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ORIGINAL ARTICLE

BIOBADADERM, the Spanish Registry of Adverse Events Associated With Biologic Drugs in Dermatology: First Report

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KEYWORDS
Biologic therapies;
Psoriasis;
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Registry;
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Cohort

Abstract

Background and objectives: The Working Group on Psoriasis of the Spanish Academy of Dermatology and Venereology has initiated BIOBADADERM, a registry of patients with psoriasis receiving treatment with biologic drugs, in order to assess the long-term risk of adverse events (AEs).

Material and methods: A multicenter study was undertaken in 2 cohorts of patients with psoriasis: patients receiving biologic therapy and patients receiving nonbiologic systemic therapy other than phototherapy. Similar numbers of patients were included in each group. Information was recorded on demographic and clinical variables, treatment, and relevant AEs. The risk of specific AEs was determined by comparison of the frequencies for those events in the 2 cohorts.

Results: Data on the 2 cohorts were evaluated for the period from October, 2008 to November, 2009 alongside retrospective data on patients treated with biologics since 2005. Thirteen Spanish hospitals participated in the study. A total of 632 patients were included in the analysis: 417 treated with biologic drugs and 215 controls. Suspension of biologic therapy due to AEs was rare (72 cycles, 10%). A total of 232 AEs were reported in patients receiving biologic therapy. The majority were not serious. The most frequent AEs were infections (mostly upper respiratory tract infections and nasopharyngitis), followed by conditions affecting the skin or subcutaneous tissue. Forty-three AEs were reported in control subjects. The most frequent events were metabolic and nutritional abnormalities and abnormal transaminase levels. Comparison of the incidence of any AE in patients treated with biologics compared with control subjects revealed a relative risk of 2.2 ($P<.001$) The relative risks of infections or infestations and disorders of the skin or subcutaneous tissue in patients receiving biologic drugs were 23 ($P<.01$) and 4.9 ($P<.05$), respectively.

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Conclusions: Patients treated with biologic drugs had a greater number of AEs, particularly infections and skin conditions. Definitive conclusions, however, are difficult to draw due to the small number of patients included in the registry, particularly in the control cohort, and the short follow-up period. Differences in the percentages of events reported by the different hospitals reveal the difficulties associated with the concept of AEs in clinical practice and highlight the need to harmonize criteria in the future. Since the problems identified in this analysis should be overcome in future years, we expect BIOBADADERM to become an important source of information on the safety profile of biologic drugs in dermatology.

PALABRAS CLAVE
Tratamientos biológicos;
Psoriasis;
Acontecimientos adversos;
Registro;
Incidencia;
Pronóstico;
Cohorte

BIOBADADERM: registro español de acontecimientos adversos de terapias biológicas en Dermatología. Primer informe

Resumen

Introducción y objetivos: El Grupo de Psoriasis de la Academia Española de Dermatología y Venereología (AEDV) ha puesto en marcha un registro de pacientes con psoriasis en tratamiento con agentes biológicos, con el objetivo de analizar el riesgo de acontecimientos adversos (AA) relevantes a largo plazo: BIOBADADERM.

Material y métodos: Es un estudio de cohortes multicéntrico, con una cohorte de pacientes con psoriasis en terapia biológica y otra cohorte control de pacientes con psoriasis con tratamiento sistémico no biológico, excluida la fototerapia, en una relación 1:1. Se registraron los datos básicos de cada paciente, de los tratamientos y de los AA relevantes. Se analizó el riesgo asociado a un AA concreto, comparando su frecuencia de aparición en ambas cohortes.

Resultados: Se evaluaron los datos desde octubre de 2008 hasta noviembre de 2009 junto con datos retrospectivos desde 2005 sobre pacientes tratados con agentes biológicos. Participaron 13 hospitales de España. Se incluyeron 632 pacientes, 417 con biológicos y 215 controles. La suspensión del tratamiento biológico por AA fue poco frecuente (72 ciclos, 10%). Se comunicaron 232 AA en los pacientes con biológicos, la mayoría no graves, los más frecuentes las infecciones (la mayoría del tracto respiratorio superior/nasofaringitis), seguidos de los trastornos de la piel y el tejido subcutáneo. Entre los controles se notificaron 43 AA. Los más frecuentes fueron los trastornos del metabolismo y la nutrición y las alteraciones en las transaminasas. En términos de incidencia de AA, los biológicos presentaron un riesgo relativo (RR) de AA de 2,2 respecto a los controles ($p < 0,001$). En particular destacaron las infecciones e infestaciones (con un RR de 23 con $p<0,01$) y los trastornos de la piel y el tejido subcutáneo (RR: 4,9 con $p < 0,05$).

Conclusiones: Los pacientes tratados con fármacos biológicos presentan mayor número de AA que los controles, en particular en referencia a las infecciones y los trastornos de la piel. Sin embargo, debe tenerse en cuenta que tanto el tiempo de seguimiento como el limitado número de pacientes reclutados —en particular en el grupo de controles— impide extraer conclusiones definitivas. Por otro lado, la diferencia de porcentajes de AA referidos por los distintos centros pone de manifiesto la dificultad de la consideración del concepto de AA en la práctica clínica, siendo necesario homogeneizar los criterios. Aun a pesar de los problemas planteados, que deberán superarse en los próximos años, BIOBADADERM puede convertirse en la referencia obligada en la evaluación del perfil de seguridad de los fármacos biológicos en Dermatología.

Introduction

The safety and efficacy of new biologic therapies for psoriasis is essentially based on clinical trials, as a result of which, 4 drugs with an appropriate risk/benefit profile are currently approved in Europe for the treatment of psoriasis. These drugs are etanercept, infliximab, adalimumab, and ustekinumab. However, little is known about the long-term efficacy and safety of these drugs in nonselected populations. Clinical trials are necessary but not sufficient to establish the safety profile of new drugs, essentially for 3 reasons. The first reason is that clinical trials are usually performed on selected populations, which exclude groups of patients with higher comorbidity or risk of toxicity. The second reason is that the size of the clinical trials only provides sufficient statistical

power to detect the most common adverse events (AEs). Rare AEs, those with a frequency of less than 1 per 1000 patients, are not expected to be detected before the drug is marketed. Cases or series of cases are a starting point and make it possible to detect rare effects but not to prove a causal relationship. Cohort studies and case-control studies are better at detecting AEs.[1] The third reason is that clinical trials do not allow definition of long-term toxicity, as the follow-up periods of the trials are too short.

The usual systems of pharmacovigilance are spontaneous notification and phase IV studies carried out by the laboratories. Spontaneous notification is subject to limitations such as underreporting. The most appropriate pharmacovigilance strategy is the establishment of treatment records. The Spanish Agency for Medicines and Health Care Products (AEMPS) and the Spanish Society of Rheumatology established the BIOBADASER registry in 2000; the registry included biologic drugs used in rheumatologic diseases. However, the safety data on biologic drugs in other indications, such as rheumatologic diseases, cannot be entirely extrapolated to dermatology patients. The comorbidity of each of the underlying diseases is different. For this reason, for instance, metabolic syndrome is more common in patients with psoriasis. Furthermore, concomitant treatments are also different. Other examples of specific problems include the risk of exacerbation of psoriatic arthritis and episodes of psoriasis associated with a biologic drug. The Working Group on Psoriasis of the Spanish Academy of Dermatology and Venereology (AEDV) therefore decided in 2007 to start a registry of patients with psoriasis receiving treatment with biologic drugs (BIOBADADERM). The objectives of BIOBADADERM are the following:

1. To identify relevant AEs that appear during treatment of psoriasis using biologic therapies and to estimate their frequency.
2. To identify unexpected AEs, particularly those that can occur after long periods of exposure.
3. To identify relevant AEs that appear after suspension of treatment.
4. To estimate the relative risk of appearance of AEs in patients with psoriasis receiving biologic therapies compared to those receiving other systemic (nonbiologic) treatments.
5. To identify risk factors for adverse reactions to these treatments.

We describe the methodology of the registry and the preliminary results after the first year since BIOBADADERM was initiated.

Materials and Methods

Design

A cohort study was performed in 2 groups of patients with psoriasis, one treated with biologic drugs and the other with nonbiologic systemic drugs.

Study Sites

At the time the study was carried out, the hospitals taking part in BIOBADADERM were those shown in Table 1; these are essentially large hospitals with psoriasis units. Inclusion of patients began in October 2008 and biologic drugs were first sold in Spain in 2005. The national health system covers most of the cost of the treatments included in this study.

Patient Inclusion

BIOBADADERM is a treatment registry, and patients are included prospectively as they begin to receive the target treatment. Each hospital undertakes to include all consecutive patients who meet the inclusion criteria and provide informed consent. All patients who received a biologic drug for the first time are included in the cohort of patients receiving biologic drugs (initiation cohort). For each patient included in the cohort exposed to biologic drugs, another patient from the department must be included who has been prescribed a systemic, nonbiologic drug (methotrexate, cyclosporine or acitretin) and who has not previously received a biologic drug.

Some of the participating centers already had a high number of patients who were receiving biologic drugs when BIOBADADERM was started. Therefore, data were initially collected retrospectively in hospitals with a list of all patients who had received biologic drugs between 1 January 2005 and 30 October 2008. These patients were included if clinical follow-up with at least a 6-month frequency and including patient data and AEs could be shown.

Definition of Exposure

While other analysis methods may be chosen in the future to study long-term effects, in this study, which has a short follow-up time, it has been considered that patients are exposed to the biologic drug during treatment and for up to 2 half-lives thereafter. Patients in the control cohort who receive biologic drugs become part of the exposed cohort. Comparisons have been made with the cohort not exposed to biologic drugs. In order to attribute a side effect to a treatment, the time relationship was taken into account, with a lag for each side effect of between 0 days and 5 years (for example, 0 days for injection site reactions, 3 months for infections, and 5 years for tumors. The list of times used may be requested by writing to the corresponding author).

Follow-up

Patients included in BIOBADADERM will be followed indefinitely—initially, the scheduled 5 years' duration of the registry, with the option to extend this period. As clinical changes occur, the information is entered into the database. Patients must be seen at least once a year. They are also telephoned once a year to confirm their vital status and the data in the registry. To facilitate a uniform and thorough follow-up, standardized questions and a patient diary are used. The exposed and unexposed cohorts are followed in the same way.

Table 1 Participating Hospitals

Center	Autonomous Community	Patients		Treatments		Adverse Events	
Hospital Universitario Dr. Negrín	Canary Islands	121	19%	174	17%	33	12%
12 de Octubre	Madrid	101	16%	218	22%	66	24%
La Princesa	Madrid	90	14%	137	14%	64	23%
Hospital General U. de Valencia	Valencia	82	13%	128	13%	17	6%
Germans Trias i Pujol	Catalonia	81	13%	135	13%	54	20%
Hospital Clínico de Málaga	Andalusia	38	6%	48	5%	9	3%
Hospital Clinic	Catalonia	35	6%	58	6%	6	2%
Hospital del Mar	Catalonia	29	5%	41	4%	11	4%
Hospital de Alcorcón	Madrid	21	3%	29	3%	11	4%
Complejo Hospitalario de Pontevedra	Galicia	12	2%	12	1%	0	0%
Hospital Reina Sofía	Andalusia	12	2%	18	2%	4	1%
Hospital Infanta Leonor	Madrid	10	2%	10	1%	0	0%
Total		632	100%	1008	100%	275	100%

Variables Measured

To be able to describe the included population and evaluate potential confounding factors, the data shown in Table 2 are collected for each patient. The treatments administered and reasons for suspension of treatment are also recorded.

Results Measured

The principal objective of the registry is to describe the safety profile of the drugs. To this end, the relevant AEs are recorded using the nomenclature of the Medical Dictionary for Drug Regulatory Activities (MedDRA, available at http://www.meddramsso.com).

Relevant AEs are defined as any unfavorable events that meet the following criteria, regardless of the drug or dose received:

1. The event satisfies the legal definition of an AE (Royal Decree 711/2002 on Pharmacovigilance. EU Directive 2001-83) in that it causes death, endangers life (in real, rather than hypothetical, terms), requires admission to hospital or prolongs the patient's stay in hospital, causes a persistent or major disability, or causes congenital malformations.
2. The following are also considered as AEs that should be recorded: a) important medical events that do not immediately endanger life or cause death, but which compromise the patient or require intervention to prevent any of the results listed in the previous definition; and b) events that, while not considered severe, require suspension of treatment or nonscheduled medical care, including changes in the disease (worsening or changes in the type of psoriasis).

Information on concomitant treatments, severity of event, outcome, and, in the case of an infection, causal microorganism and infection site are also recorded for all patients who present an AE.

Table 2 Patient Data

General data: Date of birth, sex, weight, height, phototype
Psoriasis diagnosis: date of diagnosis, clinical form
Previous diseases: ischemic heart disease, heart failure, hypertension
Previous infectious diseases: hepatitis B virus, hepatitis C virus, human immunodeficiency virus
Risk habits: alcohol consumption and smoking
Previous treatment received for psoriasis (excluding topical treatments)
Current drug, start date, initial PASI score, date of suspension and reason
Tuberculosis date: prior history, vaccination, contacts, chemoprophylaxis, chest x-ray, Mantoux test, booster vaccinations

Abbreviation: PASI, Psoriasis Area and Severity Index.

Data Processing

The data for each patient have been reversibly anonymized and entered into a database. Data are entered over the Internet (http://biobadaser.ser.es/biobadaderm/). The data are stored in the Research Department of the Spanish Rheumatology Foundation.

Statistical Analysis

Statistical analysis was performed using the software package Stata 10 (StataCorp, College Station, TX, USA, 2009). The collected data have been described using conventional statistics (mean and SD, absolute and relative frequencies, and incidence density [person-years]).

The raw relative risks of the specific AEs were obtained by comparing their frequency of appearance in the 2

Table 3 Description of Patients

	Biologic Treatments	Controls	BIOBADADERM
Number of patients	417	215	632
Women, n (%)	115 (37)	93 (43)	248 (39)
Current age, y, mean (SD)	47 (14)	49 (16)	48 (14)
Age at start of treatment, y, mean (SD)	44 (14)	47 (15)	46 (14)
Duration of disease at start of treatment, y, mean (SD)	18 (12)	17 (15)	18 (13)
PASI score, mean (SD)	17 (11)	11 (7)	15 (11)
Principal diagnosis, n (%)			
Psoriasis			632 (100)

Abbreviation: PASI, Psoriasis Area and Severity Index.

cohorts, with and without biologic drugs, expressed with a 95% confidence interval.

Calculation of Sample Size

In the initially scheduled 5 years' duration of BIOBADADERM, data are expected to be collected for 5704 person-years in each group (patients exposed to biologic drugs and controls). These data will be sufficient to detect relative risks of between 1.5 and 2, with a power of 80% and a significance of 0.05, with incidences of between 4 and 10 cases per 1000 person-years in the control group.

Quality Assurance

The included data are continually revised on line by a study monitor to verify consistency, comprehensiveness, and absence of anomalies. An in situ follow-up visit is made every year, during which the data in the database are compared with those in the clinical records. Furthermore, patients are telephoned once a year to verify the information contained in the database.

Ethical Aspects

The study is carried out in accordance with the standards of good clinical practice and the legislation in force. The study protocol, drawn up at the request of the AEMPS, was approved by the ethics committee of Hospital 12 de Octubre, Madrid, Spain. Treatment is prescribed prior to and independently of participation in the registry.

BIOBADADERM receives funding from the Spanish Academy of Dermatology and Venereology, the Spanish Agency for Medicines and Health Care Products, and the pharmaceutical industry. The collaborating companies contribute similar amounts and do not take part in the analysis or interpretation of the results.

Results

BIOBADADERM began in October 2008. Data available in the database until November 2009 have been included. Thirteen hospitals from different Spanish autonomous communities voluntarily took part in the registry. The data corresponding to each of the hospitals are shown in Table 1.

A total of 632 patients were included. Most of the patients were men (n=384), with a mean (SD) age at start of treatment of 46 (14) years and a disease duration of 18 years. Table 3 shows the main characteristics of the patients in both cohorts. Although patients should ideally be included uniformly in both cohorts, in a proportion of 1:1, the data from the first year show a greater number of patients receiving biologic treatment (n=417) than controls (n=215). Patients receiving biologic drugs had a higher mean Psoriasis Area and Severity Index (PASI) than the controls (17 compared to 11) and had received a higher number of previous treatments.

Table 4 shows the description of the treatment cycles used. Treatment cycles are analyzed because the periods of exposure of each person to a treatment are compared to calculate the incidence of an AE. Data on the treatment periods or cycles in which patients are not exposed to biologic drugs are included. In this period of nonexposure, the study differentiates between pure controls (patients who are not receiving biologic drugs and who have not received them previously), which make up 25%, and contaminated controls (patients who are not receiving biologic drugs but who have been exposed to them previously), which make up 5% of the total treatment cycles.

Table 4 Description of Treatments

Drug	No. (%)
Etanercept	270 (27)
Infliximab	106 (10)
Adalimumab	172 (17)
Efalizumab	157 (15)
Ustekinumab	17 (2)
Receiving treatment with systemic drugs (controls previously exposed to biologic drugs)	48 (5)
Controls (not previously exposed to biologic drugs)	238 (24)
Treatment cycles	1008 (100)

Table 5 Survival and Reasons for Suspension of Treatment

Survival	No.	Percentage (95% CI)
First year	284	64 (59-68)
Second year	181	41 (37-46)
Third year	140	30 (26-34)
Reasons for suspension of treatment, n (%)		
Lack or loss of efficacy	209 (45)	
Adverse event	72 (16)	
Pregnancy or intention to become pregnant	6 (1)	
Loss of patient	9 (2)	
Remission	83 (18)	
Other	85 (18)	
Total suspensions	464 (100)	

Abbreviation: CI, confidence interval.

The most commonly used treatment is etanercept, followed by adalimumab, which together account for 40% of the treatments. Efalizumab is the third most frequently used drug but has not been used since the European Medicines Agency (EMA) suspended the drug in late February 2009. The number of controls is smaller than the number of patients receiving biologic drugs and represents little more than a quarter (29%) of all treatments. If the patients who are not pure controls are eliminated, the control subjects are reduced to 25%.

The median survival time for the biologic therapies is approximately 1.5 years. Follow-up times are still quite short. A total of 284 patients, who had been in follow-up for more than a year, were excluded from the analysis, as insufficient data were available. The reasons for interrupting treatment are shown in Table 5. The most common reason is lack or loss of efficacy, which represents almost half of all suspensions. The next most frequent reasons are remissions and the *Other* category, both with 18% (most of the cases under *Other* are due to suspension of efalizumab due to withdrawal of the drug by the authorities). Treatment was also suspended in 6 women due to pregnancy or the intention to become pregnant. Two pregnancies were recorded, which resulted in 2 healthy neonates.

The frequency and percentage of the different recorded AEs by large groups of organs and systems are shown in Table 6. This table shows the AEs that occur in the period when the patients are exposed to biologic therapy. Table 7 shows the AEs that occur when the patients are not exposed to biologic drugs (pure and contaminated controls). The most common AEs in patients receiving biologic drugs are infections and infestations, which account for almost 30% of all recorded AEs. Most infections (44%) involved the upper respiratory tract/nasopharyngitis. Two cases of tuberculosis were recorded—1 case of pulmonary tuberculosis and 1 case of pleural tuberculosis. Three

Table 6 Frequency of Adverse Events in Patients Receiving Biologic Drugs by Groups

AE in Patients Receiving Biologic Drugs	No.	Total Percentage of AEs
Infections and infestations	68	29.3
Skin and subcutaneous-tissue disorders	30	12.9
Laboratory abnormalities	22	9.5
Blood and lymphatic-system disorders	22	9.5
Musculoskeletal and connective-tissue disorders	16	6.9
Neurologic disorders	13	5.6
General disorders and injection site reactions	12	5.2
Hepatobiliary disorders	12	5.2
Benign, malignant, and nonspecified tumors (including cysts and polyps)	7	3.0
Traumatic lesions, poisoning, and treatment complications	5	2.2
Eye disorders	5	2.2
Metabolic and nutritional disorders	4	1.7
Gastrointestinal disorders	4	1.7
Respiratory, thoracic, and mediastinal disorders	4	1.7
Vascular disorders	4	1.7
Renal and urinary disorders	3	1.3
Reproductive-apparatus and breast disorders	1	0.4
Total	232	100

Abbreviation: AE, adverse event.

Table 7 Frequency of Adverse Events in Controls by Groups

AE in Controls	N	Total Percentage of AEs
Laboratory abnormalities	9	20.9
Metabolic and nutritional disorders	8	18.6
Hepatobiliary disorders	6	14.0
Vascular disorders	6	14.0
Skin and subcutaneous-tissue disorders	3	7.0
Gastrointestinal disorders	3	7.0
Cardiac disorders	2	4.7
Neurologic disorders	2	4.7
Psychiatric disorders	2	4.7
Infections and infestations	1	2.3
Renal and urinary disorders	1	2.3
Total	43	100

Abbreviation: AE, adverse event.

cases of latent tuberculosis were recorded (2 of these were reported under *Laboratory abnormalities* as positive Mantoux tests). Three cases of herpes zoster and 1 case of herpes simplex were also recorded. The second most common AEs are skin and subcutaneous-tissue disorders, at 13%. This section includes many similar and poorly specified terms from a dermatologic perspective. Most of the AEs reported are psoriasiform dermatitis, papular rash, papulosquamous rash, psoriasiform rash, general rash, psoriasis (in some cases, this is specified as a relapse or exacerbation of the patient's psoriasis and in others, as the symptoms reported with efalizumab, especially transitory papular rash). The next most common AEs are laboratory abnormalities (9.5%), especially liver abnormalities (increased transaminase) (7.5%) and blood abnormalities (9.5%). Tumors were recorded in 2 patients—1 with basal-cell carcinoma and 1 with breast cancer (0.43%).

The most common AEs in the control group are liver disorders (18.6%) and metabolic and nutritional disorders (hyperlipemia—raised levels of triglycerides and cholesterol) in 21% of patients, accounting for almost 40% of all recorded AEs. Infections account for little more than 2% and cardiovascular disorders represent almost 20% of AEs. No tumors were recorded in the controls.

Of the AEs recorded, 88% (241) were considered nonsevere events. The percentages are similar for the control group (93%) and the group of patients receiving biologic drugs (87%). However, the rate of severe AEs is 13% in the group of patients receiving biologic drugs and 5% in the control group. One death due to chronic renal failure was reported in the control group; however, this was a contaminated control, ie, the patient had previously been exposed to the biologic drug efalizumab.

Table 8 shows the incidences of all the AE that occurred during the first year of follow-up of the registry. We have differentiated between periods of exposure to biologic drugs and pure controls and the relative risks of both groups have then been calculated. The patients receiving biologic therapies present a higher number of AEs and more severe AEs than the controls. Infections and infestations, skin and subcutaneous-tissue disorders, and blood and lymphatic-system disorders are all more frequent in the group of patients receiving biologic drugs. The controls, however, present more metabolic and nutritional disorders (mainly raised levels of triglycerides and cholesterol), gastrointestinal disorders and vascular disorders. Both groups show equal numbers of hepatobiliary disorders and laboratory abnormalities.

Discussion

Registries such as this make it possible to follow the long-term safety and, in some cases, the efficacy of treatments (traditional and emerging treatments) in clinical practice in nonselected populations. The utility of safety registries for biologic drugs has been established by the proliferation of these drugs in Europe and by the results obtained from some of these registries, of which BIOBADASER is a consolidated example. This registry, the first in Spain and a predecessor of and example for BIOBADADERM, made it possible to detect a higher incidence of tuberculosis infection associated with biologic therapies,[2] which led to changes in clinical practice. There are several biologic-drug registries for psoriasis in Europe. The largest of these are in Italy, the United Kingdom, Sweden, Israel, Germany, and the Netherlands, and are part of the PSONET network (http://www.psonet.eu)—an initiative of the Italian Medicines Agency to merge registry data. This network currently includes 13 registries and a total of 15 000 patients with psoriasis who are receiving treatment with biologic drugs, although few data have yet been published.[3,4] BIOBADADERM is also part of the PSONET network, as part of an attempt to increase the efficiency and statistical power of the study. The PSONET project has been registered as a European contact network promoted by EMA, as part of the European Network of Centres of Pharmacovigilance and Pharmacoepidemiology.[5]

BIOBADADERM was designed based on the BIOBADASER model and adapted to Spanish patients with psoriasis. The cohort of patients exposed to biologic drugs includes all the biologic drugs approved to date and new drugs will continue to be added, as has happened with ustekinumab. The control cohort included patients receiving traditional systemic treatments (methotrexate, cyclosporine, and acitretin). As in other registries, phototherapy has been excluded in an attempt to make the patients of both cohorts as homogeneous as possible in terms of severity (PASI score), incidence of arthritis, etc.

This first report shows that biologic therapies are associated with a higher number of AEs than the controls. The cohorts are not completely homogeneous, as a larger number of patients has been included in the biologic-drug group than in the control group. Moreover, patients receiving biologic therapies had a somewhat higher PASI score and had received a higher number of previous treatments, which suggests that these patients had more severe psoriasis. This may explain the higher frequency of AEs. The inclusion of more patients receiving biologic treatments than controls is due, in the first place, to the fact that patients receiving biologic treatments were included retrospectively since 2006, as all their data was available, whereas control patients were only included prospectively. It should also be noted that many of the researchers are heads of psoriasis departments where mainly severe and moderate cases are seen—many of which require continuous treatment and are therefore candidates for new biologic therapies.

The most widely used biologic drug is etanercept, according to this first report. This may be partly explained by the fact that etanercept was approved earlier, resulting in greater knowledge of the drug and familiarity with its use in dermatology, and a longer history of prescription.

It should be noted that a large number of treatment cycles were suspended (464 out of 722 cycles). Suspension due to adverse effects is rare (72 cycles; 10%). The percentage of treatments suspended due to lack or loss of efficacy (45% of all suspensions of biologic drugs;

Table 8 Incidence of Adverse Events

Incidence (95% CI) x 1000	Patients Receiving Biologic Drugs	Controls	Relative Risk
Total adverse events	280 (248-316)	127 (91-175)	2.2 (1.6-3.1)***
Severe adverse events	41 (30-56)	7 (2-28)	5.8 (1.4-24.1)*
Fatal adverse events	-	-	-
Infections and infestations	81 (64-101)	4 (0-25)	23 (3.2-165.3)**
General disorders and injection site reactions	13 (7-23)	-	-
Skin and subcutaneous-tissue disorders	34 (24-49)	7 (2-28)	4.9 (1.2-20.5)*
Gastrointestinal disorders	5 (2-13)	11 (3-33)	0.5 (0.1-2.1)
Neurologic disorders	15 (9-25)	7 (2-28)	2.1 (0.5-9.4)
Laboratory abnormalities	25 (16-37)	25 (12-52)	1 (0.4-2.4)
Cardiac disorders	-	7 (2-28)	-
Musculoskeletal and connective-tissue disorders	20 (13-32)	-	-
Benign, malignant, and nonspecified tumors (including cysts and polyps)	13 (7-23)	-	-
Respiratory, thoracic, and mediastinal disorders	4 (2-11)	-	-
Vascular disorders	4 (2-11)	14 (5-37)	0.3 (0.1-2.1)
Blood and lymphatic-system disorders	29 (20-42)	-	-
Medical and surgical procedures	-	-	-
Traumatic lesions, poisoning, and treatment complications	6 (3-14)	-	-
Eye disorders	6 (3-14)	-	-
Renal and urinary tract disorders	3 (1-10)	-	-
Hepatobiliary disorders	14 (8-24)	21 (9-47)	0.7 (0.3-1.8)
Psychiatric disorders	-	7 (2-28)	-
Reproductive-apparatus and breast disorders	1 (0-8)	-	-
Immune-system disorders	-	-	-
Metabolic and nutritional disorders	4 (2-11)	25 (12-52)	0.2 (0.1-0.6)**
Endocrine disorders	-	-	-
Disorders of the middle and inner ear	-	-	-
Pregnancy, puerperium, and perinatal diseases	-	-	-
Congenital, family, and genetic disorders	-	-	-
Social circumstances	-	-	-
Heart failure	-	-	-
Acute myocardial infarction	-	4 (0-25)	-
Tuberculosis	3 (1-10)	-	-
Lymphoma	-	-	-
Demyelination	-	-	-
Chickenpox	-	-	-
Herpes zoster	2 (1-9)	-	-

*$P<.05$; **$P<.01$;***$P<.001$.
Abbreviation: CI, confidence interval.

29% of instated cycles) may seem surprising. In order to appropriately evaluate this figure, it should be noted that all the treatments in this category were either treatments that were suspended after the maximum treatment period indicated in the summary of product characteristics had expired and the expected improvement had not been achieved, or treatments in which the decision was made to change to another biologic drug. This change probably occurs with greater frequency now due to the greater expectations of patients and dermatologists and the availability of different drugs.

Only 9 patients (2%) were lost to follow-up. This fact, together with the follow-up of the data, carried out by an external monitor on line almost in real time and in situ once a year, gives an idea of the high quality of the information gathering. However, it is also true that there is some discrepancy in the percentages of AEs notified by the different hospitals, with some hospitals not reporting any AEs. It is very difficult to standardize the notification of AEs in clinical practice, but we believe that, with the follow-ups and the different meetings of the researchers, these differences will gradually be reduced.

As mentioned, the incidence of AEs is higher in patients receiving biologic drugs than in controls, particularly infections and infestations. However, as we have stated, most of these are infections of the upper respiratory tract, which were not severe and resulted in recovery without sequelae. The differences are significant and, although there are many confounding factors, as discussed below, these results lead us to continue to be vigilant and watch future analyses. We must note that, although statistically significant differences exist, the incidence figures are not consistent, as the follow-up periods and the number of individuals are still relatively small. Moreover, the values used to interpret relative risks were not adjusted for other possible confounding factors, such as indication, comorbidity, sociodemographic factors, concomitant treatments, and severity of the disease. It would also be interesting for future analyses to be able to include the time between the appearance of the AEs and the start of treatment in order to determine whether notification is higher at the beginning, as happens in some clinical trials.[6]

The following factors also need to be taken into consideration:

1. Possible information bias. Patient follow-up is not blinded with regard to patient exposure and this may lead physicians to be more thorough in reporting AEs in exposed patients. To try to minimize this bias, an attempt will be made to use standard definitions and objective measurements of the AEs,[7] and to reach standardized consensus of expert groups in notification of AEs.[8] Furthermore, the follow-up telephone calls (to obtain data on patients' vital status and hospital admissions) will be blinded regarding the group to which the patient belongs. If this bias exists, it would favor the objectives of pharmacovigilance (detection of AEs).
2. Heterogeneity of exposure. We have initially considered all biologic drugs and all systemic drugs as a single group. The different drugs should have different toxicity profiles. It is also probable that many patients will receive several drugs from each group. In order to evaluate this confusion of possible etiologic agents, it will be necessary to divide the sample in real terms or by means of statistical techniques such as multivariate analysis. For these analyses to provide satisfactory results, a very large initial sample should be used for rare adverse reactions. These questions can probably only be answered by means of the PSONET network or by combining the BIOBADASER and BIOBADADERM data on drugs commonly used in dermatology and rheumatology.

We will also have difficulty detecting rare adverse effects. PSONET will be a useful tool for detecting these adverse effects (it is estimated that, in 5 years, it will contain data on 150 000 person-years of treatment with biologic drugs).

Despite the difficulties, these registries are currently the best available means of studying the medium-term and long-term safety of new treatments. The objective of this registry is to provide practitioners with quality information on the adverse effects of these new treatments in the short, medium, and long term, to allow them to make therapy decisions based on scientific evidence and to contribute to improving management of patients with severe or moderate psoriasis. The registry is not a clinical guide for the treatment of psoriasis, as BIOBADADERM does not analyze efficacy or cost, and good Spanish and international guidelines based on expert opinion and analysis of the literature are already available.[9,10,11,12] Nor is it a series of patients with psoriasis treated with biologic drugs, such as that already published by another member of the AEDV Working Group on Psoriasis,[13] which also provides us with considerable information, although with the biases inherent to this type of study (retrospective, noncontrolled study). BIOBADADERM is a project with a future and was specifically designed to detect adverse effects.

In conclusion, we describe the results of the first BIOBADADERM report. The importance of this prospective cohort study designed to detect AEs in patients with psoriasis who are receiving treatment with biologic drugs should be noted. In this first report, while there are statistically significant differences between AEs in patients receiving biologic drugs and controls, the incidence figures for the AEs are not consistent, as the follow-up period and number of individuals are still small. Patients receiving biologic drugs appear to present a higher number of AEs than controls. The most frequent AEs in patients receiving biologic drugs are infections, infestations, skin and subcutaneous-tissue disorders, blood and lymphatic-system disorders, and laboratory abnormalities. The most frequent AEs in controls are metabolic, nutritional, gastrointestinal, and vascular disorders. The difference in the percentages of AEs reported by the different hospitals highlights the difficulty involved in collecting data on AEs in clinical practice.

The efforts of all those taking part in BIOBADADERM are laudable. The information arising from this project will help us to improve the way we treat our patients. This information will be available to all academics, in the form of annual reports, from the AEDV website (http://www.aedv.es).

Conflict of Interest

BIOBADADERM receives funding from the Spanish Academy of Dermatology and Venereology, the Spanish Agency for Medicines and Health Care Products, and the pharmaceutical industry (Abbott, Merck-Schering Plough, Pfizer-Wyeth). The collaborating laboratories contribute similar amounts and do not take part in the analysis or interpretation of the results.

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