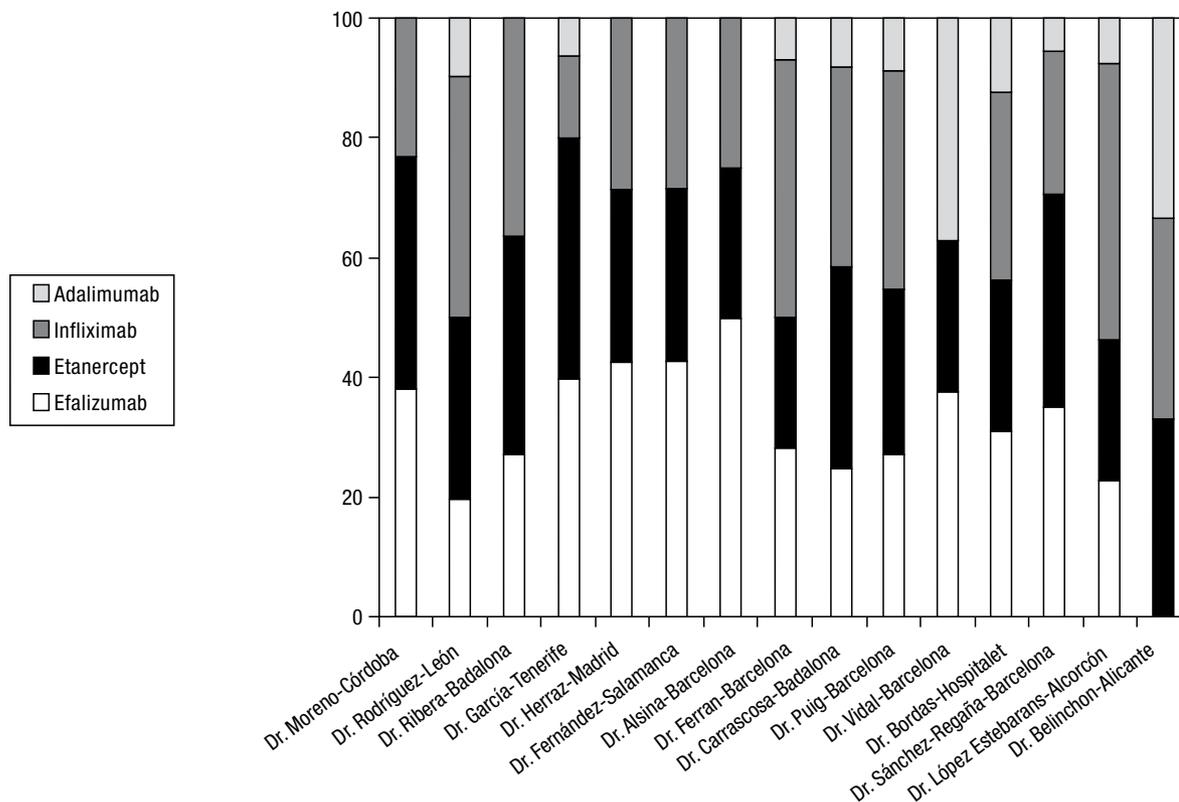
### Results

Fifteen members of the SPG responded to the survey (Figure 1). The respondents reported 988 patients treated with the following biologics, which have been introduced gradually over the last few years: efalizumab (306), etanercept (439), infliximab (181), and adalimumab (62). The lower number of patients treated with adalimumab is explained by its relatively recent approval for use in moderate-to-severe plaque psoriasis. There were some differences among the remaining 3 drugs in terms of the number of years for which they had been prescribed by the respondents (Figure 2).

The appearance of local reactions at the subcutaneous injection site is one of the main adverse events observed during therapy with biologic drugs (for those drugs administered subcutaneously). Such reactions were reported for 8% of patients treated with adalimumab, 4.2% of those treated with efalizumab, and 2.96% of those treated with etanercept. Most local reactions were categorized as grade II or III (mild or moderate intensity and low frequency).



**Figure 2** Patients reported by each member of the Spanish Psoriasis Group who responded to the survey.



**Figure 2** Number of years for which respondents reported prescribing each biologic drug.

**Table 1** Infusion Reactions During Treatment With Infliximab

	Symptom	Number of Cases
Mild-acute	Palpitations	7
	Nausea	7
	Sweating	5
	Facial erythema	7
Severe-acute	Dyspnea	7
	Stridor	7
	Chest pain	4
	Hypotension/ hypertension	6
	Fever	3
	Urticaria	5
Delayed	Rash	3
	Pruritus	1
Total		62

Infusion reactions were observed in 62 patients (34%) treated with infliximab (Table 1). In most cases these reactions were acute, and few delayed reactions were observed.

Efalizumab was associated with the highest rate of influenza-like syndrome. Of the 306 patients who received this drug, 116 suffered influenza symptoms (37.9% of all cases). These symptoms were much less common in patients treated with the other biologic drugs: 4.8% of those treated with adalimumab, 2% of patients treated with etanercept, and 1.1% of those treated with infliximab.

Efalizumab was once again the biologic drug associated with the highest frequency of headache. Of the 306 patients treated with this drug, 40 (13.07%) complained of headaches. The number of patients with headaches was lower among those treated with other biologic drugs: 4.8% for adalimumab, 3.8% for infliximab, and 1.3% for etanercept.

Laboratory abnormalities were observed in 131 patients (13.25%) from the entire group, with infliximab and efalizumab showing the highest rates (15.46% and 15.36%, respectively). Abnormalities were observed in 6.6% of patients treated with etanercept and 1.6% of those treated with adalimumab.

The most common abnormality observed with infliximab and etanercept was the presence of antinuclear antibodies. Increased white cell count was the most common abnormality reported in patients treated with efalizumab. Only 1 case of laboratory abnormalities (increased platelet count) was observed among patients treated with adalimumab. Table 2 shows the laboratory abnormalities and their frequency for each biologic drug.

Infections were reported for 121 patients (12.24%) out of all those considered in the survey: 13.8% of patients treated with infliximab, 8.2% of those treated with etanercept, 8% with adalimumab, and 6.2% with efalizumab. Most of the infections observed corresponded

**Table 2** Laboratory Abnormalities

	Abnormal Variable	Number of Cases
Infliximab	ANA +	16
	↑AST-ALT	6
	Anti-DNA+	4
	↓NaHCO <sub>3</sub>	1
	↑Cholesterol	1
	Total	28
	Efaluzimab	↑WCC
↑AST-ALT		5
↑Triglycerides		3
↑Platelet count		3
↑Alkaline phosphatase		2
Sezary cells +		1
Total		47
Etanercept	ANA+	14
	↑Triglycerides	4
	Anti-DNA+	3
	↑WCC	2
	↑AST-ALT	1
	↑Platelet count	1
	↑Bilirubin	1
	↑Monocytes	1
	Pancytopenia	1
	↑Creatinine	1
Total	29	
Adalumimab	↑Platelet count	1
	Total	1

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; WCC, white cell count.

to upper respiratory tract infections, acute gastroenteritis, or urinary tract infections. Table 3 shows the frequencies of the different infections reported. Notably, only 1 case of pulmonary tuberculosis was observed (in a patient treated with infliximab).

New onset psoriatic arthritis was observed in 5.8% of patients treated with efalizumab. In contrast, this occurred in only 0.45% of those treated with etanercept and 0.55% of those who received infliximab. Table 4 shows the frequency of arthritis observed with the different treatments.

There were few cases of congestive heart failure, demyelinating disease, or autoimmune diseases (Table 5). Notably, class III heart failure leading to treatment suspension was reported in a patient treated with efalizumab and another treated with etanercept. Two patients treated with infliximab presented demyelinating disease: one developed mixed polyneuropathy and the other a worsening of existing multiple sclerosis. Finally, a case of autoimmune disease (autoimmune hepatitis) was reported for a patient treated with infliximab.

Tumors were only reported for 2 patients included in the survey. One patient treated with etanercept had a breast

**Table 3** Infections

	Efaluzimab	Etanercept	Infliximab	Adalumimab
URTI	9	7	1	2
Cellulitis	5	1	1	0
UTI	2	5	7	0
Pneumonia	1	1	0	0
Orchiepididymitis	1	0	0	0
Parotitis	1	0	0	0
Gastroenteritis	0	7	3	1
Herpes zoster	0	4	2	0
Furunculosis	0	3	1	0
Bronchitis	0	2	0	1
Perianal abscess	0	2	0	0
Lung abscess	0	1	0	0
Pyelonephritis	0	1	0	0
Sinusitis	0	1	1	0
Whitlow	0	1	0	0
Otitis externa	0	0	2	0
Bronchitis	0	0	1	0
Leg ulcer	0	0	1	0
Dental infection	0	0	1	0
Mastoiditis	0	0	1	0
Varicella	0	0	1	0
Throat infection	0	0	1	0
Prostatitis	0	0	0	1
Pulmonary tuberculosis	0	0	1	0
Total	19	36	25	5

URTI, upper respiratory tract infection; UTI, urinary tract infection.

**Table 4** Arthritis

Efaluzimab	Etanercept	Infliximab	Adalumimab
5.8%	0.45%	0.55%	0%

tumor and another treated with infliximab had a squamous cell carcinoma.

The capacity of efalizumab to trigger a series of side effects was assessed independently. Transient papular eruptions were observed in 16% of cases, generalized inflammatory exacerbations in 14%, and rebound psoriasis in 20.9% (Table 6).

Paradoxical reactions (palmoplantar pustulosis) were observed in 7 patients: 4 patients treated with etanercept and 3 treated with efalizumab.

## Discussion

For some years it has been possible to treat psoriasis with molecules generated using recombinant DNA technology. Biologic therapies for the treatment of psoriasis block specific steps in the pathogenesis of the disease by targeting cytokines and proteins on the surface of lymphocytes.

Molecules generated using molecular biology to treat immune-mediated diseases can be subdivided into monoclonal antibodies, fusion proteins, and cytokines.<sup>5</sup> The monoclonal antibodies bind cell-surface proteins and can be chimeric, humanized, or human. Human monoclonal antibodies are 100% human in origin, chimeric antibodies are made up of a human constant fragment (Fc) and a murine antigen-binding fragment (Fab), and humanized antibodies contain a human Fc fragment and a mixed (human and murine) Fab fragment. Fusion proteins are molecules generated by joining portions of different proteins. Those used in the treatment of psoriasis contain a receptor for a human protein fused to the Fc fragment of an immunoglobulin. The origins of the different drugs are indicated in the suffixes used: -ximab for chimeric antibodies, -zumab for human antibodies, and -cept for fusion proteins.

Biologic drugs act by selectively inhibiting the activation and maturation of antigen-presenting cells, by blocking the secretion of cytokines, or by inhibiting the proliferation of T lymphocytes, their migration to the skin, their effector function, or their reactivation, without causing generalized immunosuppression.

There are more than 40 molecules being investigated for the treatment of psoriasis. When the survey was circulated, 4 biologic drugs had been approved by the European Medicines Agency (EMA) for use in plaque

**Table 5** Heart Disease, Demyelinating Disease, and Autoimmune Diseases in Patients Treated With Biologic Drugs

	Efaluzimab	Etanercept	Infliximab	Adalimumab
CHF	0.3%	0.2%	1.10%	0%
Demyelination	0%	0%	1.10%	0%
Autoimmune disease	0%	0%	0.55%	0%

CHF, congestive heart failure.

**Table 6** Adverse Effects Attributed to Efaluzimab

Transient papular eruption	16%
Generalized inflammatory exacerbation	14%
Rebound	20.9%
Arthritis	5.8%

psoriasis: etanercept, infliximab, efalizumab, and adalimumab. Recently, Spanish evidence-based guidelines were published for the treatment of moderate-to-severe psoriasis with biologic drugs.<sup>6</sup> These represent an important tool for optimizing the use of this emerging treatment option.

Efaluzumab is a recombinant humanized monoclonal anti-CD11a antibody. It acts by binding CD11a, the  $\alpha$  subunit of LFA-1, on the surface of T lymphocytes and prevents binding of LFA-1 to ICAM-1 on antigen-presenting cells, endothelial cells, and keratinocytes. It is administered by weekly subcutaneous injection. The initial dose in the first week is 0.7 mg/kg and this is increased to 1 mg/kg in the following weeks. Treatment duration is 12 weeks and can be continued in patients with a good response to the drug. It should not be used in pustular, erythrodermic, or guttate psoriasis.<sup>7</sup> In February 2009, EMEA suspended marketing approval for the drug due to reporting of 3 cases of confirmed and 1 case of suspected progressive multifocal leukoencephalopathy. Despite the methodological limitations of this study, the results can be compared with those obtained in other studies performed recently in Spain. For instance, Costanzo et al<sup>8</sup> reported a series of 100 patients treated with efalizumab. They observed 25% of patients with headache and 16% with influenza-like syndrome, compared with 13.07% and 37.9%, respectively, in our study. Most studies have obtained similar results to those reported here for laboratory abnormalities, with elevated lymphocyte counts and white cell counts being the most frequent. However, in some cases the frequencies were even higher, such as in the Greek study by Antoniou et al,<sup>9</sup> where elevated white cell counts were reported in 39% of cases, compared with 10.78% in our survey. This study differed from others in terms of the characteristic side effects of efalizumab. Whereas we observed transient papular eruptions in 16% of cases, generalized inflammatory exacerbations in 14%, rebounds in 20.9%, and new onset arthritis in 5.8%, Selenko-Gebauer et al<sup>10</sup> reported rates of 5%, 3%, 14%, and 1% to 2%, respectively. Likewise, in

a Danish study, Kragballe<sup>11</sup> observed papular eruptions in 10% of cases and inflammatory exacerbations in 16%. The rates of infection and tumors observed in our study were similar to those reported by other authors.

Etanercept is a recombinant human dimeric protein. It comprises 2 soluble TNF receptors (p75) fused to the Fc fragment of human IgG1. It acts as a competitive inhibitor by irreversibly binding to circulating and membrane-bound TNF- $\alpha$  and TNF- $\beta$  and preventing binding to membrane receptors on immune effector cells. It does not induce lysis of cells expressing transmembrane TNF. TNF- $\alpha$  is implicated in keratinocyte proliferation, dermal inflammation, angiogenesis, and endothelial expression of molecules that favor adhesion and extravasation of activated T lymphocytes. The recommended dose of etanercept is 25 or 50 mg subcutaneously twice weekly for 24 weeks.<sup>12</sup> Etanercept was the most commonly used drug in our study (439 patients). Consequently, we can draw interesting conclusions regarding its safety, and in particular, make comparisons with the results of other studies. Firstly, there was a low frequency of injection-site reactions, which were observed in only 3% of patients, whereas other studies have reported frequencies of up to 37% in patients treated with etanercept.<sup>6</sup> Secondly, as in other studies, we found that the appearance of antinuclear antibodies was the most common laboratory abnormality, despite only occurring in 3.18% of patients compared with up to 18.3% seen in other studies involving long-term follow-up.<sup>13</sup> Infections were reported for 8.2% of patients during treatment. None of these were serious and upper respiratory tract infections were the most common, as reported in other studies.<sup>14</sup> We also observed only 1 case in which a tumor was reported during treatment with etanercept. In recent years, cases have been reported in which anti-TNF agents led to induction or exacerbation of psoriasis. In a series of 127 cases described recently, this occurred in patients treated with infliximab (55.1%), etanercept (27.6%), and adalimumab (17.3%), with palmoplantar pustular psoriasis the most common clinical presentation (40.5%).<sup>15</sup> In our study, this type of paradoxical reaction was observed in 4 patients treated with etanercept and 3 treated with efalizumab.

Infliximab is a chimeric monoclonal antibody comprising a human Fc fragment fused to a murine variable domain specific for TNF- $\alpha$ . It binds both soluble and transmembrane TNF- $\alpha$  with high affinity and neutralizes its activity. It also induces complement-mediated lysis in cells that synthesize TNF- $\alpha$ . The recommended dose is 5 mg/kg body weight in weeks 0, 2, and 6, and

then every 8 weeks thereafter.<sup>16</sup> One of the most striking results in our study was the high frequency of infusion reactions with infliximab. Some type of reaction was observed following intravenous infusion in 34% of patients. The majority were acute reactions. This type of reaction has been described in between 3% and 22% of patients treated with infliximab, and reactions were more common in cases involving intermittent therapy.<sup>17</sup> The SPG consensus document by Puig et al<sup>17</sup> describes the steps to follow in the event that such reactions occur. In terms of laboratory abnormalities, in addition to the appearance of autoantibodies, elevated transaminases were detected in 3.3% of patients, a rate that is lower than encountered in other studies (20%).<sup>18</sup> Although 25 infections were reported (13.8% of patients), most were mild. There were 7 cases of urinary tract infection and only 1 patient developed pulmonary tuberculosis.

Adalimumab is a recombinant human IgG1 antibody with a high affinity and specificity for TNF- $\alpha$ . Similar to infliximab, it binds both soluble and membrane-bound TNF- $\alpha$  and prevents binding to the cell-surface receptors p55 and p75 on target cells, thereby blocking subsequent activation of the proinflammatory cascade. The recommended starting dose of adalimumab is 80 mg subcutaneously, followed by 40 mg subcutaneously on alternate weeks beginning a week after the initial dose.<sup>19</sup> Since adalimumab is the most recently approved biologic, only 62 patients were reported in this survey. Compared with previous studies,<sup>20</sup> the rates of laboratory abnormalities (1.62%) and infections (8%) were very low.

This is the first study of its nature to assess the safety of biologic drugs in Spain. Given that it involved hospital dermatologists who are experts in the use of biologic drugs and members of the SPG, we believe the results to be of unquestionable value, despite the inherent limitations of surveys.

The methodology used clearly makes it impossible to perform statistical comparisons between the different drugs analyzed. Based on our observations in a large number of patients, however, we believe the following conclusions can be drawn:

1. Efalizumab differs from other biologic drugs in its side effects. It is associated with a higher frequency of headaches and influenza-like syndrome following administration, a higher rate of generalized inflammatory exacerbations and arthritis during treatment, and more frequent rebounds following treatment.
2. Infliximab is associated with a high frequency of infusion reactions, particularly acute reactions. This drug requires closer monitoring of administration and it is possible that survey respondents applied different criteria when defining the types of reaction.
3. Laboratory abnormalities were generally infrequent and could be subdivided into 2 main groups: increased white cell count in patients treated with efalizumab and appearance of autoantibodies in patients treated with anti-TNF drugs.
4. Infections occurred in 121 patients (12.24%). Most notably, only 1 patient developed pulmonary tuberculosis during treatment with infliximab.

## Conflicts of Interest

The authors declare no conflicts of interest.

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