ORIGINAL ARTICLE

Risk of adverse events in psoriasis patients receiving classic systemic drugs and biologics in a 5-year observational study of clinical practice: 2008–2013 results of the Biobadaderm registry

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Abstract

Background Biobadaderm is the Spanish registry of psoriasis patients receiving systemic treatment in clinical practice.

Objective To compare the safety of biologics and classic systemic treatment.

Methods Prospective cohort of patients receiving biologics and classic systemic therapies between 2008 and 2013 in 12 hospitals are included. We registered demographic data, diagnoses, comorbidities, treatments and adverse events (AE). We obtained raw relative risks (RR) for specific AE.

Multivariate analysis consisted of Cox models adjusting for age, gender, chronic hepatic disease and previous cancer.

Results A total of 1030 patients received biologics (2061 AE in 3681 person-years), 926 patients classic systemic drugs (1015 AE in 1517 person-years). Ninety-three per cent of AE in both groups were non-serious, 6% serious and 0.003% fatal. The age- and gender-adjusted hazard ratio of AE was lower in the biologics group [hazard ratio 0.6 (95% CI: 0.5–0.7)].We found no differences in rates of serious and mortal AE. Some system organ class AE rates differed between both groups. As limitations: Prescription bias might affect the incidence of AE in both groups. Association of drug and AE was based on timing: associations might not be causal.

Conclusion Patients receiving biologics had lower risk of AE. We did not find differences in the risk of serious or fatal AE.

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Conflicts of interest

Dr G. Carretero served as a consultant and investigator for Abbott Laboratories, Janssen-Cilag Pty Limited, MSD, and Pfizer Inc and received grants from Abbott, Jannsen and Pfizer and equipment from MSD and Pfizer Inc.

Dr C. Ferrandiz served as a consultant and speaker for Abbott Laboratories, Janssen Pharmaceuticals Inc, Pfizer, and Almirall SA; as a speaker for Abbott Laboratories, Janssen Pharmaceuticals Inc, and Almirall SA received honoraria from Abbott Laboratories, Almirall SA, Janssen Pharmaceuticals Inc, and received grants from Abbott Laboratories.

Dr E. 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 from 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, and Pfizer Inc.
Dr F. Vanaclocha participated as speaker for Abbott Laboratories, Pfizer Inc, MSD, and Janssen Pharmaceuticals Inc.
Dr E. Herrera-Ceballos served as a consultant and speaker for Abbott Laboratories, Janssen Pharmaceuticals Inc, and Pfizer-Wyett.
Dr P. De la Cueva acted as a consultant for Janssen-Cilag, Abbott, MSD, Pfizer, and Leo-Pharma.
Dr I. Belinchón acted as a consultant for Pfizer-Wyeth; Janssen Pharmaceuticals Inc, MSD, Almirall SA and Leo-Pharma, and as a speaker for Abbott-Abbvie, Pfizer-Wyeth, Janssen Pharmaceuticals Inc and MSD.
Dr J.L. Sánchez-Carazo acted as a consultant for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer-Wyeth.
Dr M. Alsina acted as a consultant for Abbott Laboratories and Merck/Schering-Plough.
Dr J.L. López-Estebaranz served as a consultant for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer-Wyeth and as a speaker for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer-Wyeth.
Dr M. Ferrán participated in advisory boards for MSD, Pfizer, Abbvie, and Jannsen, as a speaker for MSD, Abbvie and Janssen, as investigator for MSD, Abbvie, Pfizer and Janssen.
Dr J.M. Carrascosa served as a consultant and speaker for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer-Wyeth.
Dr R. Rivera participated in advisory boards for Abbott Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer-Wyeth.
Dr I. Garcia-Doval received travel grants for congresses from Merck/Schering-Plough Pharmaceuticals, Pfizer and Janssen.
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Introduction

Biologics have entailed important changes in the treatment of psoriasis. These drugs are effective and present an acceptable short-term safety profile.[1] The safety data, however, come mainly from randomized controlled trials or their extensions[2] and spontaneous reporting of adverse reactions.[3] Clinical trials have short follow-up periods and recruit a select population which might present a more favourable safety profile than the general drug users.[4] Up to 30% of patients in clinical practice have risk factors that would preclude their enrolment in clinical trials.[5] Moreover, clinical trials comparing the safety profile of classic treatments and biologics are scarce. There are some clinical trial extension studies with long follow-ups, but they also represent a selected population (both due to the initial selection of the clinical trial and by the fact that these patients continued therapy after the whole trial). Spontaneous notification is another source of safety data, being able to detect rare adverse events (AE).[6] However, it introduces bias due to underreporting, lacks denominators for calculating incidence rates and is unlikely to detect unexpected AE or those with prolonged latency periods. Cohort studies can give data that reflects use of drugs in unselected populations and avoid previous disadvantages. Several studies have given observational safety data for psoriasis therapy, but only for isolated biologics,[7] in the short term,[8] or without control group.[9]

Biobadaderm (The Spanish Registry of Adverse Events Associated with Psoriasis Systemic Therapy) is a cohort registry of psoriasis patients treated with systemic drugs. The main objective of this registry is to assess the risk of AE related to biologics therapy compared to classic systemic therapy in patients with moderate to severe psoriasis. The registry intends to be representative of real use of systemic drugs. We report follow-up results.

BIOBADADERM Study Group: This work was conducted within the group. The following members participated in acquisition of data and review of the manuscript: Beatriz Pérez Zafrilla Ph.D., B.Pharm., Unidad de Investigación Fundación AEDV; Carlos Muñoz-Santos, M.D., Hospital Clinic of Barcelona, Barcelona; Victoria Mendiola-Fernández, M.D., Cristina Sánchez Roldán, M.D., Hospital Universitario Virgen de la Victoria, Malaga; Diana Ruiz-Genao, M.D., Begoña Echeverría, M.D., Hospital Universitario Fundación Alcorcón, Madrid; José Bañuls Roca, Ph.D., Juan Francisco Silvestre Salvador, M.D., Pilar Albarés Tendero, Ph.D. and Isabel Betlloch Mas, M.D., Hospital General Universitario de Alicante, Alicante and Sagrario Galiano Mejías, M.D., Hospital Universitario Infanta Leonor, Madrid, Spain.

Materials and methods

Since 2005, biologics are commercially available in Spain. The national health system covers the cost of all study drugs. Biobadaderm has previously been described elsewhere.[5,10,11] It is a multicentre cohort study composed of 12 dermatology departments, widely distributed over Spain. All patients receiving biologics (efalizumab, etanercept, infliximab, adalimumab and ustekinumab) in these centres were included in the study, as well as a systematic sample of patients on other classic systemic therapies (the first patient starting acitretine, cyclosporine or methotrexate for the first time after the entry of a patient with biologics). The only exclusion criteria were unwillingness to participate or patients who moved to an area not covered by the registry in the following 3 months. Although previous Biobadaderm studies included a small percentage of retrospectively collected data, for this study only prospectively collected data of patients receiving biologics between January 2008 and October 2013 were used.

We systematically collected demographic data, diagnoses and comorbidities. Each starting patient was registered with the corresponding drug, start and discontinuation dates and reasons for discontinuation. We recorded AE with date of occurrence, diagnosis with MedDRA (Medical Dictionary for Regulatory Activities) coding, concomitant therapies, severity and outcome.

We contacted patients at least once a year, although most patients visited the centres more frequently as part of their regular care. We used patient diaries with questions relating to serious AE to improve outcome reporting. We validated the data once a year through on-site monitoring of a random sample of patients, which focused on drug exposures and serious AE, and through reviewing patient records. In case of disagreement, we used the information from patient records.

All AE that were serious (according to the International Conference on Harmonisation E2A Guideline[12]) or lead to a change in therapy or to unexpected medical attention were included in the registry. A serious adverse event 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.'[12]

Periods of exposure to drugs were defined as the time from first dose until twice the drug's half-life after the last dose, censoring date, death or database download date (20 October 2013), whichever occurred first. Drug withdrawal was defined as two consecutive missing doses. A drug cycle is the time between the first drug administration and the date of drug withdrawal (last dose). We considered AE as temporarily related to a drug treatment if the time of exposure to the drug overlapped with a lag window before the event (on-drug + lug window method). Lag windows are given on the BIOBADADERM webpage.[13] Most exceed 30 days and are similar to the 'Manchester template'. For infections, the lag window is 90 days and for neoplasms 5 years. If an AE could be related to more than one drug class, we associated it with both. For estimation of exposure, incidence rates and risks of patients on classic systemic drugs we only took into account exposure to these drugs before any exposure to biologics. Due to its market withdrawal shortly after the start of the study, efalizumab exposures were excluded from the analysis (41.2 patient-years).

Statistical analysis

Univariate analysis consisted of description of frequencies and rates. To calculate rates we counted all AE in a group (even if more than one adverse event was present in the same patient) and used as exposure time the total exposure to the drug group. If one event was linked to several drug exposures we counted the adverse event in both groups. AE that were not temporarily related to drug exposures were excluded. We obtained raw relative risks (RRs) for specific AE (classified by severity or MedDRA System Organ Class) by comparing their crude rates between the cohorts, expressed with a 95% confidence interval. Multivariate analysis consisted of Cox proportional hazards models, allowing for multiple failures per subject, and using robust standard errors to take into account clustering of AE in the same patients. We chose possible confounding factors to include in the analysis on the basis of previous descriptions,[5] and baseline differences in the sample. All analyses were done using Stata 13.1 (Stata Corp., College Station, TX, USA 2013).

BIOBADADERM has been approved by the *Hospital 12 de Octubre* Ethics Committee, and all patients gave their written consent to participate.

Results

Patients

A description of the 1956 patients can be found in Table 1. Less than 0.3% of the patients refused to participate. The median follow-up time was 3.3 years (range: 0.0–5.1 years). Five per cent of the patients were lost to follow-up during the study (the proportion was similar for patients on biologics and classic systemic drugs). Patients receiving treatment with biologics had a higher proportion of men with a longer disease span, higher severity of psoriasis and more frequent psoriatic arthritis. They also showed a distinct distribution of comorbidities (with more frequent chronic hepatic disease and less frequent history of previous cancer) and had received more previous treatments. Those receiving classic treatments included a higher percentage of psoriasis types different from plaque psoriasis, and in particular a higher proportion of palmoplantar pustulosis.

Treatments

In Table 2, we present a summary of treatment cycles and exposure times. Of the 3753 treatment cycles, 1572 (42%) refer to treatments with classic drugs in biologic naive patients and 2181 (58%) are biological treatment cycles.

Table 1 Description of patients included in the analysis. Only biologic-naïve patients were included in the classic systemic drugs group

	Biologics	Classic systemic drugs	P-value for the difference between previous groups	Biobadaderm
Demographic data				
Number of patients	1030 (100%)	926 (100%)		1956 (100%)
Women, n (%)	383 (37)	400 (43)	**0.007**	783 (40)
Age, years, mean (SD)	49 (14)	49 (16)	0.75	49 (15)
Age at start of treatment, years, mean (SD)	45 (14)	46 (16)	0.11	45 (15)
Duration of disease at start of treatment, years, mean (SD)	19 (12)	15 (13)	**<0.001**	17 (13)
Psoriasis Area Severity Index (PASI), mean (SD)	15 (9)	10 (7)	**<0.001**	13 (9)
Diagnosis at registration in cohort, n (% of total)				
Plaque psoriasis	981 (95)	835 (90)	**<0.001**	1816 (93)
Guttate psoriasis	51 (5)	50 (5)	0.66	101 (5)
Erythrodermic psoriasis	27 (3)	17 (2)	0.24	44 (2)
Generalized pustular psoriasis	11 (1)	11 (1)	0.80	22 (1)
Palmoplantar pustulosis	14 (1)	59 (6)	**<0.001**	73 (4)
Annular pustular psoriasis	4 (0)	2 (0)	0.49	6 (0)
Acrodermatitis continua of Hallopeau	0 (0)	1 (0)	0.29	1 (0)
Psoriatic arthritis	187 (18)	77 (8)	**<0.001**	264 (14)
Comorbidities, n (% of total)				
Ischaemic cardiopathy	25 (2)	30 (3)	0.28	55 (3)
Cardiac insufficiency	7 (1)	11 (1)	0.24	18 (1)
Arterial hypertension	212 (21)	213 (23)	0.20	425 (22)
Diabetes	125 (12)	104 (11)	0.53	229 (12)
Hypercholesterolaemia	254 (25)	256 (28)	0.13	510 (26)
Chronic pulmonary obstructive disease	23 (2)	23 (2)	0.72	46 (2)
Chronic hepatopathy	69 (7)	29 (3)	**<0.001**	98 (5)
Renal insufficiency	13 (1)	11 (1)	0.88	24 (1)
Prior cancer	21 (2)	41 (4)	**0.003**	62 (3)
Cancer in the last 5 years, excluding non-melanoma skin cancer	2 (0)	8 (1)	**0.04**	10 (1)
Lymphoma	4 (0)	5 (1)	0.62	9 (1)
Hepatitis B infection	41 (4)	31 (3)	0.46	72 (4)
Hepatitis C infection	23 (2)	14 (2)	0.24	37 (2)
HIV infection	11 (1)	9 (1)	0.83	20 (1)
Number of prior classic treatments, n (% of total)				
0	124 (12)	525 (57)	**<0.001 for all groups**	649 (33)
1	272 (26)	240 (26)		512 (26)
2	317 (31)	118 (13)		435 (22)
3	190 (18)	29 (3)		219 (11)
4 or more	127 (12)	4 (0)		141 (7)
Prior classic treatments, n (% of total)				
PUVA	355 (34)	119 (13)	**<0.001**	474 (24)
Narrow-band UVB	179 (17)	107 (12)	**<0.001**	286 (15)
Broad-band UVB	55 (5)	22 (2)	**0.001**	77 (4)
Methotrexate	556 (54)	117 (13)	**<0.001**	673 (34)
Cyclosporine	465 (45)	105 (11)	**<0.001**	570 (29)
Acitretine	324 (31)	127 (14)	**<0.001**	451 (23)

Bold value represents statistical significant.

Table 2 Description of treatments

Drug	Number of treatment cycles (%)
Etanercept	672 (18)
Adalimumab	724 (19)
Ustekinumab	491 (13)
Infliximab	181 (5)
Efalizumab*	113 (3)
Biologics (total)	2181 (58)
Acitretine	406 (11)
Cyclosporine	401 (11)
Methotrexate	765 (20)
Classic systemic therapy (total)	1572 (42)
Total treatment cycles	3753 (100)
Drug	**Exposure time in patient-years**
Etanercept	1129.9
Adalimumab	1305.2
Ustekinumab	891.4
Efalizumab*	41.2
Infliximab	365.4
Biologics (total)	3721.9
Acitretine	404.3
Cyclosporine	251.0
Methotrexate	861.2
Classic systemic therapy (total)	1516.5
Total follow-up time	5383.4

*Efalizumab data were excluded from risk analysis.

Median survival time of biological treatment cycles was 1.4 years. Main reason for treatment discontinuation (24% of biological treatment cycles started) was inefficacy, unexpectedly low efficacy or loss of efficacy. Fourteen per cent of treatment cycles were discontinued due to remissions and 7% of treatments were suspended due to AE. Median survival time of classic treatments was 0.7 years. Twenty per cent of treatment cycles were discontinued due to inefficacy, unexpectedly low efficacy or loss of efficacy; and 20% of treatment cycles were discontinued due to remissions and 11% of treatments were suspended due to AE.

Adverse events

The incidences of different AE, sorted by MedDRA System Organ Class, can be found in Table 3. Ninety-three per cent of AE were classified as non-serious, 6% as serious and 0.003% as fatal. The overall crude incidence rate of AE was lower for biologics [RR: 0.8 (95% CI: 0.8–0.9)]. We did not find differences in risk of serious or fatal AE between patients treated with biologics and those treated with classic systemic therapies. There were 11 fatal AE, eight of which occurred in the biologics group (one suicide, two-stage IV non-small cell lung cancer, one stomach cancer, one aortic dissection, one stroke, one pneumonia and one unspecified death) and three in the classic treatment group (one-stage IV squamous cell lung cancer and two strokes).

In both groups, most frequent AE were infections and infestations (for biologics 20.7% of all events, for classic drugs 13.8%) and alterations of investigations (the name given by MeDRA to alterations of laboratory studies and tests) (biologics: 10.0%, classic drugs: 12.5%).

We observed an increased raw risk of infections and infestations in patients who had received biologics [RR 1.5 (95% CI: 1.2–1.8)]. Patients receiving classic systemic therapy had an increased absolute risk of gastrointestinal disorders, nervous system disorders, alterations of investigations, vascular disorders, blood and lymphatic system disorders, metabolism and nutrition disorders, endocrine disorders and congenital, familial and genetic disorders (see Table 3).

When the results were adjusted for age, gender, previous history of cancer and chronic hepatic disease at the start of each treatment, patients exposed to biologics had a lower global risk of AE. Multivariate analysis modified the findings of the increased risk of infection and blood and lymphatic system disorders that disappeared after adjustment. As shown in Table 3, many of the AE rates are significantly associated with age, gender, previous history of cancer and chronic hepatic disease. We could not detect differences in risk of malignant tumours in the crude or adjusted analysis.

Discussion

In a representative population of people with psoriasis receiving systemic treatment under clinical conditions, the risk of AE (adjusted for age and sex) is lower in patients receiving biologics than in those receiving classic systemic treatments. We did not find differences in the risk of serious or fatal AE (although the results in the latter have wider confidence intervals). When the adjusted results were divided by diagnostic groups (MedDRA system organ class groups), patients treated with classic systemic drugs present an increased risk of gastrointestinal disorders, nervous system disorders, alterations of investigations, vascular disorders, metabolic and nutrition disorders, endocrine disorders and congenital, familial and genetic disorders.

In most of the previous publications on biologics, patients come from randomized clinical trials and their extensions. These groups have been selected to minimize the risk for the participants, as patients with previous relevant pathology are excluded.[5] This selection will tend to give better safety results for biologics than in real patients. Biobadaderm recruits successive patients in centres of differing complexity all over Spain. We believe this to be most representative of the general drug use. In our study, we included all patients receiving biologics, including the 30% not adequately represented in most clinical trials,[5] either because of their comorbidities, the 7% of patients treated with systemic therapy that had forms of psoriasis different from chronic plaque psoriasis and the first-line use of biologics in a small group. These results for non-selected populations are more representative of clinical practice than derivatives of clinical tri-

Table 3 Incidence of adverse events (AE) by diagnostic group

	Biologics		Classic systemic drugs			
	Number of AE	Incidence per 1000py (CI 95%)	Number of AE	Incidence per 1000py (CI 95%)	Crude relative risk (CI 95%)	Adjusted hazard ratio in biologics (CI 95%)†
Overall rates						
All AE	2061	554 (530–578)	1015	669 (62–711)	**0.8 (0.8–009)*** **	**0.6 (0.5–0.7)*** g, h**
Serious AE	139	37 (32–44)	61	40 (31–52)	0.9 (0.7–1.3)	1.3 (0.8–1.9)a,c,h
Mortal AE	8	2.9 (1.3–5.7)	3	1.9 (0.4–5.8)	1.5(0.4–8.7)	1.4 (0.5–41)a,h
Rates for MeDRA System Organ Class groups						
Infections and infestations	495	133 (122–145)	139	92 (78–108)	**1.5 (1.2–1.8)*** **	1.2 (0.9–1.7)a,g
General disorders and administration site conditions	115	31 (26–37)	47	31 (23–41)	1.0 (0.7–1.4)	1.3 (0.7–2.1)g
Skin and subcutaneous tissue disorders	162	44 (37–51)	71	47 (37–59)	0.9 (0.7–1.2)	0.7 (0.5–1.1)g.h
Gastrointestinal disorders	102	27 (23–32)	104	69 (57–83)	**0.4 (0.3–0.5)*** **	**0.3 (0.2–0.4)*** g**
Nervous system disorders	102	27 (23–33)	64	42 (33–54)	**0.6 (0.5–0.9)** **	**0.5 (0.3–0.8)** a,g,h**
Investigations‡	165	44 (38–52)	126	83 (70–99)	**0.5 (0.4–0.7)*** **	**0.4 (0.3–0.5)*** h**
Cardiac disorders	25	7 (5–10)	14	9 (5–16)	0.7 (0.4–1.4)	1.0 (0.4–2.7)a
Musculoskeletal and connective tissue disorders	189	51 (44–59)	68	45 (35–57)	1.1 (0.9–1.5)	1.1 (0.8–1.7)g
Neoplasms benign. malignant and unspecified (incl cysts and polyps)	81	22 (18–27)	26	17 (12–25)	1.3 (0.8–2.0)	**2.0 (1.1–3.8)*a,h,c**
Respiratory. thoracic and mediastinal disorders	35	9 (7–13)	20	13 (9–20)	0.7 (0.4–1.2)	0.7 (0.3–1.6)g,h
Vascular disorders	46	12 (9–17)	53	35 (27–46)	**0.4 (0.2–0.5)*** **	**0.3 (0.2–0.5)*** h**
Blood and lymphatic system disorders	42	11 (8–15)	29	19 (13–28)	**0.6 (0.4–1.0)***	0.6 (0.3–1.1)
Surgical and medical procedures	76	20 (16–26)	33	22 (15–31)	0.9 (0.6–1.4)	0.9 (0.5–1.5)
Injury. poisoning and procedural complications	74	20 (16–25)	39	26 (19–35)	0.8 (0.5–1.1)	0.7 (0.4–1.3)
Eye disorders	25	7 (5–10)	10	7 (4–12)	1.0 (0.5–2.1)	1.5 (0.4–5.2)h,c
Renal and urinary disorders	41	11 (8–15)	15	10 (6–16)	1.1 (0.6–2.0)	1.2 (0.6–2.4)c
Hepatobiliary disorders	93	25 (20–31)	45	30 (22–40)	0.8 (0.6–1.2)	0.7 (0.4–1.1)
Psychiatric disorders	47	13 (9–17)	15	10 (6–16)	1.3 (0.7–2.3)	0.9 (0.4–1.8)
Reproductive system and breast disorder	27	7 (5–11)	13	9 (5–15)	0.8 (0.4–1.6)	0.6 (0.3–1.2)a,h
Immune system disorders	7	2 (1–4)	0			
Metabolism and nutrition disorders	68	18 (14–23)	51	34 (26–44)	**0.5 (0.4–0.7)*** **	**0.3 (0.2–0.5)*** g,h**
Endocrine disorders	6	2 (1–4)	13	9 (5–15)	**0.2 (0.1–0.5)** **	**0.1 (0.0–0.3)*** c,g,h**
Ear and labyrinth disorders	14	4 (2–6)	7	5 (2–10)	0.8 (0.3–2.0)	1.2 (0.3–4.5)
Pregnancy. puerperium and perinatal conditions	13	3 (2–6)	3	2 (1–6)	1.8 (0.5–6.2)	1.9 (0.5–7.1)a,g,h
Congenital. familial and genetic disorders	7	2 (1–4)	9	6 (3–11)	**0.3 (0.1–0.9)***	**0.1 (0.0–0.5)** **
Social circumstances	4	1 (0–3)	1	1 (0–5)	1.6 (0.2–14.6)	0.8 (0.0–14.8)a,c,g,h
Events of special interest						
Malignant tumours (excluding in situ tumours and basal cell carcinoma)	25	7 (5–10)	15	10 (6–16)	0.7 (0.4–1.3)	0.7 (0.3–1.8)a

Rates per 1000 person-years, relative risks and adjusted hazard ratios. py, patient-years.

*p<0.05;**p<0.01;***p<0.001.

†Adjusted for age at the start of therapy, gender, chronic hepatic disease and history of previous cancer.

‡Name given by MedDRA to alterations of laboratory studies and tests.

a: significantly associated with age; g: significantly associated with gender; h: significantly associated with chronic hepatic disease; c: significantly associated with history of previous cancer. Sum of follow-up time is 3680.7 patient-years for biologics and 1516.5 patient-years for controls.

als. There are other ongoing psoriasis registries that are likely to produce medium and long-term safety data,[8,14–17] but they are not available yet.

The results of our study have some limitations: In the absence of blinding to exposure, it is possible that in groups receiving biologics, physicians are most likely to describe AE. To avoid this bias, we have used a clear definition of AE to be included, frequent training of participants to ensure similar description of AE in both groups, a patient-diary, and on-line and in situ monitoring. The expected effect of this bias, however, would be worse safety results in the biologics group, which is why this effect is probably not relevant in the study results.

As in any observational study, the results can be affected by confounding, both by known and unknown variables. Table 1 indicates basal differences between groups exposed to biologics and groups exposed to classic treatment that could explain some of the observed differences. Most patients on biologics have been previously exposed to classic drugs. It is possible that patients with previous pathology might be prescribed classic drugs more often (channelling bias). Table 1 shows that history of a tumour are more frequent in the classic drugs group, while chronic liver disease is more frequent in the biologics group. We have adjusted for age, gender, presence of chronic hepatic disease and previous history of cancer. Many of these factors are statistically associated with AE rates as shown in Table 3. The modification of results after multivariable analysis shows that they are acting as confounders in this study. However, after adjusting for these confounding factors the only relevant changes in the rates of AE are that use of biologics is no longer associated with higher risk of infections or blood and lymphatic system disorders. There is also a possibility of confounding by variables not included in the models.

In our study, we have grouped all biologics and all classic drugs. Toxicity profiles differ foreseeably among the different drugs of each group. On the other hand, many patients might receive several of the drugs in each group. To evaluate this puzzle of possible aetiological agents, the sample will have to be divided, either formally or with the help of statistical methods like multivariate analysis. For these analyses to give satisfying results in the context of infrequent AE, the sample size must be very large, which is currently not possible. That is why we have maintained the division of exposure of only two groups (classic drugs and biologics). This division is representative of the clinical decision between keeping the patient in the classic treatment group or introducing biologics. However, this grouping has the disadvantage of making the generalization of our results more difficult, as the proportion that each drug represents in the group of classic drugs or biologics can differ among countries.[18]

We have also grouped outcomes, both according to severity and to the System Organ Class group of MedDRA. A more refined division by diagnosis could possibly give us more detailed information but is currently not feasible due to its low statistical power. The use of outcome groups has the advantage of being clinically relevant and of common use in pharmacovigilance, which allows us to compare our study with others.

Our study shows that under conditions of general use (confounding by prescription might skew patients with previous pathology towards classic systemic treatments and those with more serious psoriasis towards biologics) and for the length studied (median follow-up of 3.3 years with a maximum of 5 years), patients receiving biologics have a lower risk of AE than those receiving classic systemic drugs. We did not find differences in the risk of serious or fatal AE.

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