BJD
British Journal of Dermatology

A standardization approach to compare treatment safety and effectiveness outcomes between clinical trials and real-world populations in psoriasis

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Accepted for publication
28 February 2019

Funding sources
Funding sources can be found in the Appendix.

Conflicts of interest
Conflicts of interest statements can be found in the Appendix.

DOI 10.1111/bjd.17849

Summary

Background Patients recruited in randomized controlled trials (RCTs) for biologic therapies in psoriasis are not fully representative of the real-world psoriasis population.

Objectives Firstly, to investigate whether patient characteristics are associated with being included in a psoriasis RCT. Secondly, to estimate the differences in the incidence of severe adverse events (SAEs) and the response rate between RCT and real-world populations of patients on biologic therapies for psoriasis using a standardization method.

Methods Data from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) were appended to individual participant-level data from two RCTs assessing ustekinumab in patients with psoriasis. Baseline variables were assessed for association of being in an RCT using a multivariable logistic regression model. Propensity score weights were derived to reweigh the registry population so that variables had the distribution of the trial population. We measured the C-statistic of the model with trial status as the dependent variable, and the risk differences in the incidence rate of SAEs in the first year and Psoriasis Area and Severity Index (PASI) after 6 months in the BADBIR cohort before and after weighting.

Results In total 6790 registry and 2021 RCT participants were included. The multivariable logistic regression model had a C-statistic of 0.82 [95% confidence interval (CI) 0.81–0.83]. The risk differences for the incidence rate of SAEs and the proportion of patients with PASI < 1.5 were 9.27 (95% CI −3.91–22.5) per 1000 person-years and 0.95 (95% CI −1.98–4.15), respectively.

Conclusions Our results suggest that RCTs of biologic therapies in patients with psoriasis are not fully representative of the real-world population, but this lack of external validity does not account for the efficacy–effectiveness gap.

What's already known about this topic?

- Patients with psoriasis who would not be eligible for randomized controlled trials (RCTs) investigating biologic therapies have a greater risk of serious adverse events and lower treatment effectiveness than patients who would have been eligible.

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What does this study add?

- Baseline patient characteristics were shown to be predictive of whether a patient would have been eligible for enrolment in an RCT for psoriasis biologic therapy.
- We did not find any efficacy–effectiveness gap between the sample representative of the real-world population of patients with psoriasis and the sample representative of the RCT population.
- Factors outside of baseline patient characteristics, such as observer effect and higher adherence in RCTs, may be more influential in any efficacy–effectiveness gap between trial and real-world populations of patients with psoriasis.

Biologic therapies are widely used for the management of patients with moderate-to-severe psoriasis. Randomized controlled trials (RCTs) have shown that biologic therapies for psoriasis have high efficacy and a good safety profile.[1] Although RCTs have high internal validity, they are not powered to investigate rare but potentially serious adverse events (SAEs). In addition, the exclusion criteria of RCTs limit generalizability. Studies across the different specialties of cardiology, mental health, rheumatology and oncology indicate that RCT samples are often highly selected and have a lower risk profile than real-world populations.[2,3] In dermatology, a previous study in a real-world Spanish psoriasis registry[4] found a 2.6-fold increased risk of SAEs for those patients who would have been ineligible for entry into an RCT compared with those who would have been eligible. Our previous work using data from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) from the U.K. and Ireland corroborated these findings.[5] We found a 1.9–2.8-fold increased risk of SAEs in those who would have been ineligible compared with those who would have been eligible for RCTs. In addition, we also found that the ineligible patients also achieved a smaller improvement in Psoriasis Area and Severity Index (PASI), a measure of psoriasis disease severity.

These results suggest that there is a gap in the reported efficacy, which represents the effect of the biologic therapy tested under ideal conditions in an RCT, and the reported effectiveness, which represents the true effect of the drug under general conditions, in real-world populations. This has been termed the 'efficacy–effectiveness gap'. These results also suggest a difference in the safety of biologic therapies when used in RCTs compared with their use in real-world populations. However, the method of comparing the ineligible against the eligible is limited by the restricted availability of the full list of RCT exclusion criteria – a recent research letter found that only a minority of exclusion criteria from the original protocol are listed in publications of phase III trials for biologic therapies in psoriasis.[6] In addition, this method does not provide insight into the differences between the distribution of patient characteristics between RCT and real-world populations within those eligible for the trial. For example, our previous work showed that women are more likely to develop adverse events that lead to discontinuation of biologic therapies,[7] but the proportion of female participants in RCTs in psoriasis is uncharacteristically low for a disease of equal gender ratio.

Model-based standardization methods have increasingly been used to estimate the gap between RCTs and real-world populations.[8,9] In contrast to common methods of standardization, such as age- or sex-standardized rates, model-based standardization allows the standardization of a population to many different covariates.[8] A weighting approach, based on predicting an individual's probability of being a trial participant as a function of his or her baseline characteristics, can achieve this standardization and therefore has the potential to inform this gap. This in turn can allow clinicians more confidence in interpreting trial findings for the patient in the clinic.

The aims of this study were: (i) to investigate whether patient characteristics are associated with being in an RCT for biologic therapies in psoriasis and (ii) to compare the effectiveness and safety results of three biologic therapies used for the treatment of psoriasis (etanercept, adalimumab and ustekinumab) in a real-world population (BADBIR) and the weighted BADBIR patient population standardized vs. a trial population (PHOENIX 1 and 2 – trials of ustekinumab for psoriasis). We also aimed to infer the difference between the two populations after estimation.

Patients and methods

We used BADBIR as a real-world population and the ustekinumab trials PHOENIX 1 and PHOENIX 2 as the representative psoriasis biologic RCTs.

Real-world population

BADBIR is a prospective pharmacovigilance registry of patients with psoriasis that was established in 2007 in the U.K. and Ireland to compare the safety of biologic therapies against nonbiologic systemic therapies. The design of BADBIR[10] and the baseline patient characteristics[11] have been published previously. As the National Institute for Health and Care Excellence (NICE) recommends that all patients with psoriasis on biologic therapies should be registered on BADBIR, it is a

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representative sample of the real-world population of such patients. NICE requires patients with psoriasis to have a PASI ≥ 10 and a Dermatology Life Quality Index (DLQI) > 10 to qualify for treatment with a biologic therapy. We included adult patients (≥ 18 years old) registering to BADBIR on etanercept, adalimumab or ustekinumab who completed at least one follow-up as of 1 December 2016.

In BADBIR, patients are recruited and consented during routine appointments at dermatology centres within 6 months of initiating or switching to a biologic therapy. Data, including drug, clinical, anthropometric and comorbid history, are recorded onto a web-based database by a healthcare professional. Assessment data from patients are collected 6 monthly for the first 3 years, then annually thereafter. Medical records are reviewed for any adverse events since the previous visit, including SAEs, which are untoward medical occurrences that are considered to represent a significant hazard to the patient, namely associated with death, overnight hospitalization, immediately life-threatening, intravenous antimicrobial administration, significant loss of function or disability, congenital malformation or birth defect, or considered to be a medically important event.

Trial population

PHOENIX 1 and PHOENIX 2 were large phase III RCTs investigating the use of ustekinumab for the treatment of psoriasis against placebo.[12,13] PHOENIX 1 was a double-blind, placebo-controlled, multicentre trial performed between December 2005 and September 2007, at 48 sites in the U.S.A., Canada and Belgium.[12] PHOENIX 2 was also a multicentre, double-blind, placebo-controlled trial, performed at 70 sites in Europe and North America (Austria, Canada, France, Germany, Switzerland, U.K. and U.S.A.) between March 2006 and September 2007.[13] Both RCTs evaluated ustekinumab in patients aged ≥ 18 years with a diagnosis of plaque psoriasis for 6 months or longer and a baseline PASI of 12 or higher. Selected exclusion criteria, but not the full list, have been published in the respective trial reports.

For the exemplar trial population we included all participants from PHOENIX 1 and 2 who were randomized. Access to the individual participant-level data was granted through the Yale University Open Data Access Project, an academic group serving as a third party to enable researchers to access clinical trial data through a structured data request and approval process. These trials were chosen to be the representative trial population because (i) the time frame for recruitment was close to that of the start of BADBIR; (ii) ustekinumab is commonly used as a first-line biologic therapy for the treatment of psoriasis in the U.K.;[14] and (iii) this dataset was available for extraction and combination with the data from BADBIR.

Statistical analysis

The baseline covariates that were available in both BADBIR and the trials are listed in Table 1. Due to confidentiality requirements, the age of trial patients was provided to the researchers in 5-year categories, as shown in Table 1. Missing data in both the BADBIR and the trial datasets were accounted

Table 1 The baseline demographics of the trial and registry cohorts

Characteristics	Trial (n = 2021)	Registry (n = 6790)
Age category (years), n (%)		
< 20	16 (0.8)	80 (1.2)
20–24	76 (3.8)	273 (4.0)
25–29	112 (5.5)	448 (6.6)
30–34	147 (7.3)	667 (9.8)
35–39	251 (12.4)	797 (11.7)
40–44	294 (14.5)	1003 (14.8)
45–49	288 (14.3)	1026 (15.1)
50–54	285 (14.1)	874 (12.9)
55–59	234 (11.6)	691 (10.2)
60–64	155 (7.7)	413 (6.1)
65–69	74 (3.7)	297 (4.4)
70–74	23 (1.1)	129 (1.9)
75–79	7 (0.3)	66 (1.0)
80–85	2 (0.1)	21 (0.3)
> 85	1 (0.0)	5 (0.1)
Female, n (%)	630 (31.2)	2771 (40.8)
Body mass index (kg m^{-2}), mean ± SD	31.5 ± 10.4	31.4 ± 10.6
Alcohol (units per week), mean ± SD	3.4 ± 5.8	8.4 ± 14.0
Smoking (cigarettes per day), n (%)		
Nonsmoker	1393 (68.9)	4030 (59.4)
Light (< 10)	192 (9.5)	487 (7.2)
Moderate (10–20)	203 (10.0)	834 (12.3)
Heavy (≥ 20)	233 (11.5)	437 (6.4)
Comorbidities, n (%)		
Asthma	163 (8.1)	724 (10.7)
Hypertension	551 (27.3)	1849 (27.2)
Angina	13 (0.6)	184 (2.7)
Myocardial infarction	35 (1.7)	166 (2.4)
Stroke	11 (0.5)	80 (1.2)
Diabetes mellitus	212 (10.5)	637 (9.3)
Depression	300 (14.8)	1539 (22.7)
Psoriatic arthritis	559 (27.7)	1574 (23.2)
Ethnicity, n (%)		
Asian	73 (3.6)	310 (4.6)
Black	38 (1.9)	44 (0.6)
White	1871 (92.6)	6240 (91.9)
Other	39 (1.9)	187 (2.8)
Previous therapies,[a] mean ± SD		
Systemic therapies	0.9 ± 1.0	1.6 ± 1.0
Biologic therapies	0.6 ± 0.8	0.3 ± 0.6
PASI, mean ± SD	19.7 ± 7.6	15.7 ± 7.8

PASI, Psoriasis Area and Severity Index. [a]Previous systemic therapies include methotrexate, acitretin, ciclosporin or psoralen–ultraviolet A. Previous biologic therapies include adalimumab, alefacept, efalizumab, etanercept or infliximab in the trial arm, and the above with the addition of ustekinumab or secukinumab in the registry arm.

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Table 2 The associations (odds ratios and 95% confidence intervals) of the covariates and trial status from univariable and multivariable logistic regression models

	Univariable (before multiple imputation)	Multivariable (after multiple imputation)
Age (years)		
< 20	0.71 (0.41–1.24)	0.63 (0.34–1.16)
20–24	0.99 (0.75–1.32)	0.83 (0.60–1.14)
25–29	0.89 (0.70–1.14)	0.76 (0.58–1.00)
30–34	0.79 (0.63–0.98)	0.67 (0.52–0.87)
35–39	1.12 (0.93–1.36)	1.04 (0.83–1.30)
40–44	1.04 (0.87–1.26)	0.96 (0.78–1.19)
45–49	Reference	Reference
50–54	1.16 (0.96–1.40)	1.12 (0.90–1.38)
55–59	1.21 (0.99–1.47)	1.29 (1.02–1.62)
60–64	1.34 (1.07–1.68)	1.41 (1.09–1.84)
65–69	0.89 (0.67–1.18)	0.92 (0.66–1.29)
70–74	0.64 (0.40–1.01)	0.58 (0.34–1.00)
75–79	0.38 (0.17–0.83)	0.46 (0.20–1.09)
80–85	0.34 (0.08–1.46)	0.40 (0.09–1.80)
> 85	0.71 (0.08–6.12)	0.78 (0.06–9.85)
Body mass index	1.00 (1.00–1.01)	1.00 (0.99–1.00)
Female sex	0.66 (0.59–0.73)	0.53 (0.47–0.60)
Depression	0.60 (0.52–0.68)	0.59 (0.51–0.69)
Diabetes	1.14 (0.97–1.34)	0.97 (0.79–1.19)
Stroke	0.46 (0.24–0.87)	0.45 (0.22–0.93)
Myocardial infarction	0.71 (0.49–1.02)	0.78 (0.50–1.22)
Angina	0.23 (0.13–0.41)	0.19 (0.10–0.36)
Hypertension	1.01 (0.90–1.13)	0.95 (0.82–1.10)
Asthma	0.74 (0.62–0.88)	0.71 (0.58–0.88)
Number of previous systemics	0.49 (0.46–0.51)	0.42 (0.40–0.45)
Number of previous biologics	1.83 (1.71–1.96)	2.31 (2.13–2.50)
Psoriatic arthritis	1.27 (1.14–1.42)	1.03 (0.90–1.17)
Previous skin cancer	0.79 (0.54–1.16)	0.97 (0.62–1.53)
Ethnicity		
White	Reference	Reference
Black	2.88 (1.86–4.46)	2.11 (1.26–3.54)
Asian	0.79 (0.61–1.02)	0.53 (0.40–0.71)
Other	0.70 (0.49–0.99)	0.54 (0.37–0.79)
Alcohol	0.93 (0.92–0.94)	0.92 (0.91–0.92)
Smoking (cigarettes per day)		
< 10	1.14 (0.95–1.36)	1.41 (1.15–1.73)
10–20	0.70 (0.60–0.83)	0.79 (0.65–0.95)
> 20	1.54 (1.30–1.83)	1.74 (1.42–2.12)

for using multiple imputation with the generation of 20 imputed datasets using a chained equation approach.

After appending the two datasets into one dataset, we investigated the strength of association of each covariate in the determination of whether the individual would be a trial patient using univariable logistic regression models, and also a multivariable logistic regression model after multiple imputation. We calculated propensity scores from the multivariable logistic regression model, estimating the probability of each individual patient being a trial participant based on their baseline background covariates. Standardized mortality ratio weights were used to reweigh the registry population using propensity scores (p) so that all variables had the distribution of the baseline covariates seen in the trial sample (pseudotrial population). The treated patients were given a weight of 1, and the untreated patients a weight of $p/(1-p)$, so that the distribution of the covariates was that of the treated patients.

We then calculated effectiveness and safety outcomes in the BADBIR cohort before and after weighting. The safety outcome was the incidence rate of SAEs in the 12 months studied. The chosen effectiveness outcome was absolute PASI < 1.5 at 6 months, approximately equating to a 90% improvement in PASI (PASI 90). As overlapping concomitant systemic therapies, lack of a washout period of nonbiologic systemic therapy and/or the use of historical PASI are allowed at the onset of biologic treatment in the clinic, the baseline PASI is not reflective of the true baseline clinical severity of the patient. The use of the absolute PASI at 6 months mitigates this difference between the trial and real-world settings. We calculated incidence rate difference, difference in absolute PASI, incidence rate ratio and risk ratio for achieving absolute PASI score < 1.5 at 6 months. Next, 95% confidence intervals (CIs) for these outcomes were estimated using bootstrap resampling of 1000 replications. Bootstrapping is a statistical method that mimics the process of sampling from the underlying population by resampling from the original data sample with random replacement.

Sensitivity analyses

We planned several sensitivity analyses to investigate how restricting the BADBIR population to the inclusion or exclusion criteria of the trials impacts on the results. Due to the differences in baseline PASI between the two populations listed above, PASI was not included as a covariate in the main model, but in model 2 a sensitivity analysis was performed using only patients with PASI ≥ 12, an inclusion criteria in the RCTs, and including baseline PASI in the multivariable logistic regression model. Model 3 restricts the registry population to those with no concomitant therapy in the first year.

All analyses were performed with Stata 14.2 (StataCorp, College Station, TX, U.S.A.).

BADBIR was approved in March 2007 by NHS Research Ethics Committee North West England, reference 07/MRE08/9. All patients gave written consent for their participation in the registry. The protocol for this study was also reviewed and approved by the BADBIR steering committee and the Yale University Open Data Access Project (project #2017-1706).

Results

We included 6790 participants from BADBIR and 2021 participants from the trials. The baseline covariates common to both data sources are listed in Table 1. In the BADBIR cohort, 1417 (20.9%) were on etanercept, 3824 (56.3%) were on adalimumab and 1549 (22.8%) were on ustekinumab. Age was available in the trial data in 5-year categories. Eligible previous systemic nonbiologic therapies were methotrexate, acitretin,

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Table 3 Effectiveness and safety outcomes before (registry sample) and after propensity score-based standardized mortality ratio weighting (pseudotrial sample)

	Absolute PASI < 1.5 (~PASI 90) at 6 months	Incidence rate of SAEs per 1000 person-years at 1 year
Model 1 – Full registry cohort		
Before weighting	38.0 (36.6–39.5)	75.0 (68.1–82.7)
After weighting	37.1 (33.6–40.6)	65.8 (51.6–83.7)
Absolute risk difference	1.0 (−2.0–4.2)	9.3 (−3.9–22.5)
Relative risk difference	1.03 (0.94–1.11)	1.14 (0.91–1.37)
Model 2 – Population with starting PASI ≥ 12		
Before weighting	37.3 (35.4–39.3)	79.8 (70.6–90.1)
After weighting	38.6 (33.1–44.2)	54.3 (42.8–69.0)
Absolute risk difference	−1.3 (−6.4–3.8)	25.4 (14.0–37.0)[a]
Relative risk difference	0.97 (0.84–1.09)	1.47 (1.16–1.78)[a]
Model 3 – Population without any concomitant therapy during first year of therapy		
Before weighting	39.9 (38.2–41.6)	73.5 (66.0–81.9)
After weighting	38.5 (33.8–43.2)	62.2 (48.3–79.9)
Absolute risk difference	1.3 (−3.2–5.7)	11.6 (−1.4–24.6)
Relative risk difference	1.03 (0.91–1.15)	1.18 (0.93–1.44)

Data are the percentage proportion (95% confidence interval). PASI, Psoriasis Area and Severity Index; PASI 90, 90% improvement in PASI; SAE, serious adverse event. [a]Statistically significant result.

ciclosporin or psoralen–ultraviolet A, as fumaric acid esters were not consistently entered as past therapy in the trial population. Eligible previous biologic therapies were adalimumab, alefacept, efalizumab, etanercept or infliximab in both datasets, with the addition of ustekinumab and secukinumab in the registry data. High proportions of missing data for DLQI in the registry cohort (54.9%) and disease duration in the trial cohort (87.3%) led to the exclusion of these two covariates. The amount of missing data for all baseline covariates is presented in Table S1 (see Supporting Information).

The multivariable logistic regression model had a C-statistic of 0.82 (95% CI 0.81–0.83), indicating that there was a difference between the two cohorts, and that the model was able to separate these two cohorts by the inclusion of these covariates. Patients were significantly more likely to be in the trial cohort if they were in the age bands of 55–59 or 60–64 years, had been exposed to a higher number of previous biologics, were of black ethnicity, or were in the smoking categories of < 10 cigarettes per day or > 20 cigarettes per day (Table 2). Patients were significantly less likely to be in the trial cohort if they were in the age band of 30–34 years, were female, had been exposed to a higher number of previous systemic nonbiologics, were of Asian or other ethnic descent (i.e. not of black or white descent), had higher alcohol intake, or had the comorbidities of depression, angina or asthma (Table 2).

After propensity score standardized mortality ratio weighting, the standardized differences for all covariates were within a magnitude of 0.05, apart from psoriatic arthritis (27.7% in the trial sample and 31.1% in the pseudotrial sample, standardized difference −0.08) and the number of previous biologics (mean 0.57 in the trial sample and 0.62 in the pseudotrial sample, standardized difference −0.07). Both covariates also had the highest standardized differences among the covariates for models 2 and 3 in the sensitivity analyses, but the magnitude of difference was greater.

The standardized mortality ratios for the registry sample and the pseudotrial sample are presented in Table 3, and the numbers of patients included in the sensitivity analyses in Table S2 (see Supporting Information). Weighting had little effect on the proportion of participants achieving an absolute PASI < 1.5 at 6 months across all three models. However, the incidence rates of SAEs were higher in the registry sample than in the pseudotrial samples across all three models (Table 3). In the main model, the incidence rate difference was 9.27 (95% CI −3.91–22.5) per 1000 person-years, translating to an incidence rate ratio of 1.14 (95% CI 0.91–1.37). The incidence rate differences and incidence rate ratios for the sensitivity analyses are also presented in Table 3. These all suggest a higher incidence rate of SAEs but little difference in absolute PASI in the registry sample compared with the pseudotrial sample.

Discussion

We show that the distribution of baseline covariates was systematically different between a real-world and a trial population. However, using a novel reweighting and standardization method, we did not find any efficacy–effectiveness gap between the sample representative of the RCT population of patients with psoriasis and the sample representative of the real-world population. There is a suggestion that the real-

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world population had a higher incidence rate of SAEs than the trial sample, but this was not statistically significant.

However, our results from the sensitivity analyses all suggest a higher point estimate for SAEs with the real-world sample of patients with psoriasis than in the trial sample. This is congruent with published literature, which largely compared those who would not have been eligible for trials against those who would have been eligible in the real-world population.[4,5] The magnitude of difference was lower and the difference was not statistically significant in all but one of the sensitivity analyses.

The lack of efficacy–effectiveness gap was unexpected. As we investigated only effectiveness outcomes (and not efficacy), we could not adjust for any differences in adherence and observer effects that may be present between trial and real-world populations. In addition, it is unlikely that most of the covariates we were able to reweigh for that were significantly different between the 'trial' and 'real-world' samples in Table 2 had any significant impact on the short-term effectiveness of the biologic therapies. Significant covariates listed in Table 2 include comorbidities such as depression, stroke, angina and asthma; alcohol intake; number of previous systemic therapies; ethnicity and female sex. By contrast, these covariates were more likely to have a significant impact on the probability of a participant experiencing an SAE. It is also possible that the missing PASI outcome at 6 months introduced a systematic bias. This may happen if there was a reason for PASI being missing at 6 months that is associated with treatment effectiveness, for example patients who were not responding did not have their PASI measured in clinic because they were admitted for inpatient treatment.

The major strength of this study is the inclusion and the combination of the individual participant-level data of two important data sources for the first time – BADBIR, which is a large generalizable sample of patients with moderate-to-severe psoriasis from 153 dermatology centres in the U.K. and Republic of Ireland, and PHOENIX 1 and 2, two large multinational phase III RCTs in patients with psoriasis. Detailed data capture in BADBIR allowed inclusion of numerous covariates that were present in both datasets. We showed that some of these background participant characteristics were significantly different between a trial and a real-world psoriasis population, confirming that RCT inclusion and exclusion criteria and the recruitment process resulted in a reduction in external validity.

Although we were able to include many baseline covariates, there may be other covariates important for selection into a trial, and treatment effect or safety heterogeneity, that could not be included in the analysis. For instance, the amount of missing data was too high for DLQI to be included in the propensity score (Table S1; see Supporting Information). There may also be uncaptured inherent lifestyle and genetic participant differences between the U.K. and Ireland-based BADBIR and the predominantly North American-based PHOENIX 1 and 2 that could partially influence our results. Some important treatment history covariates, for example whether the previous biologic therapy had failed due to ineffectiveness or adverse events, were not available, and this may result in a decrease in the representativeness of the pseudotrial population. The results had large CIs, reflective of the uncertainty in our estimates given our sample size and our proportion of missing data.

Our results show that populations of patients with psoriasis in RCTs are very different from real-world populations. This reinforces the notion that RCTs have a lower external validity than real-world studies, and our results may help clinicians interpret and explain the differences in safety outcomes between trial results and real-world clinics.

In conclusion, RCTs of biologic therapies in patients with psoriasis are not representative of the real-world population. Our results suggest that the lack of external validity in RCTs for biologic therapies used in patients with psoriasis does not account for the efficacy–effectiveness gap. It is possible that other factors such as observer effect and higher adherence in RCTs may be more influential. Clinicians should utilize data from observational studies to present a holistic and accurate view of the true benefits and risks of biologic therapies for psoriasis when counselling patients prior to the initiation of treatment.

Acknowledgments

We thank all of the patient participants in BADBIR. The substantial contribution of the BADBIR team to the administration of the project has been vital. We also thank Ian Evans, Hassan Ali and Kayleigh Mason from the BADBIR team for their advice and support, and Sagair Hussain for his support as the clinical project manager of BADBIR. We are grateful to the members of the Data Monitoring Committee – Robert Chalmers, Carsten Flohr (Chair), Richard Weller and David Prieto-Merino – and the BADBIR Steering Committee (in alphabetical order) – Jonathan Barker, Marilyn Benham (CEO of BAD), David Burden (Chair), Christopher Griffiths (Chief Investigator), Sagair Hussain, Brian Kirby, Linda Lawson, Kathleen McElhone, Ruth Murphy, Anthony Ormerod, Caroline Owen, Nick Reynolds (Chair, Research Committee), Catherine Smith and Richard Warren. Finally, we acknowledge the enthusiastic collaboration of all of the dermatologists and specialist nurses in the U.K. and the Republic of Ireland who provided the data. The principal investigators at the participating sites at the time of data cut-off are listed at the following website: http://www.badbir.org. This study, carried out under Yale University Open Data Access project #2017-1706, used data obtained from the Yale University Open Data Access Project, which has an agreement with Janssen Research & Development, LLC. The interpretation and reporting of research using this data are solely the responsibility of the authors and do not necessarily represent the official views of the Yale University Open Data Access Project or Janssen Research & Development, LLC.

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Appendix

Funding sources

The British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) is coordinated by the University of Manchester, and funded by the British Association of Dermatologists (BAD). The BAD currently receives income from Janssen-Cilag, AbbVie, Novartis, Samsung Bioepis, Celgene, Almirall, Hexal AG and Eli Lilly for providing pharmacovigilance services. This income finances a separate contract between the BAD and the University of Manchester, who coordinate BADBIR. 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 and standard operating procedures. Z.Z.N.Y. is funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship (no. DRF-2015-08-089). BADBIR acknowledges the support of the NIHR through the clinical research networks. The research was supported by the NIHR Manchester and the Guy's and St Thomas' Biomedical Research Centres. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health. C.E.M.G. is an NIHR senior investigator. C.E.M.G., C.H.S. and R.B.W. are funded in part by the Medical Research Council (MR/L011808/1).

Conflicts of interest

M.L., K.M. and Z.Z.N.Y. declare no conflicts of interest. K.J.M. has received honoraria from Janssen-Cilag and Eli Lilly. J.N.W.N.B. has received honoraria for advisory boards and lectures at sponsored symposia together with grants for research in the past 5 years from AbbVie, Amgen, Celgene, Janssen, Lilly, Novartis and Pfizer. The department of C.H.S. has received funding for research support from AbbVie, Janssen-Cilag, Novartis, Wyeth and Pfizer. P.J.H. has received honoraria from AbbVie, LEO Pharma and Novartis. R.B.W. has acted as a consultant and/or speaker for and/or received research grants from AbbVie, Amgen, Almirall, Celgene, Eli Lilly, Pfizer, LEO Pharma, Novartis, Janssen-Cilag, Medac and Xenoport. C.E.M.G. has received honoraria and/or research grants from AbbVie, Actelion, Amgen, Celgene, LEO Pharma, Eli Lilly, GSK-Stiefel, Janssen-Cilag, MSD, Novartis, Pfizer, Sandoz and UCB Pharma. A.D.B. consults and lectures for AbbVie, Amgen, Eli Lilly, Novartis, Pfizer, Celgene, Janssen and Boehringer Ingelheim.

The BADBIR Study Group includes Anthony D. Ormerod, Ian Evans, Nick J. Reynolds, Ruth Murphy, Marilyn Benham, Sagair Hussain, Brian Kirby, Linda Lawson and Caroline M. Owen

Supporting Information

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

Table S1. Missing data.

Table S2. Number of patients included in each sensitivity analysis.

Video S1 Author video.

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