STUDY

Risk of Serious Adverse Events Associated With Biologic and Nonbiologic Psoriasis Systemic Therapy

Patients Ineligible vs Eligible for Randomized Controlled Trials

Ignacio Garcia-Doval, MScEpid, PhD; Gregorio Carretero, PhD; Francisco Vanaclocha, PhD; Carlos Ferrandiz, PhD; Esteban Daudén, PhD; Jose-Luis Sánchez-Carazo, MD; Mercé Alsina, MD; Enrique Herrera-Ceballos, PhD; Francisco-José Gómez-García, MD; Marta Ferrán, MD; Jose-Luis López-Estebaranz, MD; Jose-Manuel Hernanz, MD; Isabel Belinchón-Romero, PhD; Jaime Vilar-Alejo, MD; Raquel Rivera, MD; Jose-Manuel Carrascosa, PhD; Cristina Carazo, MD

Objective: To describe the use of systemic therapy for psoriasis (biologic and nonbiologic [classic] drugs) in patients not adequately represented in randomized controlled trials (RCTs) and the risk of serious adverse events (SAEs) in these patients.

Design: A registry inception cohort was used.

Setting: Thirteen dermatology departments in Spain participated.

Patients: A consecutive sample of patients treated with biologics and a systematic sample of patients treated with classic systemic therapy were evaluated. A total of 1042 patients (2179 person-years) were included.

Exposure: Inadequate representation in trials was defined as the presence of any of the following factors: elderly age (>70 years); type of psoriasis other than chronic plaque psoriasis; history of infection caused by hepatitis B, hepatitis C, or human immunodeficiency virus; history of cancer (excluding nonmelanoma skin cancer); and chronic renal or hepatic disease.

Main Outcome Measures: Serious adverse events as defined by the International Conference on Harmonization were evaluated.

Results: In all, 29.8% of patients receiving systemic therapy for psoriasis would not have been eligible for RCTs. These individuals had an increased risk of SAEs (incidence rate ratio, 2.7; 95% CI, 1.5-4.7). Patients exposed to biologics had an adjusted increased risk of SAEs (incidence rate ratio, 2.3; 95% CI, 1.1-4.8) that was similar in patients eligible and ineligible for RCTs.

Conclusions: Patients ineligible for RCTs are an important proportion (30%) of those receiving systemic therapy for psoriasis. These patients have a higher risk of SAEs and should be closely monitored. Patients exposed to biologics (whether these patients are eligible for RCTs or ineligible) are susceptible to the same increase in risk of SAEs, but biologics add to a higher baseline risk in patients who are ineligible for RCTs. The risk-benefit ratio in ineligible patients receiving biologics might be different from the ratio in eligible patients.

Arch Dermatol. 2012;148(4):463-470

PSORIASIS HAS A PREVALENCE OF 1% to 3% in the general population.[1,2] Several systemic therapies are available for the treatment of moderate-to-severe psoriasis. Methotrexate sodium, cyclosporine, and retinoids are the main classic therapies; biologics are a newer group of drugs with different, immune-centered mechanisms of action. Given their frequent and long-term use, safety of systemic treatments for psoriasis is a relevant issue.[3,4] Knowledge about the safety of systemic drugs in psoriasis, especially biologics, has been obtained mainly from randomized controlled trials (RCTs) or their extensions.[5,6] A meta-analysis[5] of RCTs of biologics for any indication has shown that they are associated with adverse events more frequently than the control agents are, although the rate of serious adverse events (SAEs) was not statistically significantly different between biologics and controls. However, patients enrolled in RCTs are selected using inclusion and exclusion criteria that aim to, among their other goals, avoid risks to participants.[7] When drugs are approved and prescribed in clinical practice, they are administered to more varied patients, including some who might not be adequately represented in RCTs and for whom RCT results on efficacy and safety might not apply.[8]

Author Affiliations are listed at the end of this article.

Registries may be more representative of clinical practice.[9] Some rheumatology studies[10] have shown that many patients who are treated with biologics would not be eligible for RCTs and explored the differences between patients enrolled in RCTs and those receiving these drugs in clinical practice. Efficacy of anti–tumor necrosis factor drugs in rheumatoid arthritis was lower in patients not eligible for RCTs.[11,12] Overall, the risk-benefit ratio in the real-world setting could be worse than in RCTs.

The Spanish Registry of Adverse Events Associated With Biologic Drugs in Dermatology (BIOBADADERM) includes patients with psoriasis who are receiving systemic therapy, including biologics. The goal of BIOBADADERM is to document safety outcomes. We used this registry as the source of data for this study.

Our objective was to describe the proportion of patients receiving systemic drugs for psoriasis in clinical practice who were not adequately represented in RCTs, a change in the proportion over time, and whether these patients have a different risk of SAEs. A secondary objective was to evaluate differences in the risk of SAEs associated with the administration of biologics in patients not represented in RCTs.

METHODS

A description of BIOBADADERM has been published.[13] Thirteen dermatology departments, widely distributed across Spain, participate in this registry. Biologics have been commercially available in Spain since 2005. Package information indicates that they should be used after failure of classic systemic therapy, and some hospitals have additional restrictions for prescription. The National Health System includes the cost of all study drugs in most circumstances. All BIOBADADERM data from January 1, 2005, to November 1, 2010, were included in this study. In participating hospitals, all patients receiving biologics were included in BIOBADADERM, as well as a systematic sample of patients receiving other systemic therapies (ie, the next patient who starts a systemic therapy for the first time). Only patients who did not agree to participate were excluded. The BIOBADADERM registry was started in October 2008. Because many patients in some centers received biologic drugs at the time that they joined BIOBADADERM, we accepted data collected retrospectively given that participating departments included all patients who had received biologics in the center, had all the required information, and had monitored patients at least twice each year. For this retrospective collection group, some centers included patients starting phototherapy as a comparison group for biologics, since those were the only patients systematically registered. From October 2008, the study included prospective data collection (66% of the total follow-up periods), and patients who had received phototherapy were not included.

The following data were collected systematically. At baseline, demographic data, diagnosis, and comorbidities were documented. For each new therapy that was started, we recorded the drug, start and discontinuation dates, and reasons for discontinuation. Data on adverse events were collected as they occurred, including date of occurrence, diagnosis using Medical Dictionary for Regulatory Activities (MedDRA, version 7.1; http://www.meddramsso.com/index.asp) coding, concomitant therapies, severity, and outcome. (MedDRA terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.) Patients must have been contacted at least once each year, although more frequent visits are usually part of their standard care. A patient diary, with questions relevant to detect SAEs, is also used to improve outcome reporting. Once a year, data are validated by on-site audits mainly focused on measure of drug exposure and SAEs and review of the entire record for a sample of patients. In case of inconsistency between the documents, information from the patient records was accepted as true.

Following the *International Conference on Harmonisation E2A Guideline*,[14(p3)] an SAE is defined as "any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect." Serious adverse events were reviewed to avoid duplicates, as some of them were part of the same pathologic process (ie, melanoma and metastasis or diplopia and neurodegenerative disease), and we included the time of the first sign and the most general name.

To define patients not eligible for RCTs, we reviewed the inclusion and exclusion criteria of RCTs included in a recent systematic review[4] of systemic therapy for psoriasis, including biologics and nonbiologic agents, and selected the most common exclusion criteria. Twenty-four RCTs were included in the meta-analysis in this review. Some articles did not fully describe selection criteria but used expressions such as "key exclusion criteria were" or "included patients were candidates for systemic therapy." Description of hepatitis B virus infection as an exclusion criterion was frequently inadequate, without making a clear distinction between active and past infection. The factors that we chose were elderly age (>70 years) (reported to be an exclusion criterion in 12 of the 24 RCTs); type of psoriasis different from plaque psoriasis (21 RCTs); history of infection caused by hepatitis B, hepatitis C, or human immunodeficiency viruses (19 RCTs); history of cancer (excluding nonmelanoma skin cancer) (17 RCTs); and chronic renal or hepatic disease (18 RCTs).

Because the original aim of BIOBADADERM was to compare risks of biologics with those of classic systemic therapy, we defined periods of exposure to classic systemic therapy as the time from a patient's entry into the cohort (on the basis of first administration of a classic systemic therapy) to their first exposure to biologics, censoring date, death, or November 1, 2010, whichever occurred first. Patients' exposure to biologics in each treatment cycle was defined as the time from the first administration until twice the drug's half-life after the final dose of that cycle. An adverse event was considered to be temporally related to a drug if there was overlap between the time of exposure and a lag window before the event. Lag windows can be observed at the BIOBADADERM website.[15] Most of these windows are longer than 30 days. The lag window is 90 days for infections and reaches a maximum of 5 years for neoplasms.

We used the unpaired 2-tailed t test and χ^2 test to compare baseline data. Univariable analysis consisted of description of frequencies and rates, both crude and stratified. Data across strata were compared using tests for heterogeneity and were combined, when there was no evidence of heterogeneity, using the Mantel-Haenszel method. Multivariable analysis consisted of Cox regression after graphically checking the proportional risks assumption. Confounding was explored by observing the change in each association after including the possible confounder in the model. To assess interaction terms, we included the interaction term in the model and evaluated the difference with the model without the interaction term using the likelihood ratio test. For missing data in the measured exposures, we took a conservative approach by considering that missing data were negative (ie, exposure had not occurred). We repeated the analysis on data with missing values and checked that none of the results was significantly changed. Sensitivity analysis was also performed excluding retrospectively collected data. All analysis was performed using commercial software (Stata 10.1; StataCorp).

Table 1. Baseline Characteristics of Patients Included in the BIOBADADERM Cohort: Factors Leading to Ineligibility and Other Comorbidities[a]

Characteristic	No. (%)		
	Classic Systemic Therapy	Biologics	BIOBADADERM, Total
Patients	463 (44.4)	579 (55.6)	**1042** (100)
Person-years	626.1	1553.2	**2179.3**
Female sex[b]	192 (41.5)	205 (35.4)	**397** (38.1)
Age, mean (SD), y[b]	46 (15)	44 (13)	45 (14)
Age >70 y[b]	46 (10.0)	31 (5.4)	**77** (7.4)
Psoriasis different from chronic plaque psoriasis	60 (13.0)	67 (11.6)	**127** (12.2)
Length of disease when treatment began, mean (SD), y[b]	16 (14)	19 (12)	17 (13)
PASI when included in BIOBADADERM, mean (SD)[b]	10 (7)	16 (10)	14 (9)
Ineligible for RCTs	149 (32.2)	161 (27.8)	**310** (29.8)
Treatment cycles	Acitretin, 127 (22.7) Cyclosporine, 136 (24.3) Methotrexate sodium, 232 (41.5) PUVA, 14 (2.5) UV-B of 311 nm, 49 (8.8) UV-B wideband, 1 (0.2)	Adalimumab, 343 (27.4) Efalizumab, 199 (15.9) Etanercept, 447 (35.7) Infliximab, 163 (13.0) Ustekinumab, 101 (8.1)	
Comorbidity at enrollment			
Ischemic heart disease	18 (3.9)	13 (2.2)	**31** (3.0)
Heart failure	2 (0.4)	4 (0.7)	**6** (0.6)
Hypertension	106 (23.0)	122 (21.1)	**228** (21.9)
Diabetes mellitus	52 (11.2)	64 (11.1)	**116** (11.1)
Hypercholesterolemia	81 (17.5)	122 (21.1)	**203** (19.5)
Chronic obstructive pulmonary disease	6 (1.3)	14 (2.4)	**20** (1.9)
Chronic hepatic disease	16 (3.5)	45 (7.8)	**61** (5.9)
Chronic renal failure	7 (1.5)	6 (1.0)	**13** (1.2)
History of cancer[b,c]	22 (4.8)	10 (1.7)	**32** (3.1)
History of hepatitis B infection	23 (5.0)	24 (4.1)	**47** (4.5)
History of hepatitis C infection	8 (1.7)	12 (2.1)	**20** (1.9)
History of HIV infection	6 (1.3)	5 (8.6)	**11** (1.1)

Abbreviations: BIOBADADERM, *Spanish Registry of Adverse Events Associated With Biologic Drugs in Dermatology;* HIV, human immunodeficiency virus; PASI, Psoriasis Area and Severity Index; PUVA, psoralen–UV-A; RCTs, randomized controlled trials.

[a] Within BIOBADADERM in November 2010.

[b] Statistically significant difference (χ^2 or *t* test, $P < .05$).

[c] Excluding nonmelanoma skin cancer.

The BIOBADADERM registry has been approved by the Hospital 12 de Octubre Ethics Committee, and all patients provided written consent to participate.

RESULTS

PARTICIPANTS

Patients are described in **Table 1**, with statistically significant baseline differences indicated. Mean follow-up was 2.1 years (median, 1.9 years). Only 2 patients refused to participate in the study. The mean (SD) number of treatment cycles per patient during the study period was 1.6 (0.9; range, 1-8). Five percent of the treatment cycles were classic systemic therapies started after withdrawal of a biologic drug. These were excluded as control periods. Only 19 treatment cycles consisted of a biologic drug and a classic drug—these periods were considered as times of exposure to biologics. Further details have been published.[13]

PATIENTS NOT ELIGIBLE FOR RCTs: DESCRIPTION AND CHANGE

In all, 29.8% of the patients were ineligible for RCTs. The prevalence of factors leading to ineligibility for RCTs is detailed in Table 1. The most frequent factors were treatment of psoriasis other than chronic plaque psoriasis (12.2% of patients), age older than 70 years (7.4%), chronic hepatic disease (5.9%), and history of hepatitis B infection (4.5%).

Other forms of psoriasis being treated included guttate psoriasis (54 cases [5.2% of patients]), palmoplantar pustular psoriasis (35 [3.4%]), erythrodermic psoriasis (28 [2.7%]), generalized pustular psoriasis (15 [1.4%]), and annular pustular psoriasis (5 [0.5]).

The percentage of patients not eligible for RCTs was similar in patients treated with classic systemic therapy and those receiving biologics and did not change significantly during the study in any of the groups (for classic drugs: χ^2, $P = .29$ [test for trend, $P = .63$]; for biologics: χ^2, $P = .29$ [test for trend, $P = .68$]) (**Figure**).

OUTCOME: SAEs

Fifty-nine SAEs were reported during the study (**Table 2**). The overall rate of SAEs in BIOBADADERM was 23.4 per 1000 person-years (95% CI, 17.8-30.8). The rates were 16.5 (95% CI, 11.2-24.2) for patients eligible for RCTs and 41.6 (95% CI, 28.1-61.6) for those not eligible. The

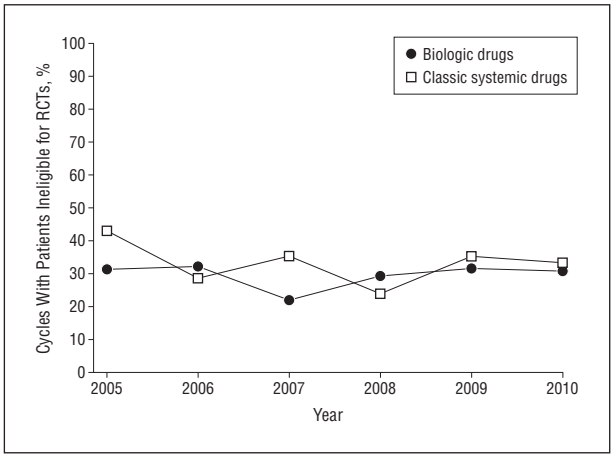

Figure. Evolution of the percentage of treatment cycles with systemic therapy (either classic or biologic drugs) in patients who would be ineligible for randomized clinical trials (RCTs). Biologics have been commercially available in Spain since 2005.

rates of SAEs were 14.4 (95% CI, 7.5-27.6) for patients exposed to classic systemic drugs and 27.0 (95% CI, 20.0-36.6) for those receiving biologics.

Clinical outcomes of SAEs are detailed in Table 2. Overall, most patients (35 of 59 [59.3%]) recovered without sequelae; 12 (20.3%) had not recovered at the time of data collection, 9 (15.3%) recovered with sequelae, and 3 (5.1%) died, but none of the deaths was considered to be related to the drugs. Clinical outcomes distribution was similar for those eligible and ineligible for RCTs (χ^2, $P=.99$) and for those exposed and unexposed to biologics (χ^2, $P=.53$).

UNIVARIABLE ANALYSIS

We report the results of univariable analysis in **Table 3**. Possible risk factors for SAEs (reasons for ineligibility for RCTs) were stratified on exposure to biologics with the aim of detecting interactions. Because results of none of the statistical tests for interaction was significant, even if we used a $P=.10$ threshold to take into account the low power of these tests, we report the overall incidence rate ratios (IRRs) for each risk factor, obtained using the Mantel-Haenszel method.

The crude IRR of SAEs for exposure to biologics in the whole data set was 1.90 (95% CI, 0.90-4.40).

MULTIVARIABLE ANALYSIS

We used Cox regression to further analyze the results from univariable analysis. Incidence rate ratios of SAEs for each risk factor, unadjusted and adjusted for exposure to biologics, were similar to those reported in the univariable analysis (within 10% variation) (Table 3). None of the likelihood ratio tests comparing models with and without interaction terms produced results that met the threshold of $P<.10$ (Table 3). A Cox model including ineligibility for RCTs and exposure to biologics produced adjusted IRRs of 2.6 (95% CI, 1.5-4.5) for ineligibility for RCTs and 2.3 (95% CI, 1.1-4.8) for exposure to biologics. Age was a very important risk factor; to check for the role of residual confounding when age was categorized in 2 groups, we used a model including age as a continuous variable. This confirmed that adding the other significant factors detailed in Table 3 to the model was associated with significant improvement using the likelihood ratio test, and significant risk factors were unchanged. A best-fit model obtained using backward selection included the variables ineligibility for RCTs, exposure to biologics, age older than 70 years, and previous infection with hepatitis B virus, but the IRR for each factor remained unchanged from those of univariable analysis.

SENSITIVITY ANALYSIS

We repeated the analysis without any modification in missing values and found no relevant changes in the results except for wider CIs. There were no significant differences in the rates of SAEs between prospectively and retrospectively collected data ($P=.89$). The results did not show relevant changes if only prospectively collected data were analyzed.

COMMENT

PREVALENCE OF INELIGIBILITY FOR RCTs

We have shown that 29.8% of the patients receiving systemic therapy for severe psoriasis in clinical practice in Spain were not adequately represented in RCTs. This large percentage did not change during the study and was not significantly different for patients receiving biologic vs classic drugs.

This finding might depend on the definition of ineligible patients. We believe that we used the less-biased approach to define this group. We selected all RCTs included in the only systematic review[4] that mixed biologic and nonbiologic therapies and used nearly universal exclusion criteria. Exclusion criteria in this review were homogeneous because all drugs in the quantitative analysis of the systematic review, except for fumaric acid derivatives, affect the immune system. A limitation is that there were no RCTs of retinoids, which are likely to have different exclusion criteria.

We believe that our study population is representative of the use of systemic therapy in Spain, with 29.8% of the patients being ineligible for RCTs. Some selection bias is possible because facilities participating in BIOBADADERM are mainly large dermatology departments, but they mostly serve as secondary care centers for psoriasis, receiving patients from their geographic area rather than from other dermatology departments. This percentage of ineligible patients might not be generalizable to other countries, since the prevalence of some of the ineligibility factors varies geographically (eg, percentage of elderly people or prevalence of chronic infections). However, we believe that the results reported herein are likely to be generalizable to most settings and that data on the risks associated with each factor are widely generalizable.

Our results suggest that once biologics were introduced into the market, they were administered to most patients in need of therapy, and there is no evidence of a precautionary, stepped-wedge introduction that took into

Table 2. Description of SAEs

	Eligibility for RCT			
	Eligible		Not Eligible	
MedDRA Diagnostic Group of SAEs	No. of Cases[a]	MedDRA Diagnosis[b]	No. of Cases[a]	MedDRA Diagnosis[b]
Infections and infestations	6	Abscess, bacterial[c] AIDS[c] Encephalitis, viral Pulmonary tuberculosis[c,d] Skin infection[c] Tuberculous pleurisy[c]	2	Herpes simplex[c] Pneumonia, bacterial[c]
Neoplasms: benign, malignant, and unspecified	4	Acral lentiginous melanoma, stage II[d] Gastric cancer[c,e] Large-cell lung cancer, stage IV[c,d] Lymphoproliferative disorder in remission[c]	6	Basal cell carcinoma[c] Basal cell carcinoma[f] Breast cancer[c] Breast cancer in situ[c] Lung adenocarcinoma, stage I Lung neoplasm, malignant[c,d]
Skin and subcutaneous tissue disorders	4	Psoriasis (2 cases)[c] Rash, papulosquamous (2 cases)[c]	2	Rash, psoriaform (2 cases)[c]
Nervous system disorders	3	Cerebral infarction[c,f] Demyelination[c,f] Neurodegenerative disorder[c,d]	2	Ischaemic stroke[c,f] Thrombotic stroke[c]
Musculoskeletal and connective tissue disorders	2	Arthritis, reactive[c] Psoriatic arthropathy[c,f]	2	Localized osteoarthritis[c] Psoriatic arthropathy[c,d]
Blood and lymphatic system disorders	1	Autoimmune neutropenia[c]	3	Anaemia Haematotoxicity[c] Thrombocytopenia[c]
Cardiac disorders	1	Acute coronary syndrome[c,f]	4	Acute myocardial infarction[c] Acute myocardial infarction Acute coronary syndrome[c,f] Angina, unstable[d]
Gastrointestinal disorders	1	Crohn disease[c,d]	0	
General disorders and administration-site disorders	1	Localized edema[c]	2	Death[e] Influenza-like illness[c]
Hepatobiliary disorders	1	Hepatic function abnormal[c]	1	Hepatic function abnormal[c]
Immune system disorders	1	Drug hypersensitivity[c]	0	
Injury, poisoning, and procedural complications	1	Transfusion reaction[c]	0	
Psychiatric disorders	1	Completed suicide[c,e]	0	
Respiratory, thoracic, and mediastinal disorders	1	Pneumonitis[c]	0	
Vascular disorders	1	Peripheral vascular disorder[c]	0	
Metabolism and nutrition disorders	0		4	Diabetes mellitus, inadequate control[c,d] Hypercalcaemia[c] Hyperkalaemia[c,f] Hypertriglyceridaemia[f]
Renal and urinary tract disorders	0		1	Renal failure, acute[c]
Vascular disorders	0		1	Hypertensive emergency[c]
Total	**29**		**30**	

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; RCT, randomized controlled trial; SAEs, serious adverse events.
[a] The number of cases should not be assessed in terms of risk because the period at risk for each group was different. Because of the low number of cases, risk calculations for each group are not meaningful.
[b] Outcomes are indicated. If not specified, the patient recovered without sequelae.
[c] Indicates SAE occurred while the patient was exposed to biologics.
[d] Patient had not yet recovered.
[e] Patient died.
[f] Patient recovered with sequelae.

account the limitations of generalizability of RCTs. This suggests the need for adjustments on both sides. Clinicians should be aware of this probably inappropriate extrapolation of results of RCTs to many patients in common clinical practice and should probably integrate information from different sources, such as registries. On the other side, as we increase our knowledge about the safety of new drugs, clinical trial investigators should use inclusion criteria that better fit the group needing therapy in the real-world setting.

RISK OF SAEs ASSOCIATED WITH INELIGIBILITY FOR RCTs

Patients not eligible for RCTs were more likely to experience SAEs. Among the ineligibility factors, previous cancer (excluding nonmelanoma skin cancer) and age older than 70 years showed significant associations with the risk of SAEs. Other factors were present in small percentages of the population, leading to wide CIs for the estimation of their risks. Numbers needed to treat to harm are fre-

Table 3. Risk of Serious Adverse Events Associated With Reasons for Ineligibility for RCTs[a]

Factor Leading to Ineligibility for RCTs	Univariable Analysis, IRR (95% CI)				Multivariable Analysis of Risk After Adjustment for Exposure to Biologics, HR (95% CI)[d]
	Risk in Patients Not Exposed to Biologics	Risk in Patients Exposed to Biologics	*P* Value[b]	Combined Crude IRR[c]	
Age >70 y	3.3 (0.5-15.4)	3.5 (1.2-8.3)	.95	**3.4 (1.6-7.1)**	**3.4 (1.6-7.1)**
Psoriasis different from chronic plaque psoriasis	1.9 (0.2-9.8)	1.8 (0.7-4.1)	.95	1.8 (0.9-3.7)	1.8 (0.9-3.6)
History of hepatitis B infection	7.1 (0.7-37.1)	1.6 (0.3-5.0)	.13	2.3 (0.9-5.8)	2.3 (0.9-5.8)
History of hepatitis C infection	0 (0-48.1)	3.3 (0.4-12.8)	.84	2.9 (0.7-11.8)	2.6 (0.6-10.6)
History of HIV infection	0 (0-51.1)	0 (0-13.1)	>.99	. . .	. . .
History of cancer[e]	12.5 (2.0-58.5)	3.7 (0.7-11.6)	.12	**4.9 (1.9-12.7)**	**4.8 (1.9-12.0)**
Chronic renal disease	0 (0-28.3)	5.6 (0.7-21.8)	.61	3.9 (0.95-15.9)	4.1 (0.99-17.0)
Chronic hepatic disease	6.3 (0.1-47.2)	2.0 (0.6-5.2)	.32	2.3 (0.99-5.4)	2.2 (0.94-5.2)
Overall ineligibility	7.2 (1.4-70.8)	2.2 (1.1-4.2)	.17	**2.7 (1.5-4.7)**	**2.6 (1.5-4.5)**

Abbreviations: HIV, human immunodeficiency virus; HR, hazard ratio; IRR, incidence rate ratio; RCT, randomized controlled trial.

[a] Statistically significant results are shown in boldface type. Because an interaction with exposure to biologics was a major area of evaluation, we report the results stratified on exposure to classic drugs vs biologics, as well as a test for interaction.

[b] Test of homogeneity of IRR of serious adverse effects in patients not exposed and in those exposed to biologics (test for interaction between ineligibility and exposure to biologics).

[c] Mantel-Haenszel test used.

[d] Cox HR.

[e] Excluding nonmelanoma skin cancer.

quently used to easily compare absolute risks of alternative therapies. They are not exactly applicable to our data because we cannot change the baseline characteristics of our patients, and numbers needed to treat to harm implies a causal relationship that might not be present in some of the reported associations; however, they serve the purpose of illustrating the absolute risks associated with each significant risk factor. If we treat 40 patients not eligible for RCTs (numbers needed to treat to harm; 95% CI, 23-130), we would observe 1 extra SAE in a mean follow-up of 2.1 years compared with eligible patients.

There are some limitations of this result. Because the measure of outcome was not blinded, information bias could explain part of the increased risks in the exposed groups. To minimize this effect, we used a clear-cut definition of SAEs that was reinforced by the researchers' training, use of a patient diary, and in situ monitoring of patient records. This possible information bias might not have the same effect for all exposures. In particular, being ineligible for RCTs might be less likely to cause information bias compared with being exposed to biologics. Our data collection form includes a question on causality of the adverse event as perceived by the treating physician. This question is not used for analysis; instead, it triggers a pop-up window reminding the physician of the compulsory reporting of treatment-related SAEs. We used these data as an indirect measure of information bias. Although none of the differences was statistically significant, physicians were more likely to think that SAEs were related to drug exposure in patients receiving biologics compared with classic drugs (54% vs 38%; χ^2, $P=.38$) and were less likely to associate SAEs with drugs in patients not eligible for RCTs compared with those eligible (43% vs 61%; χ^2, $P=.18$). Overall, we believe that information bias might slightly increase the reported risks in our study, but it is not likely to be a large effect and is probably less relevant for the effect of being ineligible for RCTs.

Another limitation of our study is that the exposures measured might be heterogeneous. We grouped several factors under the global definition of ineligibility for RCTs. Description of these causes showed that age and a history of cancer are the clearest risk factors for SAEs. Some of the nonsignificant results for other risk factors can be the result of low power to analyze individual factors (results were borderline significant for chronic renal or hepatic disease). This information should come from larger studies, longer periods of analysis of our study, or data aggregation as provided by networks such as the Psonet initiative.[16]

Serious adverse events are a composite outcome made up of different outcomes. This might not be very helpful to improve our understanding of the pathogenesis of the events, but it has the advantages of providing more power to detect differences and of being a very relevant outcome for patients and clinicians.

Overall, age was the best predictor for SAEs, and studies on SAEs should always control for this variable. We used an arbitrary cutoff age of 70 years, which is what was used in the RCTs. Some of the effect of other risk factors could result from residual confounding by age because of such wide categories. We excluded this by multivariable analysis, showing that significant individual factors (eg, history of cancer) remained significant when age was added to the model as a continuous variable.

There were also some difficulties in comparing results on drug safety from our study with results from RCTs or their extensions. Unlike most RCTs and other previous studies,[3,4] we considered patients receiving classic systemic therapy as a control group rather than a placebo group. Because classic systemic therapy is associated with SAEs, finding a significant difference in risks in our study was more unlikely. The most important limitation of our study is that risks in the control group were compounded by baseline risks owing to the characteristics

of the patients and risks associated with the use of classic systemic drugs for treatment of psoriasis. These 2 sources of risk could not be analyzed individually in our study. It is likely that an important part of the risks associated with age and a history of cancer result from these patients being sicker, without being related to psoriasis or its treatment. However, the increased risk of SAEs is important information that should lead to more careful risk-benefit evaluation in this large group.

SUBANALYSIS: EFFECT OF BIOLOGICS ON THE RISK OF SAEs ASSOCIATED WITH INELIGIBILITY

Serious adverse events were more common in patients receiving biologics than in those receiving classic systemic therapy. The heterogeneity of exposure also affects this result. We grouped all classic drugs and all biologics, but different drugs might have different safety profiles. Again, sample size and the difficulties in linking SAEs to a specific drug kept us from analyzing SAE rates of the individual agents. This information should come from larger studies, a longer period of analysis of our study, or data aggregation as provided by networks such as the Psonet initiative.[16] Phototherapy was only marginally represented in our study, and at least psoralen–UV-A has a better known and probably better safety profile.[17]

An important question in our study was to recognize a possible interaction between ineligibility for RCTs and exposure to biologics. We were unable to detect an interaction, even using $P > .10$ for determination. However, this interaction might exist; the power to detect it in our study was low.[18] This result means that we found no signs of biologics being intrinsically more dangerous (in relative terms) in patients ineligible for RCTs; however, use of these drugs adds (multiplying the rate of SAEs by 2.3) to a previously higher baseline risk in these patients.

In conclusion, 29.8% of the patients receiving a systemic drug for psoriasis have not been adequately represented in RCTs. This result underlines the need to move to more pragmatic RCTs evaluating treatment of psoriasis that represent the population in need of therapy and to recognize that safety data resulting from currently available RCTs are clearly not enough to answer frequent clinical questions. In particular, including elderly patients and those with psoriasis different from chronic plaque psoriasis in RCTs should be encouraged. Reporting should include subgroup analyses and enough data to allow for later meta-analysis. Patients who would not be eligible for RCTs, especially elderly individuals and those with a history of cancer, are more likely to experience SAEs and should be closely monitored. Biologics are associated with an increased risk of SAEs. We were not able to detect a significant difference in the risk associated with administration of biologics in patients ineligible for RCTs, but the risk-benefit ratio in these patients might be different from the risk in eligible patients and should be studied.

Accepted for Publication: October 27, 2011.
Author Affiliations: Departments of Dermatology, Complexo Hospitalario de Pontevedra, SERGAS (Servizo Galego de Saude), Pontevedra (Dr Garcia-Doval), Hospital Universitario de Gran Canaria Dr Negrín, Las Palmas de Gran Canaria (Drs Carretero and Vilar-Alejo), Hospital Universitario 12 de Octubre, Madrid (Drs Vanaclocha and Rivera), Hospital Universitari Germans Trias i Pujol, Badalona, Universidad Autónoma de Barcelona, Barcelona (Drs Ferrandiz and Carrascosa), Hospital Universitario de la Princesa, Madrid (Drs Daudén and Carazo), Hospital General Universitario de Valencia, Valencia (Dr Sánchez-Carazo), Hospital Clinic of Barcelona, Barcelona (Dr Alsina), Hospital Universitario Virgen de la Victoria, Málaga (Dr Herrera-Ceballos), Hospital Universitario Reina Sofía, Cordoba (Dr Gómez-García), Hospital del Mar, Parc de Salut Mar, Barcelona (Dr Ferrán), Fundación Hospital de Alcorcón, Madrid (Dr López-Estebaranz), Hospital Universitario Infanta Leonor, Madrid (Dr Hernanz), and Hospital General Universitario de Alicante, Alicante (Dr Belinchón-Romero), Spain.
Correspondence: Ignacio Garcia-Doval, MScEpid, PhD, Servicio de Dermatoloxía, Complexo Hospitalario de Pontevedra, Loureiro Crespo, 2, Pontevedra, 36001 Spain (ignacio.garcia.doval@sergas.es).
Author Contributions: Dr Garcia-Doval had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Garcia-Doval, Daudén, and Rivera. *Acquisition of data:* Carretero, Vanaclocha, Ferrandiz, Sánchez-Carazo, Alsina, Herrera-Ceballos, Gómez-García, Ferrán, López-Estebaranz, Hernanz, Belinchón-Romero, Vilar-Alejo, Rivera, Carrascosa, and Carazo. *Analysis and interpretation of data:* Garcia-Doval and Ferrandiz. *Drafting of the manuscript:* Garcia-Doval. *Critical revision of the manuscript for important intellectual content:* Garcia-Doval, Carretero, Vanaclocha, Ferrandiz, Daudén, Sánchez-Carazo, Alsina, Herrera-Ceballos, Gómez-García, Ferrán, López-Estebaranz, Hernanz, Belinchón-Romero, Vilar-Alejo, Rivera, Carrascosa, and Carazo. *Statistical analysis:* Garcia-Doval. *Obtained funding:* Carretero, Vanaclocha, Ferrandiz, and Daudén. *Administrative, technical, and material support:* Ferrán, López-Estebaranz, Hernanz, Belinchón-Romero, Vilar-Alejo, Rivera, and Carrascosa. *Study supervision:* Garcia-Doval, Carretero, Vanaclocha, and Ferrandiz.
BIOBADADERM Study Group: This work was conducted within the group. The following members participated in acquisition of data and review of the manuscript: Ángel Guillén, BPharm (Unidad de Investigación, Fundación Española de Reumatología); Carlos Muñoz-Santos, MD (Hospital Clinic of Barcelona, Barcelona); Victoria Mendiola-Fernández, MD (Hospital Universitario Virgen de la Victoria, Málaga); Rafael Jiménez Puya, MD (Hospital Universitario Reina Sofía, Cordoba); Diana Ruiz-Genao, MD (Fundación Hospital de Alcorcón, Madrid); María Pilar Albares Tendero, PhD, José Bañuls Roca, PhD, and Juan Francisco Silvestre Salvador, MD (Hospital General Universitario de Alicante, Alicante); and Pablo de la Cueva, MD (Hospital Universitario Infanta Leonor, Madrid, Spain).
Financial Disclosure: Dr Garcia-Doval received a travel grant for a congress from Merck/Schering-Plough Pharmaceuticals. Dr Carretero served as a consultant for Abbott Laboratories, Janssen-Cilag Pty Limited, MSD, and Pfizer Inc; gave expert testimony for Abbott Laborato-

ries, MSD, and Pfizer Inc; received grants from Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer Inc and equipment from MSD and Pfizer Inc. Dr Vanaclocha participated in speakers' bureaus for Abbott Laboratories, Pfizer Inc, MSD, and Janssen Pharmaceuticals Inc. Dr Ferrandiz served as a consultant for Abbott Laboratories, Janssen Pharmaceuticals Inc, and Almirall SA; received honoraria from Abbott Laboratories, Almirall SA, Janssen Pharmaceuticals Inc, and Pfizer Inc; participated in a speaker's bureau for Abbott Laboratories, Almirall SA, and Janssen Pharmaceuticals Inc; and received grants from Abbott Laboratories. Dr Daudén served as a consultant for Abbott Laboratories, Amgen, Astellas, Celgene, Centocor Ortho Biotech Inc, Galderma, Glaxo, Jannsenn-Cilag, Leo Pharma, MSD, Novartis, and Pfizer Inc; received honoraria form Abbott Laboratories, Amgen, Celgene, Janssen-Cilag Pty Ltd, Leo Pharma, MSD, Novartis, and Pfizer Inc; participated in speakers' bureaus for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer Inc; and received grants from Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer Inc. Dr Alsina gave expert testimony for Abbott Laboratories and Merck/Schering-Plough. Dr Ferrán acted as a consultant for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer-Wyeth; participated in speakers' bureaus for Janssen Pharmaceuticals Inc and MSD; and received grants from Serono. Dr López-Estebaranz served as a consultant for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer-Wyeth and participated in speakers' bureaus for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer-Wyeth. Dr Hernanz acted as a consultant for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer-Wyeth. Dr Belinchón-Romero acted as a consultant for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer-Wyeth. Dr Rivera participated in speakers' bureaus for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer-Wyeth. Dr Carrascosa served as a consultant and participated in speakers' bureaus for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer-Wyeth.

Funding/Support: This study was supported in part by the Academia Española de Dermatología y Venereología and the Agencia Española del Medicamento y Productos Sanitarios. Grants in approximately equal amounts (all less than €25 000 per year) from Abbott Laboratories, Janssen Pharmaceuticals Inc, Merck/Schering-Plough Pharmaceuticals, and Pfizer-Wyeth contributed to the support of the registry.

Role of the Sponsors: The Spanish Academy of Dermatology offered administrative support, and the Agencia Española del Medicamento y Productos Sanitarios reviewed the study protocol. Apart from these contributions, none of the sponsors had a role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review, or approval of the manuscript.

Additional Information: MedDRA is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations.

Additional Contributions: Sinead Langan, MD, reviewed the final manuscript.

REFERENCES

1. Ferrándiz C, Bordas X, García-Patos V, Puig S, Pujol R, Smandía A. Prevalence of psoriasis in Spain (Epiderma Project: phase I). *J Eur Acad Dermatol Venereol*. 2001;15(1):20-23.
2. Naldi L. Epidemiology of psoriasis. *Curr Drug Targets Inflamm Allergy*. 2004;3(2):121-128.
3. Ferrándiz C, Carrascosa JM, Boada A. A new era in the management of psoriasis? the biologics: facts and controversies. *Clin Dermatol*. 2010;28(1):81-87.
4. Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. *Br J Dermatol*. 2008;159(3):513-526.
5. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev*. 2011;2(2):CD008794.
6. Brimhall AK, King LN, Licciardone JC, Jacobe H, Menter A. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. *Br J Dermatol*. 2008;159(2):274-285.
7. Wang D, Bakhai A. *Patient Selection: Clinical Trials: A Practical Guide to Design, Analysis, and Reporting*. Chicago, IL: Remedica; 2006:47-54.
8. Nijsten T, Spuls PI, Naldi L, Stern RS. The misperception that clinical trial data reflect long-term drug safety: lessons learned from efalizumab's withdrawal. *Arch Dermatol*. 2009;145(9):1037-1039.
9. Schmitt-Egenolf M. Psoriasis therapy in real life: the need for registries. *Dermatology*. 2006;213(4):327-330.
10. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor α agents in rheumatoid arthritis. *Arthritis Rheum*. 2003;48(2):313-318.
11. Kievit W, Fransen J, Oerlemans AJ, et al. The efficacy of anti-TNF in rheumatoid arthritis: a comparison between randomised controlled trials and clinical practice. *Ann Rheum Dis*. 2007;66(11):1473-1478.
12. Zink A, Strangfeld A, Schneider M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. *Arthritis Rheum*. 2006;54(11):3399-3407.
13. Rivera R, García-Doval I, Carretero G, et al; Miembros del grupo BIOBADADERM. BIOBADADERM, the Spanish Registry of Adverse Events Associated with Biologic Drugs in Dermatology: first report. *Actas Dermosifiliogr*. 2011;102(2):132-141.
14. International Conference on Harmonisation: clinical safety data management: definitions and standards for expedited reporting: E2A. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2B/Step4/E2B_R2__Guideline.pdf. Accessed February 12, 2011.
15. BIOBADADERM. BIOBADADERM table of drug half-lives and lag windows for attribution of adverse events. https://biobadaser.ser.es/biobadaderm/cgi-bin/upload/documentacion.aspx. Accessed March 29, 2011.
16. Lecluse LL, Naldi L, Stern RS, Spuls PI. National registries of systemic treatment for psoriasis and the European "Psonet" initiative. *Dermatology*. 2009;218(4):347-356.
17. Stern RS, Lange R. Cardiovascular disease, cancer, and cause of death in patients with psoriasis: 10 years prospective experience in a cohort of 1,380 patients. *J Invest Dermatol*. 1988;91(3):197-201.
18. Marshall SW. Power for tests of interaction: effect of raising the type I error rate. *Epidemiol Perspect Innov*. 2007;4:4. doi:10.1186/1742-5573-4-4.