Br J Dermatol 2024; **00**:1–12
https://doi.org/10.1093/bjd/ljae454
Advance access publication date: 20 November 2024

BJD
British Journal of Dermatology
Epidemiology

Drug survival and safety of biosimilars for treating psoriasis compared with originator adalimumab: a multinational cohort study

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Abstract

Background The lack of evidence from routine clinical settings has limited the widespread adoption of adalimumab biosimilars for the treatment of psoriasis.

Objectives To compare the drug survival and safety of adalimumab biosimilars with Humira® in psoriasis.

Methods We conducted a prevalent new-user cohort study using data from the French National Health Data System (SNDS), the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) and the Spanish Registry of Systemic Therapy in Psoriasis (BIOBADADERM). Adalimumab-naïve patients initiating adalimumab biosimilars (new users) were compared with Humira new users. Patients switching from Humira to biosimilars (switchers) were compared with those who continued Humira treatment. Patients were matched 1 : 1 based on previous adalimumab exposure time to create equal-sized cohorts of biosimilar and Humira users. Co-primary outcomes included drug discontinuation and serious adverse events (SAEs). Hazard ratios (HRs) were calculated using Cox proportional hazard models. Meta-analyses using random-effect models were performed to combine results from the three databases.

Results In total, 7387 biosimilar new users and 3654 switchers were matched and compared with Humira users. No differences in all-cause discontinuation were found between biosimilar and Humira new users [HR 0.99, 95% confidence interval (CI) 0.94–1.04]. Switching from Humira to biosimilars was associated with a higher discontinuation rate than remaining on Humira (HR 1.35, 95% CI 1.19–1.52). Similar results were observed for discontinuation due to ineffectiveness or adverse events. Risks of SAEs were similar between biosimilar new users and Humira new users [incidence rate ratio (IRR) 0.91, 95% CI 0.80–1.05] or between switchers and continuous Humira users (IRR 0.92, 95% CI 0.83–1.01).

Conclusions Adalimumab biosimilars can be considered viable alternatives to Humira for new patients, with comparable effectiveness and safety. However, owing to the higher likelihood of discontinuation, patients who switch from Humira to biosimilars may require closer monitoring and support.

Accepted: 18 November 2024

Lay summary

Psoriasis is a long-term inflammatory skin disease that affects over 60 million people globally. Adalimumab is a drug often used to treat moderate to severe psoriasis. The original adalimumab brand (called Humira®) is expensive and adds pressure to health care systems. 'Biosimilars' are drugs that are similar to Humira. They became available in Europe in 2018. These drugs could help cut costs and make treatment more accessible.

This study looked at how long people stayed on treatment. It also looked at the safety of adalimumab biosimilars in people with psoriasis. Information from large health databases in France, the UK and Spain was used to compare two groups. The first group included people who started on either biosimilars or Humira for the first time. The second included people who switched from Humira to biosimilars compared with those who kept taking Humira. There was no difference in how long new users of biosimilars stayed on treatment compared with new users of Humira. Patients who switched from Humira to biosimilars were more likely to stop treatment than those who kept using Humira. The risk of serious side effects was similar for both biosimilar and Humira users.

Our findings suggest that biosimilars are as safe and effective as Humira. Patients who switch to biosimilars from Humira are more likely to stop treatment. More research is needed to understand the effects of switching.

What is already known about this topic?

- Adalimumab is an effective biologic treatment for patients with moderate-to-severe psoriasis.
- Evidence for the use of adalimumab biosimilars in real-world settings is insufficient.

What does this study add?

- We found no differences in all-cause discontinuation between biosimilars and new users of Humira.
- Switching from Humira to biosimilars was associated with a higher discontinuation rate than remaining on Humira.
- Risks of serious adverse events were similar between biosimilars and Humira.

Adalimumab is a tumour necrosis factor-α inhibitor used to treat moderate-to-severe psoriasis.[1,2] The introduction of adalimumab biosimilars – products highly similar to the originator, Humira® (AbbVie, North Chicago, IL, USA) – presents opportunities for cost reductions, improving patients' accessibility and public health spending sustainability. However, the uptake of adalimumab biosimilars varies across regions and countries,[3–6] with concerns regarding safety, efficacy and extrapolated indications limiting the use of biosimilars.[7,8]

Although highly similar, biosimilars are not identical to Humira owing to the molecular structure and complexity of the manufacturing process.[9] Notably, the extrapolation of regulatory approval from one to all indications allows biosimilars to gain approval for psoriasis without being directly studied in populations of people with psoriasis in randomized controlled trials (RCTs).[10] Real-world evidence comparing adalimumab biosimilars with Humira is inconsistent. In inflammatory bowel and rheumatic diseases, biosimilars and Humira show no differences in treatment persistence, effectiveness or safety.[11–15] However, in hidradenitis suppurativa, switching to biosimilars increased the risk of treatment discontinuation.[16,17] In psoriasis, a recent systematic review only found one comparative cohort study,[18] suggesting no differences in treatment discontinuation but a higher risk of adverse events (AEs) when switching from Humira to biosimilars.[19]

Evaluating the drug survival (time from initiation to discontinuation)[20] and safety of biosimilars is crucial for informed clinical decisions, ensuring cost-effectiveness and patient wellbeing.[10] Our study compared adalimumab biosimilars and Humira for psoriasis, using data from the French National Health Data System (SNDS), the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) and the Spanish Registry of Systemic Therapy in Psoriasis (BIOBADADERM).

Patients and methods

Study design

This study adopted the prevalent new-user design illustrated by Suissa *et al*.[21] The study protocol has been described previously.[22] The study followed the STROBE guidance (https://www.strobe-statement.org).

Patient and public involvement statement

An online survey was conducted via the UK's Psoriasis Association research network. Two patient focus group meetings were held to refine the research question and objectives.[22]

Setting and data source

BADBIR and BIOBADADERM are longitudinal multicentre registries for people with psoriasis on systemic treatment in the UK and Spain. Both registries collect data on demographics, disease characteristics, treatment history and clinical assessments at baseline, with follow-ups during healthcare visits or at least annually to track treatment changes, clinical outcomes and AEs. Both registries have previously been described in detail.[23,24] The SNDS is France's national healthcare database, covering > 99% of the population. It records

outpatient and inpatient diagnoses, medical procedures, drug deliveries, hospital admissions and sociodemographic information via unique personal identification numbers.[25–27] Study variables, outcomes and data inclusion periods in each database are described in Table S1 (see Supporting Information).

Study participants and matching

We included patients with psoriasis of all ages and sexes using Humira and adalimumab biosimilars, including adalimumab-naïve patients (new users) and those switching from Humira to biosimilars (switchers) for nonmedical reasons (switching for reasons other than effectiveness, side-effects or adherence). Patients with concomitant use of other biologics were excluded. The inclusion and exclusion criteria are detailed in the study protocol.[22] To improve the study sample size, we modified the protocol to include patients with past use of novel small-molecule inhibitors.

We allocated patients in time-based exposure sets defined in monthly intervals from the initiation of adalimumab.[21] Time-conditional propensity scores were calculated using a Cox proportional hazards model. We matched each biosimilar user with a Humira user in the same exposure set using a 1 : 1 greedy matching algorithm, starting with the first chronological index biosimilar user. The cohort entry date for biosimilar users was the date of their first biosimilar prescription, while for Humira users, it was the matching date. Thus, each biosimilar user was paired with a Humira user with a similar duration of adalimumab use before cohort entry. If Humira users later switched to a biosimilar, their follow-up was censored at the time of switching, and they were categorized as Humira-to-biosimilar switchers from that point onward. For each biosimilar brand, we identified a biosimilar cohort and a corresponding Humira comparator cohort.

Outcomes

The co-primary outcomes were all-cause drug discontinuation and serious AEs (SAEs). Drug discontinuation was any treatment gap of > 90 days or switching to another biologic, identified by physician-provided start/stop dates in registries or drug delivery dates in claims data. The discontinuation date was the final treatment stop date (BADBIR and BIOBADADERM), the end of the 90-day period after the last drug delivery (SNDS) or the earliest date of switching to another biologic. SAEs were any medical events during the use of the study drugs that resulted in death or hospitalization. Secondary outcomes included drug discontinuation owing to ineffectiveness or AEs. Follow-up started at cohort entry and ended at the last follow-up date, death or the study end date (31 December 2022).

Data analysis

We calculated the risk of drug discontinuation using Kaplan–Meier survival analysis. Cox proportional hazard models were used to estimate hazard ratios (HRs) for all-cause discontinuation. In BADBIR and BIOBADADERM, reasons for treatment changes were available for all patients. In Humira cohorts, switching to biosimilars was censored for nonmedical reasons or marked as discontinuation for medical reasons. In biosimilar cohorts, switching to Humira or other biosimilars followed the same rules. In SNDS, due to missing reasons for discontinuation, switching from Humira to biosimilars was assumed to be nonmedical, and switching to another biologic was considered discontinuation due to ineffectiveness.

One-year drug discontinuation risks and sub-HRs for discontinuation due to ineffectiveness or AEs were computed using Fine and Gray's model, treating discontinuation for other causes as competing events. Psoriasis Area and Severity Index (PASI) measured within 1 month before discontinuation was described. Incidence rates (IRs) of all SAEs occurred during follow-up per person-years; the HRs of the first occurrence of SAEs were computed; and the incidence of the 10 most common SAEs was described, stratified by Medical Dictionary for Regulatory Activities Terminology (MedDRA) system organ class.

We used a two-tier approach to adjust for confounders. The first-tier models included factors associated with biologic drug discontinuation in previous studies, including age, sex, obesity, psoriatic arthritis and duration of adalimumab treatment before cohort entry.[28,29] The second-tier models added confounders based on clinical opinions, including the number of comorbidities (excluding psoriatic arthritis), disease duration, number of previous biologic treatments (excluding recent Humira treatment for switchers), history of small-molecule inhibitor treatments, concomitant nonbiologic systemic treatments and calendar years of treatment initiation.

Multiple imputation models of 20 imputed datasets using chained equations were performed to account for missing baseline data, and the estimates were obtained according to Rubin's rules. Each database provided independent analysis for all outcomes. We combined results using meta-analyses.[30]

Subgroup analyses included stratification by biosimilar brand and by database. Biosimilar new users were compared with Humira new users. Humira-to-biosimilar switchers were compared with patients who continued Humira.

Six sensitivity analyses were conducted to enhance result robustness. Firstly, to explore the impact of prior adalimumab treatment duration, we stratified switchers and continuous Humira users by adalimumab treatment duration (less than or more than 2 years) before cohort entry. Secondly, to consider delays in AE reporting, we linked SAEs to a drug if they occurred during its use or within 90 days post-exposure. Thirdly, we used analyses weighted by inverse probability of censoring weighting to address potential bias from right-censored survival times. Fourthly, to rule out the impact of small-molecule inhibitor history on biologic drug survival, we excluded patients with previous small-molecule inhibitor treatments. Fifthly, to explore the effect of switching back to Humira among switchers on the effect estimate, we censored follow-up when switchers returned to Humira instead of classifying the event as biosimilar discontinuation. Finally, we treated nonmedical switches from Humira to biosimilars among Humira users as a different type of outcome rather than censoring them from the analysis. This allowed us to examine how the competing risk of these events might affect the results.

Data were analysed using R (R Foundation for Statistical Computing, Vienna, Austria); Stata version 17.1 (StataCorp,

Table 1 Baseline demographic and disease characteristics of the study cohorts

	New-user analysis		Switcher/continuous-user analysis	
	Humira new users (*n* = 7387)	**Biosimilar new users (*n* = 7387)**	**Humira continuous users (*n* = 3654)**	**Biosimilar switchers (*n* = 3654)**
PY of follow-up	12 423	9460	7715	6509
Age (years), mean (SD)	46.6 (43.8)	46.9 (65.8)	45.8 (30.8)	46.0 (40.0)
Male sex	3901 (52.8)	3712 (50.3)	2355 (64.4)	2398 (65.6)
Obesity	1325 (17.9)	1321 (17.9)	936 (25.6)	974 (26.7)
Psoriatic arthritis	1801 (24.4)	2163 (29.3)	1135 (31.1)	1232 (33.7)
No. of comorbidities[a]				
None	3906 (52.9)	3936 (53.3)	1496 (40.9)	1511 (41.4)
1–2	2727 (36.9)	2691 (36.4)	1535 (42.0)	1531 (41.9)
3–4	640 (8.7)	599 (8.1)	471 (12.9)	458 (12.5)
≥ 5	114 (1.5)	161 (2.2)	180 (4.9)	181 (5.0)
Disease duration (years), mean (SD)	18.4 (1.8)	16.8 (1.8)	22.5 (4.3)	22.8 (4.4)
No. of previous biologic treatments				
None	5223 (70.7)	5401 (73.1)	2946 (80.6)	3101 (84.9)
1	1608 (21.8)	1437 (19.5)	575 (15.7)	455 (12.5)
≥ 2	556 (7.5)	549 (7.4)	133 (3.6)	98 (2.7)
Concomitant conventional systemic treatment[b]	2270 (30.7)	2429 (32.9)	808 (22.1)	766 (21.0)
History of small-molecule inhibitor treatments[c]	987 (13.4)	941 (12.7)	115 (3.1)	145 (4.0)
Duration of Humira treatment before cohort entry (months), mean (SD)	NA	NA	56.1 (53.9)	56.1 (53.9)
Biosimilar brands				
Amgevita	–	3297 (44.6)	–	1878 (51.4)
Imraldi	–	1351 (18.3)	–	1082 (29.6)
Hyrimoz	–	720 (9.7)	–	187 (5.1)
Idacio	–	620 (8.4)	–	93 (2.5)
Hulio	–	1399 (18.9)	–	414 (11.3)

Data are presented as *n* (%) unless otherwise stated. NA, not applicable; PY, person-years. [a]Excluding psoriatic arthritis and including hypertension, ischaemic heart disease, stroke, pulmonary fibrosis, asthma, chronic obstructive pulmonary disease, diabetes, thyroid disease, peptic ulcers, hepatic disease, renal disease, demyelinating disease, epilepsy, depression, tuberculosis and cancer. [b]Including methotrexate, ciclosporin, acitretin, fumaric acid esters and hydroxycarbamide. [c]Including apremilast, deucravacitinib and tofacitinib.

College Station, TX, USA); and Review Manager version 5.4 (Cochrane Collaboration, London, UK).

Results

Data for five adalimumab biosimilars were available: Amgevita (Amgen, Cambridge, UK), Imraldi (Biogen Biosimilars, Maidenhead, UK), Hyrimoz (Sandoz, Camberley, UK), Idacio (Fresenius Kabi, Runcorn, UK) and Hulio (Fujifilm Kyowa Kirin Biologics, Galashiels, UK). We included 7387 biosimilar new users and 3654 switchers, matched and compared with 7387 Humira new users and 3654 continuous users, respectively (Figure S1; see Supporting Information).

Data for new users were available in all three databases. Data for switchers/continuous users were available in BADBIR and SNDS but were excluded from BIOBADADERM due to small sample size and model convergence. Patient characteristics and follow-up durations are provided in Table 1, with database-specific details provided in Tables S2 and S3 (see Supporting Information). Across the three databases, significant variations were recorded in the proportion of patients with obesity, psoriatic arthritis and taking conventional treatments. Considering these differences, we used random-effect models for the meta-analyses of the three databases. The proportional hazard assumption, tested using Schoenfeld residuals, was met in all Cox models.

All-cause drug discontinuation

Table 2 provides the drug survival functions for the first year of cohort entry. The meta-analysis of fully adjusted Cox regression models revealed no significant differences in drug discontinuation between biosimilar and Humira new users [HR 0.99, 95% confidence interval (CI) 0.94–1.04], with homogeneous results across biosimilar brands (subgroup differences $I^2 = 0\%$; Figure 1).

Higher discontinuation rates were observed among Humira-to-biosimilar switchers than in those continuing Humira (HR 1.35, 95% CI 1.19–1.52), with heterogeneity among biosimilar brands (subgroup differences $I^2 = 73.4\%$). Subgroup analysis by brand indicated higher discontinuation rates among switchers to Amgevita (HR 1.25, 95% CI 1.13–1.27), Imraldi (HR 1.53, 95% CI 1.33–1.76) and Hyrimoz (HR 1.80, 95% CI 1.29–2.52).

Unadjusted and partly adjusted models showed similar results (Figures S2, S3; see Supporting Information). The subgroup meta-analysis by database recorded consistent results across all data sources (Table 3).

Drug discontinuation due to ineffectiveness

No significant differences in discontinuation due to ineffectiveness were found between biosimilar and Humira new users (HR 0.97, 95% CI 0.88–1.08; subgroup differences $I^2 = 45.3\%$). Analysis of discontinuation due to ineffectiveness among switchers was only available in BADBIR, which

Table 2 Kaplan–Meier drug survival functions at 1 year in the biosimilar and Humira cohorts: new-user and switcher/continuous-user analyses

	Humira users				Biosimilar users			
	n	**All-cause**	**Ineffectiveness**	**AEs**	***n***	**All-cause**	**Ineffectiveness**	**AEs**
Humira new users vs. Amgevita new users								
BADBIR	445	0.74 (0.70–0.78)	0.86 (0.82–0.89)	0.91 (0.88–0.93)	445	0.73 (0.68–0.77)	0.84 (0.80–0.88)	0.91 (0.87–0.93)
BIOBADADERM	319	0.60 (0.55–0.66)	0.76 (0.71–0.81)	0.91 (0.86–0.94)	319	0.68 (0.62–0.73)	0.76 (0.70–0.81)	0.97 (0.94–0.98)
SNDS	2533	0.50 (0.48–0.52)	0.69 (0.67–0.71)	NA	2533	0.49 (0.47–0.51)	0.70 (0.68–0.72)	NA
Humira new users vs. Imraldi new users								
BADBIR	376	0.72 (0.68–0.77)	0.83 (0.79–0.87)	0.92 (0.88–0.94)	376	0.73 (0.69–0.78)	0.82 (0.78–0.86)	0.92 (0.89–0.95)
BIOBADADERM	117	0.58 (0.49–0.67)	0.75 (0.66–0.82)	0.94 (0.87–0.97)	117	0.78 (0.68–0.85)	0.84 (0.75–0.90)	0.96 (0.90–0.98)
SNDS	858	0.48 (0.45–0.52)	0.70 (0.66–0.73)	NA	858	0.48 (0.44–0.51)	0.66 (0.62–0.69)	NA
Humira new users vs. Hyrimoz new users								
BADBIR	70	0.74 (0.62–0.83)	0.85 (0.74–0.92)	0.89 (0.78–0.95)	70	0.80 (0.68–0.87)	0.91 (0.80–0.96)	0.93 (0.83–0.97)
BIOBADADERM	403	0.61 (0.56–0.66)	0.76 (0.71–0.80)	0.92 (0.89–0.95)	403	0.77 (0.72–0.81)	0.85 (0.80–0.88)	0.95 (0.92–0.97)
SNDS	247	0.56 (0.50–0.63)	0.75 (0.70–0.81)	NA	247	0.49 (0.43–0.56)	0.67 (0.61–0.74)	NA
Humira new users vs. Idacio new users								
BIOBADADERM	113	0.62 (0.52–0.70)	0.81 (0.71–0.87)	0.90 (0.81–0.94)	113	0.66 (0.55–0.74)	0.85 (0.76–0.91)	0.96 (0.89–0.99)
SNDS	507	0.51 (0.41–0.45)	0.69 (0.65–0.74)	NA	507	0.51 (0.46–0.55)	0.70 (0.66–0.75)	NA
Humira new users vs. Hulio new users								
SNDS	1399	0.51 (0.49–0.54)	0.70 (0.68–0.73)	NA	1399	0.53 (0.50–0.56)	0.71 (0.69–0.74)	NA
All Humira new users vs. biosimilar new users								
BADBIR	891	0.73 (0.68–0.77)	0.85 (0.82–0.87)	0.91 (0.89–0.93)	891	0.74 (0.70–0.78)	0.84 (0.81–0.86)	0.92 (0.89–0.93)
BIOBADADERM	952	0.61(0.57–0.64)	0.93 (0.90–0.95)	0.94 (0.91–0.96)	952	0.73 (0.69–0.76)	0.96 (0.94–0.97)	0.98 (0.96–0.99)
SNDS	5544	0.50 (0.49–0.52)	0.70 (0.68–0.71)	NA	5544	0.50 (0.49–0.51)	0.70 (0.68–0.71)	NA
Humira continuous users vs. Amgevita switchers								
BADBIR	960	0.89 (0.86–0.90)	0.95 (0.93–0.96)	0.97 (0.95–0.98)	960	0.85 (0.82–0.87)	0.92 (0.90–0.93)	0.94 (0.92–0.95)
SNDS	918	0.61 (0.58–0.64)	NA	NA	918	0.54 (0.50–0.57)	NA	NA
Humira continuous users vs. Imraldi switchers								
BADBIR	758	0.88 (0.86–0.91)	0.95 (0.93–0.97)	0.96 (0.95–0.98)	758	0.80 (0.77–0.83)	0.90 (0.87–0.92)	0.92 (0.90–0.94)
SNDS	324	0.62 (0.57–0.68)	NA	NA	324	0.45 (0.40–0.51)	NA	NA
Humira continuous users vs. Hyrimoz switchers								
BADBIR	86	0.96 (0.88–0.99)	0.99 (0.91–1.00)	0.99 (0.91–1.00)	86	0.76 (0.66–0.84)	0.97 (0.89–0.99)	0.81(0.71–0.88)
SNDS	101	0.65 (0.56–0.75)	NA	NA	101	0.43 (0.34–0.54)	NA	NA
Humira continuous users vs. Idacio switchers								
SNDS	93	0.66 (0.57–0.77)	NA	NA	93	0.55 (0.45–0.66)	NA	NA
Humira continuous users vs. Hulio switchers								
SNDS	414	0.64 (0.59–0.69)	NA	NA	414	0.62 (0.58–0.67)	NA	NA
All Humira continuous users vs. biosimilar switchers								
BADBIR	1804	0.89 (0.87–0.91)	0.95 (0.94–0.96)	0.97 (0.96–0.97)	1804	0.79 (0.77–0.82)	0.91 (0.90–0.92)	0.93 (0.91–0.94)
SNDS	1850	0.63 (0.60–0.65)	NA	NA	1850	0.54 (0.52–0.56)	NA	NA

Data are presented as drug survival rate (95% confidence interval) unless otherwise stated. AE, adverse event; BADBIR, British Association of Dermatologists Biologics and Immunomodulators Register; BIOBADADERM, Spanish Registry of Systemic Therapy in Psoriasis; NA, not available; SNDS, French National Health Data System.

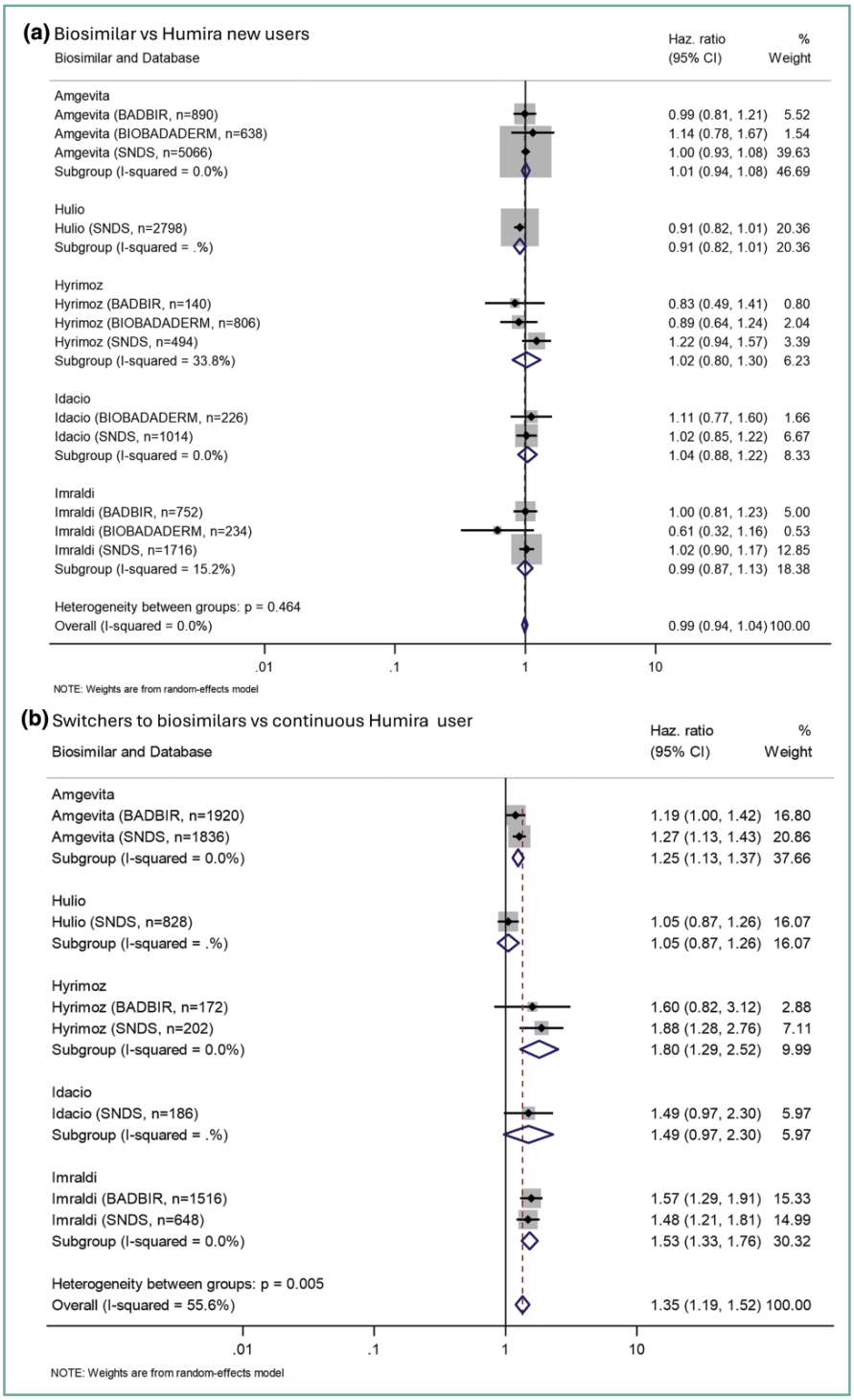

Figure 1 Meta-analysis of fully adjusted Cox regression model for all-cause discontinuation of adalimumab biosimilars and Humira. (a) New-user analysis; (b) switcher analysis. CI, confidence interval; Haz. ratio, hazard ratio.

showed higher discontinuation rates for Amgevita (HR 1.35, 95% CI 1.03–1.77) and Imraldi (HR 1.90, 95% CI 1.43–2.52) switchers than for continuous Humira users. Consistent results were obtained in all analyses [Table 3; Figures S4, S5 (see Supporting Information)].

PASI scores at treatment discontinuation were available for 38.1–52.3% of patients across the BADBIR and BIOBADADERM cohorts. The mean (SD) PASI score was 11.7 (6.0) for Humira new users vs. 10.0 (12.1) for biosimilar new users, and 10.2 (7.1) for continuous Humira users vs. 8.3 (7.0) for switchers (Table S4; see Supporting Information).

Drug discontinuation due to adverse events

Data on discontinuation due to AEs were available in BADBIR and BIOBADADERM. For new users, all biosimilars showed

Table 3 Meta-analyses of study outcomes stratified by each database

		Biosimilar new users vs. Humira new users		Biosimilar switchers vs. Humira continuous users	
		Unadjusted	**Fully adjusted**	**Unadjusted**	**Fully adjusted**
All-cause discontinuation, HR (95% CI)	BADBIR	0.99 (0.86–1.14)	0.98 (0.85–1.13)	1.27 (1.12–1.44)	1.35 (1.19–1.53)
	BIOBADADERM	0.68 (0.50–0.92)	0.98 (0.80–1.20)	NA	NA
	SNDS	0.99 (0.95–1.03)	0.99 (0.94–1.04)	1.25 (1.16–1.36)	1.28 (1.18–1.40)
	Total	0.89 (0.81–0.99)	0.99 (0.94–1.04)	1.26 (1.18–1.35)	1.35 (1.19–1.52)
	Heterogeneity I^2	64.6	0	0	0
Discontinuation due to ineffectiveness, HR (95% CI)	BADBIR	1.01 (0.84–1.20)	0.98 (0.82–1.17)	1.22 (0.79–1.89)	1.54 (1.27–1.87)
	BIOBADADERM	0.74 (0.53–1.04)	0.95 (0.71–1.27)	NA	NA
	SNDS	1.01 (0.90–1.13)	0.95 (0.88–1.02)	NA	NA
	Total	0.94 (0.84–1.05)	0.97 (0.88–1.08)	NA	NA
	Heterogeneity I^2	31.3	0	NA	NA
Discontinuation due to AEs, HR (95% CI)	BADBIR	0.92 (0.73–1.17)	0.92 (0.72–1.18)	1.60 (1.28–2.01)	1.60 (1.27–2.02)
	BIOBADADERM	0.50 (0.34–0.72)	0.47 (0.34–0.65)	NA	NA
	SNDS	NA	NA	NA	NA
	Total	NA	NA	NA	NA
	Heterogeneity I^2	NA	NA	NA	NA
Occurrence of first SAE, HR (95% CI)	BADBIR	0.65 (0.45–0.93)	0.65 (0.45–0.93)	0.94 (0.71–1.25)	0.95 (0.71–1.27)
	BIOBADADERM	0.29 (0.18–0.47)	0.31 (0.19–0.51)	NA	NA
	SNDS	0.96 (0.88–1.04)	0.93 (0.88–1.00)	0.94 (0.84–1.06)	0.92 (0.82–1.03)
	Total	0.80 (0.68–0.94)	0.83 (0.72–0.96)	0.94 (0.85–1.05)	0.92 (0.83–1.03)
	Heterogeneity I^2	92.5	91.0	0	0
SAEs, IRR (95% CI)	BADBIR	0.80 (0.66–0.97)	NA	0.89 (0.74–1.07)	NA
	BIOBADADERM	0.34 (0.20–0.58)	NA	–	NA
	SNDS	1.05 (0.98–1.11)	NA	0.93 (0.83–1.04)	NA
	Total	0.91 (0.80–1.05)	NA	0.92 (0.83–1.01)	NA
	Heterogeneity I^2	90.9	NA	0	NA

AE, adverse event; BADBIR, British Association of Dermatologists Biologics and Immunomodulators Register; BIOBADADERM, Spanish Registry of Systemic Therapy in Psoriasis; CI, confidence interval; HR, hazard ratio; IRR incidence rate ratio; NA, not available; SAE, serious adverse event; SNDS, French National Health Data System.

no statistically significant differences in AE-related discontinuation rates compared with Humira, except for Hyrimoz (HR 0.54, 95% CI 0.35–0.85) (Figures S5, S6; see Supporting Information). For switchers, only data from BADBIR were available, which revealed higher AE-related discontinuation rates for Amgevita (HR 1.48, 95% CI 1.09–2.01) and Imraldi (HR 1.77, 95% CI 1.25–2.51) switchers than for continuous Humira users (Figures S6, S7; see Supporting Information). Owing to limited data, a pooled analysis was not feasible.

Discontinuation due to neoplasms (benign, malignant and unspecified) was more common in Humira users than in biosimilar new users (1.7% vs. 0.5%; $P<0.001$). Discontinuations due to skin and subcutaneous tissue disorders (1.8% vs. 0.4%; $P<0.001$) and general disorders and administration site conditions (2.8% vs. 1.2%; $P<0.001$) were more common in switchers than in continuous Humira users (Table S5; see Supporting Information).

Serious adverse events

The incidence rates of SAEs were similar between biosimilar and Humira new users [IR ratio (IRR) 0.91, 95% CI 0.80–1.05; subgroup differences $I^2=52.6\%$] and between switchers and continuous Humira users (IRR 0.92, 95% CI 0.83–1.01; subgroup differences $I^2=0\%$) (Figure 2). No significant differences were observed across all MedDRA system organ classes (Table S6; see Supporting Information).

The rate of first SAE occurrence was significantly lower in biosimilar new users compared with Humira new users (HR 0.83, 95% CI 0.72–0.96; subgroup differences $I^2=26.0\%$). However, no significant differences were found in the subgroup analysis by biosimilar brands. The rate of first SAE occurrence was comparable between switchers and continuous Humira users (HR: 0.94, 95% CI 0.85–1.05, subgroup differences $I^2=0\%$). Consistent results were recorded across all analyses (Figures S8–S10; see Supporting Information).

Sensitivity analyses

All sensitivity analyses, except the fifth model, showed similar results to the main analysis (Tables S7–S12; see Supporting Information). In the fifth model, when switching back to Humira was censored from the analysis, discontinuation rates were lower among switchers than in continuous Humira users (HR 0.89, 95% CI 0.80–0.99; $I^2=52.6\%$) (Table S11). In BADBIR, where reasons for switching back were available, switching back was recorded in 10.4% ($n=188/1084$) of switchers, with reasons including ineffectiveness ($n=110$), AEs ($n=64$) and other reasons ($n=14$).

Discussion

Our study found comparable drug survival between adalimumab biosimilars and Humira for new users. However, switching from Humira to biosimilars was associated with a higher discontinuation rate than remaining on Humira. The rate of developing the first SAE was lower in biosimilar new users and similar between switchers and continuous Humira users. SAE IRs did not differ significantly between biosimilar and Humira new users or between switchers and continuous Humira users.

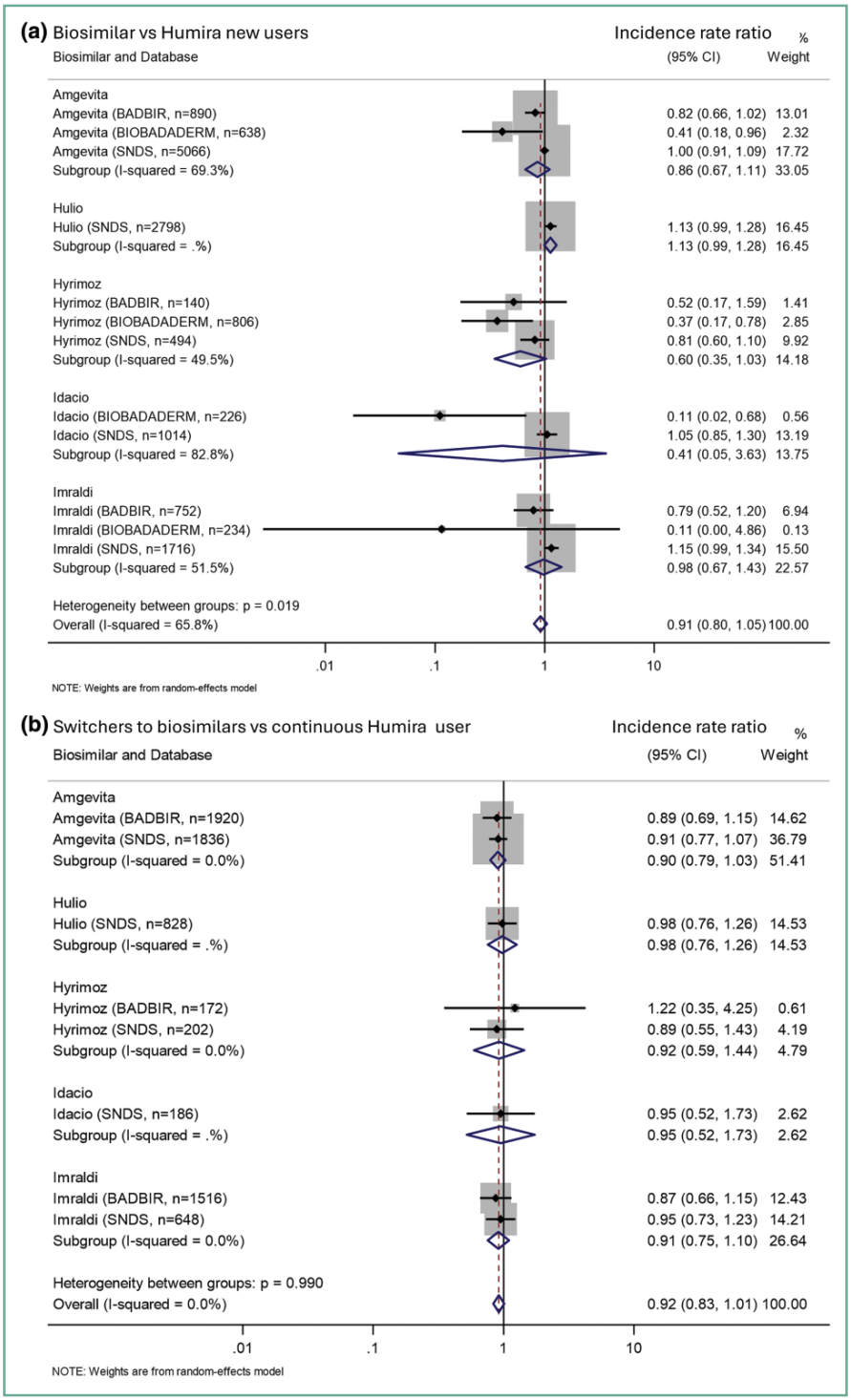

Figure 2 Meta-analysis of incidence rate ratios of serious adverse events of adalimumab biosimilars and Humira. (a) New-user analysis; (b) switcher analysis. CI, confidence interval.

Although most relative outcomes were consistent between the three databases, exceptions included drug discontinuation due to AEs, occurrence of the first SAE and SAE IRs recorded in BIOBADADERM, which showed lower effect estimates than BADBIR and SNDS. Variations in database design and monitoring, and small cohort size and differences in data recording contributed to these heterogeneities.

Differences among biosimilar brands may arise from variations in manufacturing and formulation. Subgroup meta-analysis by brand found no significant heterogeneities among new users. However, significant heterogeneities were observed among switchers, with higher discontinuation rates for switchers to Amgevita, Imraldi and Hyrimoz. While no significant differences in drug survival were found for switchers to Idacio and Hulio, limited data and short

follow-up durations may have affected these results. For SAEs, no significant differences were observed between any biosimilar brands.

Imraldi and Hulio have not been compared with Humira in any RCTs for psoriasis. Only Amgevita, Hyrimoz and Idacio have been directly compared with Humira in psoriasis RCTs, showing no differences in efficacy or safety.[18,31–33] Real-world comparative evidence was limited to one cohort study by Loft *et al*. using the Danish Dermatology (DERMBIO) database,[19] which showed similar 1-year drug survival rates between switching to Hyrimoz and Imraldi and continuing Humira.

Our new-user analysis results mirrored the results of clinical trials, indicating comparable drug survival between Humira and biosimilars. New biosimilar users had a lower rate of first SAEs, but this was only seen in registries where most Humira users were recruited before biosimilars were available. The evolving practices and increased treatment options over time could explain these results.

Switcher analysis found a higher discontinuation rate in patients switching from Humira to biosimilars, which is different from RCT results. This suggests a gap between controlled trial settings and real-world practice. Compared with the previous real-world study by Loft *et al*.,[19] variations in national practices may explain the differences in our results. In Denmark, switching to biosimilars was made mandatory, while in the UK, France and Spain, the decision to switch still depends on clinician–patient consultation.[34]

The high discontinuation rates among switchers suggested that switching may negatively affect treatment outcomes. Differences in the pharmaceutical formulations between biosimilars and Humira might influence how patients respond to the switch. In addition, switching could alter the immunogenicity profile, potentially leading to the development of antidrug antibodies. This can decrease the effectiveness or heighten the risk of AEs, leading to more discontinuations.

However, we cannot exclude the possibility that patients' beliefs of being switched to a 'cheaper' product can affect their willingness to continue with biosimilars. Compared with objective measures like PASI, treatment persistence is more influenced by patients' negative perceptions, such as the nocebo effect.[35] A UK survey of patients switching from Humira to biosimilars found that 34% reported poor satisfaction and 47% reported worsened symptoms after switching.[36] Similar trends have also been observed in other conditions, including rheumatoid arthritis and hidradenitis suppurativa.[37–39]

In registries, we found lower PASI scores at the end of treatment in biosimilar users than in Humira users, suggesting that treatment was stopped at lower PASI thresholds for biosimilars. Compared with Humira users, biosimilar users were recruited later, when more biologics were available. As treatment options increased, clinicians could increasingly demand greater drug effectiveness, influencing treatment discontinuation trends.[40]

Although switchers have similar risks of SAEs, they have higher discontinuation rates due to AEs, primarily due to administration site and skin reactions. Differences in ingredients and injection devices between Humira and biosimilars could explain these results. This aligned with the previous survey of UK patients, with 71% of switchers reporting worsened injection pain after switching.[36]

The differences between the main analysis and the fifth sensitivity analysis, which censored patients switching back to Humira, indicated that switching back significantly contributed to the high discontinuation rates among switchers. Data from BADBIR highlighted ineffectiveness and AEs as the primary reasons for switching back. However, the absence of such data in SNDS imposed uncertainty. Thus, future studies are needed to fully understand the trends of switching back to Humira after biosimilar discontinuation.

The strengths of this study include combining pharmacovigilance registries and claims data from three countries, providing a large and diverse sample of patients, thus enhancing the generalizability of our findings. The prevalent new-user design, including all biosimilar users regardless of previous Humira treatment, minimized selection bias typical in traditional cohort designs. Matching for previous adalimumab exposure and propensity scores ensured cohort balance, allowing unbiased comparisons.

This study had limitations. Firstly, most Humira users in registries were enrolled before biosimilars became available, making it impractical to match new users of biosimilars and Humira based on treatment initiation years. Additionally, owing to the limited number of patients in registries, it was not feasible to match switchers with those who continued Humira based on both treatment initiation years and the duration of adalimumab use before cohort entry. As a result, only the SNDS was able to match patients by treatment initiation year. To address the impact of time, we adjusted for the calendar year of cohort entry in our regression models. Secondly, reasons for discontinuation were not available in SNDS. Although there was uncertainty, results from SNDS aligned with that of BADBIR, where discontinuation reasons were well documented. Thirdly, data on disease severity (PASI) at baseline were not available in SNDS and therefore were not adjusted for in the analyses. Fourthly, rare incidences of SAEs led to wide CIs and reduced precision, especially in small cohorts in BIOBADADERM. Lastly, unmeasured factors, including psychological perceptions, regional policies and drug availability, could influence drug survival, making this outcome not fully reflective of treatment effectiveness or safety. Therefore, future studies with specified clinical assessments are needed to confirm the effects of switching to biosimilars.

This study found comparable drug survival and safety between adalimumab biosimilars and Humira in adalimumab-naïve patients, supporting the use of biosimilars as viable alternatives for new patients. However, patients who switched to biosimilars were more likely to discontinue treatment than those who remained on Humira. Changes in treatment response, skin or injection site reactions and nocebo effects may contribute to treatment discontinuation after switching. Thus, patients who switch from Humira to biosimilars may require closer monitoring and support to alleviate these challenges. Further research with detailed clinical assessments is necessary to better understand the effects of switching on treatment outcomes.

Acknowledgements

The authors acknowledge the substantial contribution of the BADBIR team to the administration of the project. BADBIR acknowledges the support of the National Institute for Health

Research (NIHR) through the clinical research networks and its contribution in facilitating recruitment into the registry. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of BADBIR, the NIHR, the National Health Service (NHS) or Department of Health. The authors are grateful to the members of the Data Monitoring Committee [Anja Strangfeld (Chair); Girsh Gupta; Imke Redeker; and Richard Weller] and the BADBIR Steering Committee (in alphabetical order): Alexa Shipman, Anja Strangfeld, Anthony Bewley, Brian Kirby, Catherine Smith, Christopher Griffiths, Elise Kleyn, Jonathan Barker, Kathy McElhone, Nick Reynolds, Olivia Hughes, Oras Alabas, Philip Laws (Chair), Philip Hampton, Richard Warren, Shernaz Walton, Teena Mackenzie, Tess McPherson and Zenas Yiu. Finally, we acknowledge the enthusiastic collaboration of all of the dermatologists, specialist nurses and patients in the UK and Ireland who provided the data. The principal investigators at the participating sites at the time of data cutoff are listed at http://www.badbir.org. We are thankful to the following BIOBADADERM members who participated in recruiting patients and maintaining the registry: Raquel Rivera Diaz, José Luis López Estebaranz, Enrique Herrera-Acosta, Esteban Daudén Tello, Pablo de la Cueva Dobao, Francisco José Gomez Garcia, José Manuel Carrascosa Carrillo, Alicia Quesada, Marta Ferran Farres, Josep Riera, Isabel Belinchón Romero, Ofelia Baniandrés Rodriguez, Lourdes Rodríguez Fernández-Freire, Rafael Botella Estrada, Almudena Mateu Puchades, Ángeles Flórez Menéndez, Vicenç Rocamora Morad, Monica Roncero Riesco, Salvador Arias Santiago, Jose Carlos Ruiz Carrascosa, Mariano Ara Martín, Diana Ruiz Genao, Carmen Garcia Donoso, Elena Garcia Zamora, Jorge Suarez Perez, Mar Llamas Velasco, Kevin Díez Madueño, Elena del Alcázar, Miriam Sidro Sarto, Belén Rodríguez Sánchez, Antonio Sahuquillo, Conrad Pujol Marco, Laura Salgado, Beatriz Gonzalez Sixto, Maria Teresa Abalde Pintos, Aina Vila, Antonio Martínez López, Ricardo Ruiz Villaverde, Victoria Lezcano Biosca and Andrea Montes Torres.

Funding sources

BADBIR is coordinated by the University of Manchester. British Association of Dermatologists Biologic Register Ltd (BADBRL) is a registered company within the British Association of Dermatologists (BAD) and funds the BAD Biologics and Immunomodulators Register (BADBIR) study. BADBRL receives income from AbbVie, Almirall, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen Cilag, LEO Pharma, Novartis, Samsung Bioepsis and UCB for providing pharmacovigilance services. All decisions concerning analysis, interpretation and publication are made independently of any industry contribution. All relevant information regarding serious adverse events mentioned in this publication has been reported to the appropriate company as per the contractual agreements/standard operating procedures. In the UK, the research is funded by the Psoriasis Association PhD studentship and supported by the NIHR Manchester Biomedical Research Centre (NIHR203308). The BIOBADADERM project is supported by the Fundación Piel Sana of the Academia Española de Dermatología y Venereología, which receives financial support from the Spanish Medicines and Health Products Agency (*Agencia Española de Medicamentos y Productos Sanitarios*) and from pharmaceutical companies (Abbott/AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Janssen and UCB). The following companies have also collaborated in the past (LEO Pharma, Novartis Pharma, Lilly, MSD and Pfizer). Collaborating pharmaceutical companies were not involved in any way in the following: the design and execution of the study; the collection, management, analysis and interpretation of data; the preparation, review and approval of the manuscript; or the decision to submit the manuscript for publication. In France, the authors are employees of the French National Health Insurance (CNAM), the French National Agency for Medicines and Health Products Safety (ANSM) and the Assistance Publique-Hôpitaux de Paris (AP-HP) and received no funding for this study. The funding sources did not intervene at any step of the study. The funding sources had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; or decision to submit the manuscript for publication.

Conflicts of interest

R.B.W. reports receiving research grants from AbbVie, Almirall, Amgen, Celgene, Janssen, Lilly, LEO, Novartis, Pfizer and UCB; and consulting fees from AbbVie, Almirall, Amgen, Arena, Astellas, Avillion, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, DiCE, GSK, Janssen, Lilly, LEO, Novartis, Pfizer, Sanofi, Sun Pharma, UCB and UNION.

A.G.-Q. has acted as consultant and/or speaker for and/or participated in clinical trials for AbbVie, Pfizer, Novartis, Sanofi, Boehringer, Bristol Myers Squibb, LEO Pharma and Janssen. R.R.-D. has acted as a consultant and/or speaker for and/or participated in clinical trials as Principal Investigator for AbbVie, Almirall, Celgene, Janssen, LEO Pharma, Lilly, Novartis, MSD and Pfizer-Wyeth. A.S.-T. has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Celgene, Janssen-Cilag, LEO Pharma, Lilly, Novartis and Pfizer. I.G.-D. has received travel grants for congresses from AbbVie, MSD and Pfizer. The other authors declare no conflicts of interest.

Data availability

The data underlying this article cannot be disclosed publicly owing to the data accessibility policy of the database.

Ethics statement

The participating databases received approval from local ethics committees: BADBIR (NHS Research Ethics Committee North West England, reference 07/MRE08/9) and BIOBADADERM (Hospital Universitario 12 de Octubre, reference 216/07). In France, EPI-PHARE has permanent regulatory access to data via ANSM and CNAM, so this work did not require CNIL approval. The study is registered with EPI-PHARE under number T-2023-05-456.[6]

Patient consent

Not applicable.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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