ORIGINAL ARTICLE

Adverse events associated with discontinuation of the biologics/classic systemic treatments for moderate-to-severe plaque psoriasis: data from the Spanish Biologics Registry, Biobadaderm

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Abstract

Background Little is known about the adverse events (AEs) that lead to suspension of systemic treatments for psoriasis in clinical practice.

Objective The study aimed to investigate AEs associated with discontinuation of systemic therapy in patients with psoriasis in a clinical setting (Biobadaderm).

Materials and methods Multicentre, prospective, cohort study of patients with moderate-to-severe plaque psoriasis receiving systemic therapies from January 2008 to November 2015, in 12 hospitals in Spain. The incidence rate (IR) was used to compare biologics and classic systemic therapies.

Results A total of 4218 courses of treatment were given to 1938 patients. A total of 447 (11%) treatments were discontinued due to AEs. The IR of AE associated with discontinuation of systemic therapies was 13 events/100 patient-years (PY) (95% CI: 12.14–13.93), 9.34 events/100 PY (95% CI: 8.44–10.33) for biologics and 19.67 (95% CI: 17.9–21.6) events/100 PY for classics ($P < 0.001$). Of 810 discontinuation-related AEs, 117 (14%) were serious. The highest IRs were for cyclosporine [49.18/100 PY (95% CI: 41.91–57.72)] and infliximab [26.52/100 PY (95% CI: 20.98–33.51). Ustekinumab presented the lowest IR (2.6/100 PY (95% CI: 1.83–3.69).

Limitations Observational study with potential selection bias.

Conclusion Biologic therapies are associated with a lower rate of discontinuation-related AEs than are classic therapies in real clinical practice. Ustekinumab showed the lowest incidence.

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Conflicts of interest

Dr Belinchón acted as a consultant for Pfizer-Wyeth; Janssen Pharmaceuticals Inc, MSD, Almirall SA, Lilly and Leo Pharma, and as an invited speaker for AbbVie, Pfizer-Wyeth, Janssen Pharmaceuticals Inc, Novartis and MSD.

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

Dr Ferrándiz served as a consultant and/or speaker for AbbVie Laboratories, Janssen Pharmaceuticals Inc, Pfizer, Celgene, Lilly and Almirall SA, and received grants/fees from AbbVie Laboratories, Lilly and Spherium.
Dr Rivera participated in advisory boards and/or is principal investigator and/or speaker for AbbVie Laboratories, Janssen Pharmaceuticals Inc, Almirall, Novartis, Lilly, Leo Pharma, Celgene and Pfizer-Wyeth.
Dr Daudén served as a consultant and/or speaker for AbbVie Laboratories, Amgen, Astellas, Celgene, Centocor Ortho Biotech Inc, Galderma, Glaxo, Janssen-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; and received grants from AbbVie Laboratories, Janssen Pharmaceuticals Inc, MSD, and Pfizer Inc; and received grants from AbbVie Laboratories, Janssen Pharmaceuticals Inc, and Novartis.
Dr Herrera-Ceballos served as a consultant and/or speaker for AbbVie Laboratories, Janssen Pharmaceuticals Inc, and Pfizer-Wyeth. Dr De la Cueva participated in advisory boards for Almirall, Pfizer, Biogen, Celgene, Janssen, Leo Pharma, Lilly, MSD, Novartis, UCB, has acted as a speaker consultant for AbbVie, Almirall, Pfizer, Celgene, Janssen-Cilag, MSD and Leo Pharma, and as principal investigator for Celgene, Janssen, Leo Pharma, Lilly and Novartis. Dr Sánchez-Carazo acted as a consultant for AbbVie Laboratories, Janssen Pharmaceuticals Inc, MSD and Pfizer-Wyeth. Dr Alsina acted as a consultant for AbbVie Laboratories and Merck/Schering-Plough.
Dr López-Estebaranz served as a consultant for Janssen Pharmaceuticals Inc, Novartis, Leo Pharma and Lilly and as a speaker for Pfizer-Wyeth. Dr Ferrán participated in advisory boards for MSD, Pfizer, AbbVie and Janssen; as a speaker for MSD, AbbVie and Janssen; and as investigator for MSD, AbbVie, Pfizer and Janssen.
Dr Carrascosa participated in advisory boards for Pfizer, AbbVie, Janssen and invited speaker for Janssen, AbbVie and Pfizer.
Dr Llamas Velasco received travel grants for attending congresses from AbbVie, Janssen and Novartis and served as speaker for AbbVie and Novartis.
The remaining authors declare no conflicts of interest.

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Introduction

Psoriasis is an inflammatory immune-mediated chronic skin disease that affects 1–3% of the adult population, and approximately 10% suffer from severe forms.[1] The treatment includes biologic and classic systemic agents, and their safety profile is an important consideration; long-term data, in particular, have raised concerns associated with their prolonged use.[2–7]

In general, the safety data come from randomized controlled trials (RCTs) or their extensions,[8] usually with short follow-up periods, and from the spontaneous reporting of adverse reactions.[9] RCTs are governed by restrictive inclusion and exclusion criteria involving a selected population, which might have a better safety profile than the general population.[10–13] Moreover, information about the conditions that lead to therapeutic suspension in RCTs does not necessarily correspond to those described in clinical practice, in which the patient's profile is different.

IRB status: Observational study. Approved (Biobadaderm: Hospital Universitario 12 de Octubre (216/07).
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At the present time, worldwide registries on the use of biologics in the treatment for psoriasis have provided valuable data on their long-term efficacy and safety,[12–21] describing the use of these drugs in populations more likely to be representative of 'real life' use.[11,13,16]

Accordingly, with the objective to better assess the safety of currently available systemic therapies for psoriasis, we hereby study the AEs associated with the discontinuation of the biologics (i.e. adalimumab, etanercept, infliximab and ustekinumab) and classic drugs (i.e. acitretin, cyclosporine and methotrexate), and their incidence in patients with moderate-to-severe plaque psoriasis in a clinical setting registered in the Spanish Registry for Systemic Treatments in Psoriasis (Biobadaderm).[12]

Materials and methods

Biobadaderm is a prospective multicentre cohort registry of systemic therapy in patients with psoriasis that has been described previously.[12,13] The registry has been approved by the Hospital 12 de Octubre Ethics Committee (Madrid, Spain) and performed in

compliance with the Declaration of Helsinki and local regulations. All patients gave their informed consent to participate in the registry. The primary aim of the registry is to measure the safety of systemic therapy in psoriasis, including biologic and classic systemic agents.[14] Twelve dermatology departments across the country participated in Biobadaderm. We included, prospectively, from January 2008 to November 2015, all patients with moderate-to-severe psoriasis receiving a biologics (i.e. adalimumab, etanercept, infliximab and ustekinumab) for the first time in these centres, as well as a systematic sample of patients on other classic systemic therapies (i.e. acitretin, cyclosporine and methotrexate for the first time after inclusion of a patient receiving biologics). The only exclusion criterion was the patient's refusal to participate, and for this analysis, we excluded patients receiving simultaneous non-biologic and biologic drugs.

The following information was collected by our registry: age, gender, type of psoriasis, baseline Psoriasis Area Severity Index (PASI) score, psoriasis arthritis, time from diagnosis, previous treatments, comorbidities and AEs.[14]

In the registry, we systematically collected all patients starting a course of treatment, which is recorded with the start and discontinuation dates and reasons for discontinuation. We noted all serious AEs with the date of occurrence, diagnosis with Medical Dictionary for Regulatory Activities (MedDRA) coding, concomitant therapies, severity and outcome. All AEs 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.[15] In some patients, discontinued treatments were reintroduced time after (sometimes a different treatment was used between both) the AEs occurs, so it was considered as a new cycle or a new course of treatment. AEs were linked to a drug if they took place while the patient was using the drug or within 90 days after the end of exposure,[16] and discontinuation was considered to be due to an AE when this was stated by the treating physician, as previously described.[12] Drug discontinuation was defined as two consecutive missed doses. A drug cycle is the time between the date of first drug administration and the date of drug discontinuation.[14]

Statistical analysis

Demographic and descriptive data were expressed as total numbers and proportions in discrete quantitative variables, and means and standard deviations in continuous quantitative data. A descriptive analysis was performed comparing reasons for discontinuation of biologics and classic systemic therapy, using the chi-squared test, with emphasis on AEs associated with discontinuation.

We followed patients until the censorship date (last visit in a lost-to-follow-up patient or 10 November 2015, whichever occurred first). We also estimated the time to discontinuation for an AE. We obtained incidence rates (IRs), per 100 patient-years (PY) with a 95% confidence interval (CI) of different kinds of AEs associated with discontinuation of biologics and classic systemic therapy. IR ratios were used to compare different rates between biologics and classic systemic therapy. Data were analysed using Stata 14.2 (StataCorp 2015, StataCorp LP, College Station, TX, USA).

Results

Demographic and disease characteristics

A total of 4218 courses of systemic therapies were given to 1938 patients with moderate-to-severe psoriasis, including 227 (11.7%) with psoriasis and psoriatic arthritis, until November 2015, with 6228.5 PY at the end of the follow-up. Less than 0.3% of the patients refused to participate, and the number of patients lost to follow-up was 253 (13%). There were 797 women (41.1%) and 1141 (58.9%) men, with an average age at baseline of the first systemic treatment included in the registry of 45 years (SD: 16 years), a mean duration of psoriasis of 15 years (SD: 13) and a mean PASI of 12 (SD: 8). The most common comorbidities included dyslipidaemia (n = 482, 24.9%), hypertension (n = 404, 20.9%) and diabetes (n = 210, 10.8%).

Of the total cycles of treatment, 2110 (50%) used a biological treatment and 2108 (50%) used a classical systemic treatment. The most frequently used biologic agents were etanercept and adalimumab; methotrexate was the most frequently used classic systemic agent (Table 1).

Safety

Of 4218 systemic treatments, 3054 were discontinued, primarily due to ineffectiveness or loss of effectiveness in 914 (22%), remission in 832 (20%) and 447 (11%) due to an AE. Of these 447 treatment discontinuations, 810 AEs were observed. The IR of AE that led to discontinuation of total systemic therapies was 13 events/100 PY (95% CI: 12.14–13.93), 9.34 events/100 PY (95% CI: 8.44–10.33) for biological therapy and 19.67 (95% CI: 17.9–21.6) events/100 PY for classic therapy.

Of the 810 AEs associated with drug discontinuation, 117 (14%) were serious and 693 (86%) non-serious (Table 2). There were eight (1%) fatal AEs, four malignancies, three

Table 1 Description of treatments

Drugs	Number of treatment cycles (%)	Exposure time in patient-years
Biologics therapy	**2110 (50)**	**4016.5**
Etanercept	736 (17)	1228.6
Infliximab	125 (3)	264.2
Adalimumab	712 (17)	1329.7
Ustekinumab	537 (13)	1194.0
Classic systemic therapy	**2108 (50)**	**2211.9**
Acitretin	555 (13)	607.2
Cyclosporine	529 (13)	304.8
Methotrexate	1024 (24)	1299.9
Total	**4218 (100)**	**6228.5**

Table 2 Description of adverse events of biologic and systemic classic treatments associated with discontinuation

	Total	Biological therapy	Classic therapy	*P*-value
Number of AE	810	375	435	
Incidence*	13.0 (12.14–13.93)	9.34 (8.44–10.33)	19.67 (17.9–21.6)	0.001**
Numbers of serious AE (non-fatal + fatal events)	117 (109 + 8)	81 (76 + 5)	36 (33 + 3)	
Incidence*	1.88 (1.57–2.25)	2.02 (1.62–2.51)	1.63 (1.17–2.26)	0.254

*Events associated with drug discontinuation/100 PY of therapy.
**Statistically significant difference.
AE, adverse events; PY, patient-years.

cardiovascular diseases, and one suicide, and only two of these eight cases were causally linked to the treatment, according to the medical doctor.

The lower incidence of total AE for biologics was statistically different with respect to classic drugs (*P*-value < 0.001), but it was not statistically different with respect to serious AE (*P*-value = 0.254).

The highest IR of AE that led to discontinuation in biological therapy was for infliximab [26.52/100 PY (95% CI: 20.98–33.51)], and cyclosporine among the classic systemic therapies [49.18/100 PY (95% CI: 41.91–57.72)]. The lowest IR was for ustekinumab (2.6/100 PY (95% CI: 1.83–3.69).

The median duration of systemic therapy until discontinuation-related AE was 6.67 months. The longest median duration was observed with etanercept (16.75 months), followed by adalimumab (15.69 months) and ustekinumab (12.69 months) (Tables 3 and 4).

Details of the primary AE leading to drug discontinuation by specific groups, according to the MedDRA, and IRs are shown in Tables 5–7.

With respect to individual AEs leading to drug discontinuation, 116 cases of infection took place (1.86/100 PY; 95% CI: 1.55–2.23): 12 on infliximab (4.55/100 PY, 95% CI: 2.58–8), 32 on adalimumab (2.41/100 PY, 95% CI: 1.7–3.4), 13 on ustekinumab (1.09/100 PY, 95% CI: 0.63–1.88) and 29 on etanercept (2.36/100 PY, 95% CI: 1.64–3.4). Considering only biologics, infections were the most frequent AE leading to discontinuation. In classic systemic therapy, the highest risk of discontinuation was with cyclosporine (n = 8, 2.62/100 PY, 95% CI: 1.31–5.24). The most common infections were upper and lower respiratory tract infections (17% and 15%, respectively); in addition, three cases of tuberculosis were reported, all of them in patients treated with biologics.

Gastrointestinal tract disorders occurred in 96 patients (1.54/100 PY, 95% CI: 1.26–1.88), 21 on cyclosporine (6.89/100 PY, 95% CI: 4.49–10.56), 42 on methotrexate (3.23/100 PY, 95% CI: 2.39–4.37), 6 on infliximab (2.27/100 PY, 95% CI: 1.02–5.06) and 15 on etanercept (1.22/100 PY, 95% CI: 0.74–2.02). Nausea, vomiting and abdominal pain were the primary gastrointestinal tract disorders (58%).

Discontinuation of therapy due to investigations occurred in 86 courses of treatment (1.38/100 PY, 95% CI: 1.11–1.71), 15 on cyclosporine (4.92/100 PY, 95% CI: 2.96–8.16), 33 on methotrexate (2.54/100 PY, 95% CI: 1.8–3.57), 10 on infliximab (3.79/100 PY, 95% CI: 2.04–7.04) and 10 on acitretin (1.65/100 PY, 95% CI: 0.89–3.06), particularly owing to increased transaminases (48%).

Skin and subcutaneous tissue disorders occurred in 76 cases (1.22/100 PY, 95% CI: 0.97–1.53), especially related to acitretin (4.12/100 PY, 95% CI: 2.78–6.1), which had skin and subcutaneous tissue disorders as the most frequent AE linked to the discontinuation of this drug. Cyclosporine was the second drug for the most AEs related to skin disorders (3.28/100 PY: 1.76–6.09), and infliximab was the third (2.27/100 PY: 1.02–5.06). Alopecia and psoriasis accounted for 20% and 14% of cutaneous AE, respectively.

Seventeen malignancies were classified as AEs that led to discontinuation: five neoplasms of the colon, five of the liver, four of the lung, and three of the breast; there were no cases of lymphoma.

Injection site complications, including infusion-related reactions, were reported in 17 cases. Cyclosporine had the highest amount of AEs related to vascular (hypertension) and nervous system disorders [8.52% (95% CI: 5.8–12.52) and 6.23% (95% CI: 3.97–9.77), respectively].

Discussion

Discontinuation of treatments is an important issue. The primary reasons for discontinuation are as follows: inefficacy, low efficacy or loss of efficacy, remissions and AEs, which is clearly related to survival of treatments.[14,17,18,22–24] Recently, there have been several publications addressing treatment survival, mainly focused on efficacy,[18,23,24] but it is necessary to describe, in detail, the discontinuation of drugs, particularly associated with AEs, to better understand that concept and how it relates to safety.

In our study, the proportion of discontinued treatments due to AEs was of 11%, whereas the primary reason to discontinue a treatment was loss of effectiveness (22%), followed by remission (20%). Of the 447 treatment discontinuations, 810 AEs were observed (14% serious). That number of AEs can be explained because a treatment could be suspended in relation to one or several AEs, and an AE can be linked to a drug if it took place while the patient was using the drug or within 90 days after the

Table 3 Adverse events associated with discontinuation of biologic treatments

	Etanercept		Infliximab		Adalimumab		Ustekinumab	
	All AEs associated with drug discontinuation	Serious AEs associated with drug discontinuation	All AEs associated with drug discontinuation	Serious AEs associated with drug discontinuation	All AEs associated with drug discontinuation	Serious AEs associated with drug discontinuation	All AEs associated with drug discontinuation	Serious AEs associated with drug discontinuation
Number of AE	130	15	70	21	144	39	31	6
Number of treatments	736		125		712		537	
PY	1229		264		1330		1194	
Incidence *	10.58 (8.91–12.56)	1.22 (0.74–2.02)	26.52 (20.98–33.51)	7.95 (5.19–12.20)	10.83 (9.2–12.75)	2.93 (2.14–4.01)	2.6 (1.83–3.69)	0.50 (0.23–1.12)
Time to discontinuation for AE (months) Median (p25–p75)	16.75 (3.51–41.02)	6.66 (3.21–41.01)	8.26 (3.38–24.13)	16.49 (3.38–24.13)	15.69 (4.95–33.74)	16.66 (5.38–27.44)	12.69 (3.97–28.33)	16.10 (1.57–40.43)

*Events associated with drug discontinuation/100 PY of therapy.
AE, adverse events; PY, patient-years.

Table 4 Adverse events associated with discontinuation of systemic classic therapy

	Acitretin		Cyclosporine		Methotrexate	
	All AEs associated with drug discontinuation	Serious AEs associated with drug discontinuation	All AEs associated with drug discontinuation	Serious AEs associated with drug discontinuation	All AEs associated with drug discontinuation	Serious AEs associated with drug discontinuation
Number of AE	88	5	150	14	197	17
Number of treatments	555		529		1024	
PY	607		305		1300	
Incidence*	14.5 (11.76–17.87)	0.82 (0.34–1.98)	49.18 (41.91–57.72)	4.59 (2.72–7.75)	15.15 (13.18–17.42)	1.31 (0.81–2.10)
Time to discontinuation for AE (months) Median (p25–p75)	4.59 (1.93–14.26)	1.87 (1.61–4.59)	2.98 (1.15–5.67)	5.36 (1.15–8.07)	6.59 (2.36–17.57)	8.07 (3.31–22.92)

*Events associated with drug discontinuation/100 PY of therapy.
AE, adverse events; PY, patient-years.

Table 5 Adverse events leading to drug discontinuation, by specific groups according to the MedDRA

	N (%)†	Incidence‡ (95% CI)
Infections and infestations	116	1.86 (1.55–2.23)
Upper respiratory tract infection	20 (17)	0.32 (0.21–0.5)
Lower respiratory tract infection	17 (15)	0.27 (0.17–0.44)
Tuberculosis	3 (3)	0.05 (0.02–0.15)
Skin and subcutaneous infections	18 (16)	0.29 (0.18–0.46)
Dental infection	7 (6)	0.11 (0.05–0.24)
Herpes zoster	5 (4)	0.08 (0.03–0.19)
Gastrointestinal tract disorders	96	1.54 (1.26–1.88)
Nausea, vomiting and abdominal pain	56 (58)	0.9 (0.69–1.17)
Inflammatory bowel disease	4	0.06 (0.02–0.17)
Investigations	86	1.38 (1.12–1.71)
Transaminases increased	41 (48)	0.66 (0.49–0.89)
Abnormal lipid profile	11 (13)	0.18 (0.10–0.32)
High creatinine levels	8 (9)	0.13 (0.06–0.26)
Antinuclear antibodies +	7 (8)	0.11 (0.05–0.24)
Skin and subcutaneous tissue disorders	76	1.22 (0.97–1.53)
Alopecia	15 (20)	0.24 (0.15–0.4)
Psoriasis	11 (14)	0.18 (0.1–0.32)
Urticaria	5 (7)	0.08 (0.03–0.19)
General disorders and administration site conditions	64	1.03 (0.8–1.31)
Asthenia	19 (30)	0.31 (0.2–0.48)
Injection site complications (including infusion-related reaction)	17 (27)	0.27 (0.17–0.44)
Nervous system disorders	58	0.93 (0.72–1.2)
Headache	35 (60)	0.56 (0.4–0.78)
Musculoskeletal and connective tissue disorders	43	0.69 (0.51–0.93)
Osteomuscular pain	22 (51)	0.35 (0.23–0.54)
Psoriatic arthropathy	7 (16)	0.11 (0.05–0.24)
Hepatobiliary disorders	42	0.67 (0.5–0.91)
Hepatic function abnormal	25 (60)	0.4 (0.27–0.59)
Neoplasms	33	0.53 (0.38–0.75)
Malignant: colon (n = 5), liver (n = 5), lung (n = 4) and breast (n = 3)	17 (52)	0.27 (0.17–0.44)
Vascular disorders	31	0.5 (0.35–0.71)
Hypertension	26 (84)	0.42 (0.28–0.61)
Surgical and medical procedures	21	0.34 (0.22–0.52)
Trauma intervention	4 (19)	0.06 (0.02–0.17)
Blood and lymphatic system disorders	19	0.31 (0.2–0.48)
Anaemia	9 (47)	0.14 (0.08–0.28)
Metabolism and nutrition disorders	18	0.29 (0.18–0.46)
Hyperlipidaemia	8 (44)	0.13 (0.06–0.26)
Injury, poisoning and procedural complications	17	0.27 (0.17–0.44)
Fracture	4 (24)	0.06 (0.02–0.17)
Psychiatric disorders	16	0.26 (0.16–0.42)
Anxiety	5 (31)	0.08 (0.03–0.19)
Depression	4 (25)	0.06 (0.02–0.17)
Cardiac disorders	15	0.24 (0.15–0.4)
Heart failure	6 (40)	0.1 (0.04–0.21)
Renal and urinary disorders	14	0.23 (0.13–0.38)
Nephrolithiasis	5 (36)	0.08 (0.03–0.19)
Renal failure	4 (29)	0.06 (0.02–0.17)
Respiratory, thoracic and mediastinal disorders	11	0.18 (0.1–0.32)
Eye disorders	11	0.18 (0.1–0.32)
Reproductive system and breast disorders	10	0.16 (0.09–0.3)
Endocrine disorders	4	0.06 (0.02–0.17)
Ear and labyrinth disorders	3	0.05 (0.02–0.15)
Congenital, familial and genetic disorders	3	0.05 (0.02–0.15)
Immune system disorders	2	0.03 (0.01–0.13)
Social circumstances	1	0.02 (0–0.11)
Total	810 (100)	

†Percentage of 810 AEs.
‡Incidence patient-year with confidence interval (CI) 95%.
ANA, antinuclear antibodies; MedDRA, Medical Dictionary for Regulatory Activities; *N*, number of adverse events (AE).

end of exposure. The IR of discontinuations for classic systemic therapies was 13 (12.14–13.93)/100 PY, which is double that for biologics. This finding could point to a lower toxicity of biologics compared with classic systemic drugs. Nevertheless, we have to take into account that if an AE is resolved during the interdose period, it might not cause treatment discontinuation, and this will be more probable if the period between doses is longer,[23] which is more common for biologics, due to their longer dosage intervals. In the literature, some studies describe a proportion of drug cycles that end in discontinuation due to AEs[18,20,23]; however, these cannot be compared if the time of measurement and follow-up periods are different between studies.

In 2015, Kim *et al.*[7] described, in a retrospective study, a lower proportion of AEs that caused discontinuation of biologic treatment (1.97/100 PY, 4.04%) compared with our study (9.34/100 PY, 8.44–10.33), but similar to other multicentre studies (4.5%, 6%).[19,25] Also, other studies reported a discontinuation rate for biologics that is similar to ours (9.2%, 9.7%).[17,26]

With respect to biologic treatment, infliximab [26.52/100 PY] was the most common agent associated with suspension of treatment, followed by etanercept, adalimumab and ustekinumab. The highest ratio of suspension for infliximab has been previously reported.[17,24,26–28] Also, the lowest incidence of suspension

Table 6 Adverse events leading to drug discontinuation by individual biologic therapy according to the MedDRA

	Etanercept		Infliximab		Adalimumab		Ustekinumab	
	N	I (95% CI)	*N*	I (95% CI)	*N*	I (95% CI)	*N*	I (95% CI)
Infections and infestations	29	2.36 (1.64–3.4)	12	4.55 (2.58–8)	32	2.41 (1.7–3.4)	13	1.09 (0.63–1.88)
Gastrointestinal tract disorders	15	1.22 (0.74–2.02)	6	2.27 (1.02–5.06)	5	0.38 (0.16–0.9)	1	0.08 (0.01–0.59)
Investigations	6	0.49 (0.22–1.09)	10	3.79 (2.04–7.04)	11	0.83 (0.46–1.49)	1	0.08 (0.01–0.59)
Skin and subcutaneous tissue disorders	10	0.81 (0.44–1.51)	6	2.27 (1.02–5.06)	13	0.98 (0.57–1.68)	3	0.25 (0.08–0.78)
General disorders and administration site conditions	10	0.81 (0.44–1.51)	6	2.27 (1.02–5.06)	11	0.83 (0.46–1.49)	3	0.25 (0.08–0.78)
Nervous system disorders	12	0.98 (0.55–1.72)	2	0.76 (0.19–3.03)	8	0.6 (0.3–1.2)	2	0.17 (0.04–0.67)
Musculoskeletal and connective tissue disorders	7	0.57 (0.27–1.19)	2	0.76 (0.19–3.03)	14	1.05 (0.62–1.78)	4	0.34 (0.13–0.89)
Hepatobiliary disorders	3	0.24 (0.08–0.76)	2	0.76 (0.19–3.03)	10	0.75 (0.4–1.4)	1	0.08 (0.01–0.59)
Neoplasms benign, malignant and unspecified	8	0.65 (0.33–1.3)	4	1.52 (0.57–4.04)	10	0.75 (0.4–1.4)	2	0.17 (0.04–0.67)
Vascular disorders	1	0.08 (0.01–0.58)	1	0.38 (0.05–2.69)	1	0.08 (0.01–0.53)	1	0.08 (0.01–0.59)
Surgical and medical procedures	4	0.33 (1.12–0.87)	2	0.76 (0.19–3.03	6	0.45 (0.2–1)		
Blood and lymphatic system disorders	4	0.33 (1.12–0.87)	2	0.76 (0.19–3.03	3	0.23 (0.07–0.7)		
Psychiatric disorders	4	0.33 (1.12-0.87)	2	0.76 (0.19–3.03	2	0.15 (0.04–0.6)		
Metabolism and nutrition disorders	3	0.24 (0.08–0.76)	2	0.76 (0.19–3.03	1	0.08 (0.01–0.53)		
Injury, poisoning and procedural complications	5	0.41 (0.17–0.98)	1	0.38 (0.05–2.69)	5	0.38 (0.16–0.9)		
Cardiac disorders	1	0.08 (0.01–0.58)	4	1.52 (0.57–4.04)	5	0.38 (0.16–0.9)		
Renal and urinary disorders	2	0.16 (0.04–0.65)	1	0.38 (0.05–2.69)	1	0.08 (0.01–0.53)		
Respiratory, thoracic and mediastinal disorders	2	0.16 (0.04–0.65)			3	0.23 (0.07–0.7)		
Eye disorders	2	0.16 (0.04–0.65)						
Reproductive system and breast disorders	2	0.16 (0.04–0.65)			2	0.15 (0.04–0.6)		

N, number of adverse events (AEs); I, incidence: events associated with drug discontinuation/100 patient-years of therapy; MedDRA, Medical Dictionary for Regulatory Activities.

of treatment related to AEs has previously been reported for ustekinumab.[17–19,27,28]

For classic systemic therapy, the IR of discontinuation for AEs was markedly higher for cyclosporine (49.18/100 PY), followed far behind by methotrexate (15.15/100 PY) and acitretin (14.5/100 PY), as has been previously published.[23]

With regard to individual AEs, the most common cause of discontinuation for all systemic agents was infections [116 cases, incidence 1.86 (1.55–2.23)] with infliximab as the first biologic associated, and ustekinumab in the last place, which is similar to other published series,[17,19] whereas between classics, cyclosporine was the primary one, and acitretin the last one, without cases. Classically, tuberculosis is a relevant AE associated with biologics, primarily anti-TNF agents; however, after proper screening was in place, the number of cases of tuberculosis has decreased.[11] In our study, only three cases of tuberculosis were reported, which represents an incidence of 0.05 PY (0.02–0.15 PY).

Gastrointestinal tract disorders were the second highest group of AEs associated with suspension, with cyclosporine as the primary agent, followed far behind by methotrexate and biologics, particularly infliximab.

In addition, it should be noted that the elevated rate of cyclosporine suspensions was associated with vascular disorders, especially related to hypertension. Finally, acitretin followed by cyclosporine presented an elevated rate of discontinuations associated with skin and subcutaneous tissue disorders; again, infliximab had the most suspensions due to skin disorders in the biologics group.

Strengths and limitations

The primary strength of this prospective cohort study is that the studied population is highly representative of psoriasis patients treated with biologic and classic systemic therapies in clinical practice from hospitals in different areas in Spain. Other strengths were the large sample size, detailed data capture and fully independent data analysis.

However, the study has some limitations. First, it is an observational study with a potential bias in the selection of treatments for each patient, because drug prescription was not random. For example, comorbidities may influence the choice of treatment and also the development of the specific AE. Information bias in reporting of AEs by physicians or patients is also possible, although we have established a clear threshold for AE communication and have online and on-site data monitoring to avoid it.

In addition, we did not take into account dose modifications during the study, or whether the drug was the first drug used.

Finally, it should be considered that many patients had been treated with classic systemic drugs before entering the registry, which could have caused some degree of accumulated organ toxicity, possibly influencing the development of AEs.

Table 7 Adverse events leading to drug discontinuation by classic systemic therapies according to the MedDRA

	Acitretin		Cyclosporine		Methotrexate	
	N	I (95% CI)	*N*	I (95% CI)	*N*	I (95% CI)
Infections and infestations	3	0.49 (0.16–1.53)	8	2.62 (1.31–5.24)	19	1.46 (0.93–2.29)
Gastrointestinal tract disorders	6	0.99 (0.44–2.2)	21	6.80 (4.49–10.56)	42	3.23 (2.39–4.37)
Investigations	10	1.65 (0.89–3.06)	15	4.92 (2.96–8.16)	33	2.54 (1.8–3.57)
Skin and subcutaneous tissue disorders	25	4.12 (2.78–6.1)	10	3.28 (1.76–6.09)	9	0.69 (0.36–1.33)
General disorders and administration site conditions	7	1.15 (0.55–2.42)	8	2.62 (1.31–5.24)	19	1.46 (0.93–2.29)
Nervous system disorders	8	1.32 (0.66–2.64)	19	6.23 (3.97–9.77)	7	0.54 (0.26–1.13)
Musculoskeletal and connective tissue disorders	3	0.49 (0.16–1.53)	5	1.64 (0.68–3.94)	8	0.62 (0.31–1.23)
Hepatobiliary disorders	6	0.99 (0.44–2.2)	4	1.31 (0.49–3.49)	16	1.23 (0.75–2.01)
Neoplasms	1	1.65 (0.89–3.06)	1	0.33 (0.05–2.33)	7	0.54 (0.26–1.13)
Vascular disorders			26	8.52 (5.8–12.52)	1	0.08 (0.01–0.55)
Surgical and medical procedures	1	1.65 (0.89–3.06)	2	0.66 (0.16–2.62)	6	0.46 (0.21–1.03)
Blood and lymphatic system disorders			3	0.98 (0.32–3.05)	7	0.54 (0.26–1.13
Psychiatric disorders	1	1.65 (0.89–3.06)	2	0.66 (0.16–2.62)	5	0.38 (0.16–0.92)
Metabolism and nutrition disorders	6	0.99 (0.44–2.2)	5	1.64 (0.68–3.94)	1	0.54 (0.26–1.13)
Injury, poisoning and procedural complications	2	0.33 (0.08–1.32)			4	0.31 (0.12–0.82)
Cardiac disorders	1	1.65 (0.89–3.06)	3	0.98 (0.32–3.05)	1	0.54 (0.26–1.13)
Renal and urinary disorders	2	0.33 (0.08–1.32)	6	1.97 (0.88–4.38)	2	0.15 (0.04–0.62)
Respiratory, thoracic and mediastinal disorders	2	0.33 (0.08–1.32)	1	0.33 (0.05–2.33)	3	0.23 (0.07–0.72)
Eye disorders	2	0.33 (0.08–1.32)			4	0.31 (0.12–0.82)
Reproductive system and breast disorders			5	1.64 (0.68–3.94)	1	0.54 (0.26–1.13)
Congenital, familial and genetic disorders	2	0.33 (0.08–1.32)	1	0.33 (0.05–2.33)		
Endocrine disorders			4	1.31 (0.49–3.49)		

N, number of adverse events (AEs); I, incidence: events associated with drug discontinuation/100 patient-years of therapy; MedDRA, Medical Dictionary for Regulatory Activities.

Conclusions

There are a large number of variables that can influence drug discontinuation in psoriasis treatment. Although many of these variables are not related to the safety of the drug, this reason is of paramount importance. Our multicentre observational study showed that 11% of systemic treatments are suspended due to AEs in the study period, with an IR of AE associated with discontinuation of 13 (12.14–13.93)/100 PY, with only 14% of those being serious AEs. Biologics presented a lower IR of total AEs related to discontinuation than did classics drugs, but not with respect to serious AEs.

In classic systemic therapies, cyclosporine had the highest number of suspensions associated with AE, and infliximab had the highest for biologics. Ustekinumab was the drug with the lowest incidence of stopping associated with AE. Infection and gastrointestinal tract disorders were the most common AEs responsible for all systemic treatments, with infliximab associated with infections and cyclosporine associated with vascular and gastrointestinal tract disorders.

In conclusion, our study with patients in clinical practice provides data to complement safety information based on clinical trials, and shows that biologic therapies are associated with a low rate of suspension-related AEs compared with classic systemic therapies. Our results show that ustekinumab is the drug with the lowest incidence of discontinuations related to AE.

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