ORIGINAL ARTICLE

A multinational, prospective, observational study to estimate complete skin clearance in patients with moderate-to-severe plaque PSOriasis treated with BIOlogics in a REAL world setting (PSO-BIO-REAL)

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Abstract

Background Anti-tumour necrosis factor (TNF) and anti-interleukin (IL)-12/23 biologics revolutionized plaque psoriasis treatment by enabling ≥75% improvement in the Psoriasis Area and Severity Index (PASI 75) in clinical trials. Modern biologics are now reported to achieve PASI 100 (complete skin clearance) in clinical trials. However, real-world evidence of skin clearance rates with biologics is limited. PSO-BIO-REAL was conducted to understand the real-world burden of plaque psoriasis.

Objective The primary objective of this observational study was to estimate the proportion of patients who achieved complete skin clearance at 6 months. Secondary objectives included maintenance of response and evaluation of complete skin clearance at 12 months.

Methods PSO-BIO-REAL was a multinational, prospective, real-world, non-interventional study of skin clearance and patient-reported outcomes (PROs) with biologics. A total of 846 patients from the United States (32%), France (28%), Italy (22%), the United Kingdom (11%) and Germany (8%) were enrolled and followed for one year. Eligible patients were aged ≥18 years with moderate-to-severe plaque psoriasis who had initiated a biologic for plaque psoriasis. Patients could be biologic-naïve or switching biologics (biologic-experienced). Assessments were made at baseline and at months 6 and 12.

Results At 6 and 12 months, 23% and 26% of patients achieved complete skin clearance, respectively. Prior to study entry, 60% were biologic-naïve. The proportion of patients achieving complete skin clearance was lower among biologic-experienced patients (20% at both months 6 and 12) compared with biologic-naïve patients (25% at month 6, 30% at month 12). The rate of complete skin clearance decreased as the number of prior biologics and baseline comorbidities increased.

Conclusion Only one in four patients achieved complete skin clearance after 6 months of treatment with biologics. The study indicates there still is an unmet need for more efficacious biologics for patients with psoriasis.

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Conflicts of interest

J. Seneschal has been a consultant for AbbVie, Eli Lilly, Janssen, Novartis and Pfizer; J-P. Lacour has been a consultant for, has received grants from and/or has served as a speaker for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis and Pfizer; A. Bewley has been a consultant for and/or has received honoraria and/or investigator fees from AbbVie, Almirall, Bristol-Myers-Squib, Celgene, Eli Lilly, Fresenius Medical Care, Galderma, Janssen, LEO Pharma, Novartis, Sanofi and UCB Pharma; C. Paul has been a consultant for and has received grants from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Sandoz and UCB Pharma; C. De Simone has been a consultant, speaker and/or advisory board member for AbbVie, Almirall, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Pfizer, Sanofi and UCD Pharma; K. Reich has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor, Covagen, Dermira, Forward Pharma, Fresenius Medical Care, Galapagos, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Merck Sharp & Dohme, Novartis, Miltenyi Biotec, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant and Xenoport; G Pellacani has been a consultant for LEO Pharma; A. Sohrt and M. Faurby are employees of LEO Pharma; E. Hammond is an employee of AstraZeneca; L. Horne was a paid consultant to AstraZeneca at the time the work was conducted; M Augustin reports no conflicts of interest.

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Introduction

The aspirational treatment goal for all diseases is cure. The technical treatment goal is based on what drugs can realistically achieve in the majority of patients, as well as patient wants and needs. In plaque psoriasis, The Psoriasis Area and Severity Index (PASI) 75 was implemented as a technical treatment goal some years ago, because it was achievable with adalimumab, infliximab and ustekinumab in the majority of patients.[1–4] Today, PASI 90 is being discussed as a new technical treatment goal, because it is now more readily achievable[5] and because registry data indicate that significantly more patients who achieve PASI 90 are no longer bothered by their psoriasis symptoms, defined as a Dermatology Life Quality Index (DLQI) of 0/1, compared with patients who achieved PASI 75.[6]

Recently, it has been shown that high rates of efficacy – including PASI 100 – can be achieved with modern biologics, including anti-interleukin (IL)-17A (secukinumab and ixekizumab), anti-IL-17A receptor (anti-IL-17RA; brodalumab)[7–10] and anti-IL-23 (guselkumab and risankizumab) therapies.[11–13] Randomized controlled clinical trials have shown that achieving PASI 100, compared with having residual disease (e.g. PASI 75), is clinically meaningful and substantially reduces the physical burden of psoriasis, improves treatment satisfaction and reduces the impact on health-related quality of life (HRQoL).[14–16]

Clinical data on complete skin clearance of psoriasis among real-world cohorts of patients treated with biologics are limited. We identified only five multicentre observational studies with >100 patients from a literature search performed as background for this study, and reported clearance rates were highly variable, ranging from 3% to 79%.[17–21]

We therefore conducted the plaque PSOriasis treated with BIOlogics in a REAL world setting (PSO-BIO-REAL) study – a multinational, prospective, observational cohort, real-world study designed to describe the usual care of patients with plaque psoriasis over a 12-month period following initiation of a biologic treatment in both biologic-naïve and biologic-experienced patients.

Materials and methods

PSO-BIO-REAL was a multinational, prospective, observational study involving a cohort of patients with moderate-to-severe plaque psoriasis from the United States, France, Italy, Germany and the United Kingdom. The study design is illustrated in Fig. 1. Patients were eligible to participate if they were ≥18 years, had been diagnosed with moderate-to-severe plaque psoriasis, were either initiating a biologic for the first time (biologic-naïve) or in the process of switching to another biologic (biologic-experienced). Patients were excluded if they had participated in an investigational clinical trial ≤3 months prior to the start of treatment. The first patient was enrolled 05 March 2014 and the last was enrolled 26 November 2015, with the final 12-month follow-up completed 05 January 2017. The duration of patient enrolment varied by country. Written informed consent was obtained from each patient.

Baseline observations (patient demographics, disease characteristics, comorbidities and prior treatment history) were recorded at the baseline visit, which either coincided with or occurred after the enrolment visit. The index date was defined as the date the first dose of a new biologic was given and either coincided with or occurred after the baseline visit. Study

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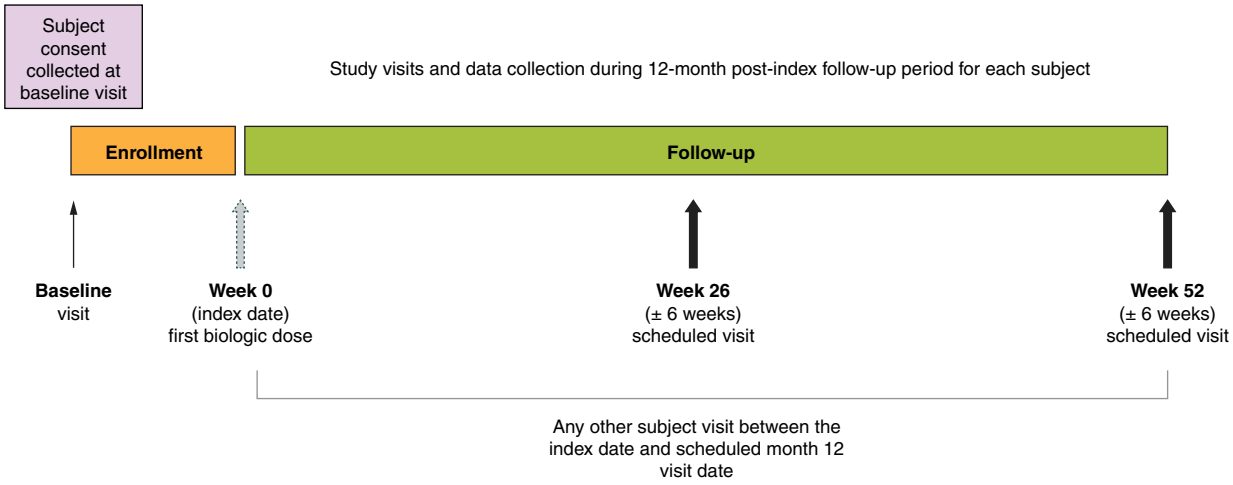

Figure 1 PSO-BIO-REAL study design.

assessments (PASI, static Physician's Global Assessment, static Patient's Global Assessment, Psoriasis Severity Index, DLQI, treatment satisfaction and global health status) were collected at baseline visit and at study visits scheduled 6 and 12 months after initiation of the index biologic. Data on comorbidities were recorded on the study case report form over the 6 months prior to study entry. Any new comorbidities of interest were reported (yes/no) by physicians at any patient visit during the study.

The primary objective was to estimate, in patients who were biologic-naïve or biologic-experienced, the effectiveness of biologics in moderate-to-severe plaque psoriasis, measured by the proportion of patients with complete skin clearance [PASI 100 or static PASI (sPASI) = 0] 6 months after initiation of a biologic. Secondary objectives were to determine the achievement of PASI 100 at 12 months and maintenance of PASI 100 from 6 to 12 months. An exploratory objective was to characterize the PASI response according to the number of baseline comorbidities. An additional objective, defined post hoc, was to describe complete clearance rates according to the index biologic treatment. In this analysis, the effectiveness in treatment groups with 30 or more patients was reported at baseline and assessed until end of the study or biologic treatment switch.

Data were analysed descriptively as observed. A sensitivity analysis on PASI 75, 90 and 100 rates using the non-responder imputation (NRI) method was performed. For continuous measures, mean, SD, minimum, median and maximum were used, and for ordinally data number and proportion were tabulated. In analyses by index biologics data, we report number and proportion switched at month 6 and 12, and have disregarded data after the switch to new treatment. All quantitative analyses were conducted using SAS Version 9.4.

Results

Patient disposition is summarized in Fig. 2. A total of 846 patients with moderate-to-severe plaque psoriasis were enrolled in the study, of which 60% were biologic-naïve and 40% were biologic-experienced and in the process of switching to a different biologic agent prior to study entry. A total of 197 patients discontinued the study, the majority (n = 136) of whom were lost to follow-up. A total of 108 patients switched from their index treatment during the study, of which 51% switched due to primary failure and 15% switched due to secondary failure. Patients were recruited from the United States (32%), France (28%), Italy (22%), the United Kingdom (11%) and Germany (8%). Baseline characteristics are summarized in Table 1. The descriptive observations indicated that biologic-experienced patients tended to be slightly older than biologic-naïve patients (50 vs. 46 years), with a longer disease duration (20 vs. 17 years) and more comorbidities (26% vs. 18% had ≥3 comorbidities), including psoriatic arthritis (35% vs. 23%) (Tables 1 and 2). The initial biologic treatment (index biologic) was an anti-tumour necrosis factor agent (anti-TNF: etanercept, infliximab, adalimumab and certolizumab pegol) in 61%, an anti-IL-12/-23 agent (ustekinumab) in 30% and an anti-IL-17 agent (secukinumab) in 9% of patients. Baseline characteristics were generally similar among all treatment groups (Table 2). During the study, 23% of the patients were treated with concomitant psoriasis medication.

A total of 603 patients completed a 6-month PASI assessment; of these, 22.7% achieved complete skin clearance (24.9% of biologic-naïve patients and 19.6% of biologic-experienced patients) (Fig. 3). At month 12, 522 patients completed a PASI assessment, in whom complete skin clearance reported for 26.1%

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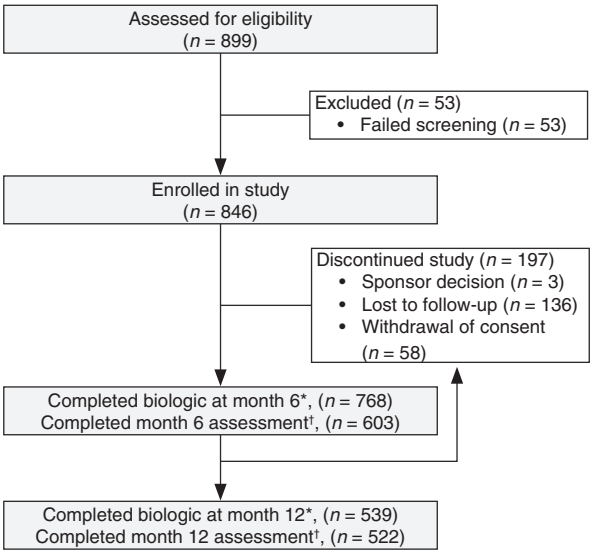

Figure 2 Patient disposition. *Completed biologic at month 6 is defined as subjects from the full analysis set who received a biologic for approximately 6 months or 183 days (up until their completed month 6 visit). Completed biologic at month 12 is defined as subjects from the full analysis set who received a biologic for approximately 1 year or 365 days (up until their completed month 12 visit). †Completed month 6/12 assessment is defined as subjects who underwent a PASI assessment within the month 6/12 visit window.

(30.4% of biologic-naïve patients and 19.5% of biologic-experienced patients). Achievement of PASI 75 and PASI 90 was reported for more biologic-naïve patients than for biologic-experienced patients. Among patients who achieved complete skin clearance at month 6, 72.4% maintained their responses through month 12; 13.4% of the patients who had not achieved complete skin clearance by month 6 achieved it at month 12.

An NRI method was applied to the efficacy analysis which showed that 16% of the patients achieved complete skin clearance at both month 6 and 12. PASI 75 and PASI 90 were achieved by 25% and 38% of the patients at month 6, respectively (Fig. S1).

The complete skin clearance rate for patients who continued their index biologic treatment throughout the course of the study ranged from 9.6% to 25.9% at 6 months and from 19.2% to 33.3% at 12 months, depending on the index biologic (Fig. 4a). Data for patients who switched to another biologic were excluded from this analysis after the switch. The proportion of patients who switched to another treatment during the study was 18.9% for etanercept, 15.2% for adalimumab and 6.6% for ustekinumab and secukinumab, respectively. Two biologics were not illustrated in Fig. 4a because of low patient numbers in both groups: infliximab (n = 12), for which the rate of complete skin clearance was 16.7% and 8.3% at 6 and 12 months, respectively, and certolizumab pegol (n = 1), for which the rate was 0% at both 6 and 12 months.

The rate of complete skin clearance decreased as the number of prior biologics received increased, from 30.4% with no prior biologics to 10.0% at month 12 with ≥3 prior biologics (Fig. 4b). Generally, rate of complete skin clearance at month 6 decreased as the number of comorbidities at baseline increased: 31.7% of patients with no comorbidities at baseline achieved PASI 100 compared with 16.4% of patients who had ≥3 comorbidities at baseline (Fig. 5).

A total of 28% of the patients had concomitant psoriatic arthritis and the level of complete skin clearance for these patients was 15.6% at month 6 and 25.2% at month 12,

Table 1 Baseline characteristics of patients enrolled in PSO-BIO-REAL

Characteristic	Biologic-naïve† (n = 509)	Biologic-experienced‡ (n = 337)	Index biologic§				Overall (N = 846)
			Adalimumab (n = 343)	Etanercept (n = 143)	Ustekinumab (n = 256)	Secukinumab (n = 76)	
Male, n (%)	321 (63.1)	214 (63.5)	207 (60.3)	98 (68.5)	158 (61.7)	52 (68.4)	535 (63.2)
Age, years, mean (SD)	45.7 (14.0)	50.0 (12.9)	46.4 (14.0)	49.4 (14.6)	46.0 (13.3)	50.8 (11.5)	59.5 (10.6)
BMI, kg/m^2, mean (SD)	28.8 (6.8)	30.3 (6.7)	29.0 (6.7)	29.0 (6.7)	29.2 (6.8)	31.0 (5.7)	29.4 (6.8)
White, n (%)	473 (92.9)	308 (91.4)	312 (91.0)	139 (97.2)	232 (90.6)	70 (92.1)	781 (92.3)
PASI at baseline, mean (SD)	14.38 (8.5)	14.18 (10.5)	13.9 (8.5)	14.0 (8.4)	13.8 (9.4)	16.6 (12.1)	14.30 (9.3)
PASI at baseline, median	13.20	11.30	16.6	12.0	11.4	14.7	12.3
DLQI at baseline, mean (SD)	12.9 (7.6)	11.6 (7.7)	12.1 (7.3)	11.9 (7.4)	12.6 (7.8)	13.8 (8.4)	12.4 (7.6)
Duration of psoriasis, years, mean (SD)	17.1 (13.3)	20.4 (12.8)	17.8 (12.9)	19.7 (14.7)	18.2 (13.1)	20.3 (12.7)	18.4 (13.2)
Psoriatic arthritis, yes, n (%)	119 (23)	119 (35)	96 (28.0)	46 (32.2)	67 (26.2)	22 (28.9)	238 (28)
Biologic-experienced, n (%)	0 (0.0)	337 (100.0)	88 (25.7)	32 (22.4)	154 (60.2)	49 (64.5)	337 (39.8)

BMI, body mass index; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; SD, standard deviation.
†Subjects who were not exposed to biologic treatment prior to study enrolment.
‡Subjects who received biologic treatment prior to study enrolment but switched to a different biologic at study entry.
§Two patients received certolizumab pegol, and 26 patients received infliximab. Aggregated baseline characteristics for these patients have not been reported separately by index biologic because of low numbers.

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Table 2 Comorbidities at baseline

Comorbidity, *n*, (%)	Biologic-naïve (*n* = 509)	Biologic-experienced (*n* = 337)	Overall (*N* = 846)
Subjects with at least one comorbidity	310 (60.9)	231 (68.5)	541 (63.9)
Number of comorbidities at baseline			
0	199 (39.3)	106 (31.7)	305 (36.3)
1	151 (29.8)	72 (21.6)	223 (26.5)
2	68 (13.4)	68 (20.4)	136 (16.2)
≥3	89 (17.6)	88 (26.3)	177 (21.0)
Comorbidities			
Hypertension	143 (28.1)	140 (41.5)	283 (33.5)
Psoriatic arthritis	119 (23.4)	119 (35.3)	238 (28.1)
Hyperlipidaemia	98 (19.3)	79 (23.4)	177 (20.9)
Diabetes mellitus	55 (10.8)	63 (18.7)	118 (13.9)
Depression	67 (13.2)	49 (14.5)	116 (13.7)
Anxiety	53 (10.4)	38 (11.3)	91 (10.8)
Liver disease	22 (4.3)	26 (7.7)	48 (5.7)
Sleep disorders	20 (3.9)	27 (8.0)	47 (5.6)
Asthma	31 (6.1)	12 (3.6)	43 (5.1)
Other rheumatological disease	19 (3.7)	12 (3.6)	31 (3.7)
Coronary artery disease	16 (3.1)	13 (3.9)	29 (3.4)
Myocardial infarction	15 (2.9)	12 (3.6)	27 (3.2)
Metabolic syndrome	13 (2.6)	13 (3.9)	26 (3.1)
COPD	16 (3.1)	3 (0.9)	19 (2.2)
Kidney disease	9 (1.8)	9 (2.7)	18 (2.1)
Cerebrovascular disease	13 (2.6)	4 (1.2)	17 (2.0)
Other cancer	12 (2.4)	4 (1.2)	16 (1.9)
Peripheral vascular disease	9 (1.8)	6 (1.8)	15 (1.8)
Congestive heart failure	8 (1.6)	4 (1.2)	12 (1.4)
Atopic dermatitis	11 (2.2)	0 (0.0)	11 (1.3)
Lymphoma	2 (0.4)	4 (1.2)	6 (0.7)
Breast cancer	4 (0.8)	1 (0.3)	5 (0.6)
Colorectal cancer	4 (0.8)	1 (0.3)	5 (0.6)
AIDS	4 (0.8)	0 (0.0)	4 (0.5)
Lung cancer	4 (0.8)	0 (0.0)	4 (0.5)
Prostate cancer	3 (0.6)	1 (0.3)	4 (0.5)
Melanoma	1 (0.2)	2 (0.6)	3 (0.4)

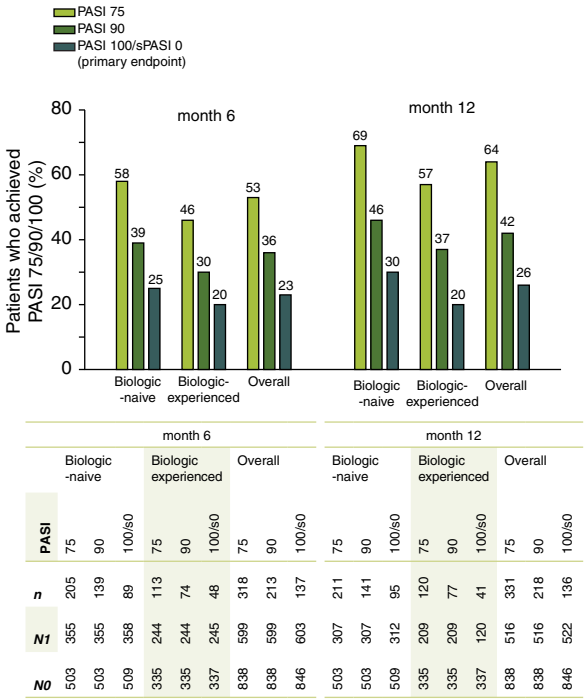

Figure 3 Patients achieving PASI 75, PASI 90 and PASI 100 or sPASI 0 at months 6 and 12 by prior biologic use: full analysis set. *n*, number of subjects achieving specified PASI; N_1, observed subjects; N_0, subjects at baseline. Percentages are based on N_1 and not the full analysis set. PASI, Psoriasis Area and Severity Index; PASI X, X% improvement from baseline in PASI score; sPASI, static PASI.

compared to 25.2% at month 6 and 26.4% at month 12 for the patients without psoriatic arthritis.

Discussion

To our knowledge, PSO-BIO-REAL is the largest multinational, observational, real-world study to date assessing the level of complete skin clearance in adult patients with moderate-to-severe plaque psoriasis undergoing biologic treatment, with 846 patients treated with any of six different biologics enrolled in multiple centres across five countries. Compared with previously published observational studies of fewer patients treated with fewer types of biologics and reporting from only one country, this study adds important evidence to the limited real-world evidence available.

In this study, approximately one in four patients with psoriasis achieved complete skin clearance after 6 months of real-world treatment with biologics. These results suggest that there remains a need for efficacious therapeutics for psoriasis. The first patient to be included in the study was enrolled in 2014 and the last in 2015; therefore, newer biologics – such as brodalumab, guselkumab, ixekizumab and tildrakizumab – were not included. Some of these newer therapies have shown greater efficacy than drugs such as ustekinumab and etanercept in clinical trials, and patients are more likely to achieve complete skin clearance.[7,8,10,13,22–25] Therefore, real-world rates of complete clearance may have improved since this study concluded.

While PASI at baseline was similar for biologic-naïve and biologic-experienced patients, rates of complete skin clearance in this study were lower in patients who had previously been exposed to biologics compared with those who were biologic-naïve, and the rate of complete skin clearance decreased with increasing numbers of prior biologics. These observations are consistent with those seen in other real-world studies.[17,19,20] A

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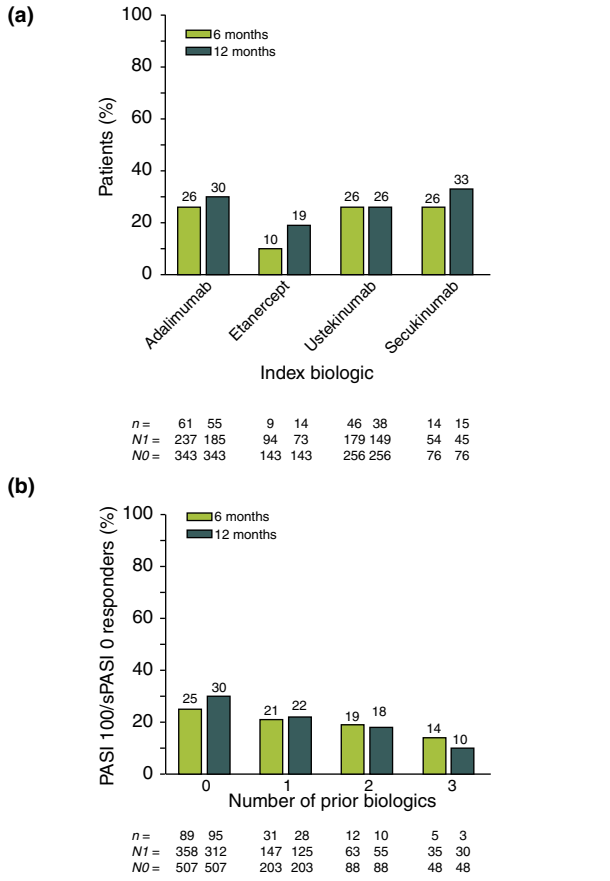

Figure 4 Summary of patients with complete skin clearance (PASI 100/sPASI 0 responders) by visit and (a) type of index biologic and (b) number of prior biologics. *n*, number of subjects achieving specified PASI; N_1, observed subjects; N_0, subjects at baseline. Percentages are based on N_1 and not the full analysis set. PASI, Psoriasis Area and Severity Index; PASI X, X% improvement from baseline in PASI score; sPASI, static PASI.

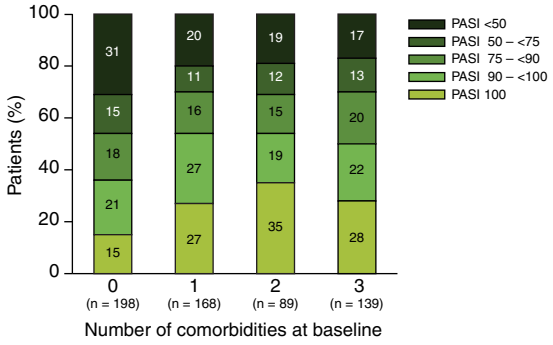

Figure 5 PASI responses at 6 months according to number of comorbidities at baseline. Columns may not add up to 100% due to rounding. PASI, Psoriasis Area and Severity Index; PASI X, X% improvement from baseline in PASI score.

similar observation was made as the number of comorbidities at baseline increased. Although clearance rates are lower in these more complex patients, some patients still experience a clinical response to treatment with more biologics. Real-world studies such as this may be valuable in providing physicians with data that can guide them to further therapeutic options for these difficult-to-treat patients. Complete skin clearance rates were generally observed to be similar at months 6 and 12 for adalimumab, ustekinumab and secukinumab. In clinical trials, however, complete clearance rates for secukinumab were observed to be higher than for adalimumab, etanercept and ustekinumab.[22] The PASI at baseline were similar across treatments; however, a little higher for secukinumab compared to the other treatments though this difference was not tested statistically (Table 1). The relatively low rate of complete skin clearance for secukinumab in this study might also be due to a high proportion of biologic-experienced patients treated with secukinumab (64.5%) compared to the patients treated with adalimumab (25.7%) and etanercept (22.4%). The proportion of biologic-experienced patients treated with ustekinumab was also higher (60.2%) compared to adalimumab and etanercept. Moreover, real-world data differ from RCTs in that it is not equally controlled and there may be underlying factors explaining the low rates of efficacy, not taken into account in this study.

This study may be subject to limitations that are common to observational studies, such as selection bias and potential confounders.[26] Specifically for this study, site selection was designed to provide geographical distribution in each country but might have tended to be located in metropolitan areas and carried out in more research-oriented or academic institutions than in a typical dermatology practice, and participating physicians might have been more likely to prescribe biologics.

In the main analysis, the rates of complete skin clearance were reported as observed. Accordingly, the effectiveness of biologics may be overestimated as patients that are lost to follow-up are not included. The rates of complete skin clearance were observed to be higher at 12 months than at 6 months which may be due to the number of patients discontinuing the study before month 12. Furthermore, a number of patients switched treatment during the study, which may have resulted in higher complete skin clearance rates per index biologic, as the patients who switched treatment might have experienced a low response on the index biologic. An NRI method was applied to the efficacy analysis which showed lower levels of complete skin clearance than the analysis reported as observed. The NRI method is a conservative approach that may underestimate efficacy, while the observed data might overestimate the efficacy.[27] Thus, response rates

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from the main analysis in this study are not directly comparable with those of randomized controlled trials (RCTs) where a non-responder imputation is commonly applied. Although NRI was applied in a sensitivity analysis, it also has limitations in terms of comparison, as patients are expected to drop out more frequently in real life than they do in a clinical trial. This will have an impact on the results when NRI is applied. This is a large, real-world study that adds important insights beyond what RCTs provide to the evidence of complete clearance among patients treated with biologics for plaque psoriasis.[28]

Conclusions

In this large, prospective, real-world study, the overall rate of complete skin clearance with the studied biologic treatments was low, achieved by 23% of patients at 6 months. The proportion achieving a response was smaller among patients who were switching biologics at study entry compared with those who were biologic-naïve. Likewise, the proportion of patients who achieved complete skin clearance decreased as the number of baseline comorbidities increased. Finally, the present study indicates that there is an unmet need for complete skin clearance in clinical practice, which may be improved with newer biologic therapies that have shown high rates of complete skin clearance in clinical trials. More insights are needed to understand how the unmet need can be addressed.

Acknowledgements

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Patients achieving PASI 75, PASI 90, and PASI 100 or sPASI 0 at months 6 and 12 by prior biologic use using the non-responder imputation method.

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