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ORIGINAL RESEARCH

Comparative Effectiveness of Biologics Across Subgroups of Patients with Moderate-to-Severe Plaque Psoriasis: Results at Week 12 from the PSoHO Study in a Real-World Setting

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ABSTRACT

Introduction: In routine clinical care, important treatment outcomes among patients with moderate-to-severe plaque psoriasis (PsO) have been shown to vary according to patient demographics and disease characteristics. This study aimed to provide direct comparative effectiveness data at week 12 between anti-interleukin (IL)-17A biologics relative to other approved biologics for the treatment of PsO across seven clinically relevant patient subgroups in the real-world setting.

Methods: From the international, non-interventional Psoriasis Study of Health Outcomes (PSoHO), 1981 patients with moderate-to-severe PsO were grouped a priori according to seven clinically relevant demographic and disease variables with binary categories, which were sex

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(male or female), age (< 65 or ≥ 65 years), body mass index (≤ 30 or > 30 kg/m^2), race (White or Asian), PsO disease duration (< 15 or ≥ 15 years), psoriatic arthritis (PsA) comorbidity (present or absent), and prior biologic use (never or ≥ 1). Across these subgroups, effectiveness was compared between the anti-IL-17A cohort (ixekizumab, secukinumab) versus all other approved biologics and ixekizumab versus five individual biologics. The proportion of patients in each subgroup who achieved 90% improvement in Psoriasis Area and Severity Index (PASI90) and/or static Physician Global Assessment (sPGA) 0/1, PASI100, or PASI90 at week 12 were assessed. Comparative analyses were conducted using frequentist model averaging (FMA). Missing data were imputed using non-responder imputation.

Results: Patients in each of the seven subgroups achieved similar response rates to those of the overall treatment cohort, apart from patients with PsA treated with other biologics who had 7–10% lower response rates. Consequently, patients with comorbid PsA had significantly higher odds of achieving skin clearance at week 12 with anti-IL-17A biologics compared to other biologics. Patients in all subgroups had significantly higher odds of achieving PASI90 and/or sPGA (0,1), PASI100, and PASI90 in the anti-IL-17A cohort relative to the other biologics cohort, except for the Asian subgroup. No sex- or age-specific differences in treatment effectiveness after 12 weeks were identified, neither between the treatment cohorts nor between the individual treatment comparisons.

Conclusions: Despite relative consistency of comparative treatment effectiveness across subgroups, the presence of comorbid PsA may affect a patient's clinical response to some treatments.

Keywords: Psoriasis; Biologic; Demographic; Subgroup; Comorbidity; Treatment; Effectiveness; Real-world

Key Summary Points

Why carry out this study?

Strict inclusion criteria for clinical trials can exclude many patients and report an averaged treatment effect, and varying demographics and disease characteristics of patient subgroups can potentially modify the effect of a treatment on clinical outcomes.

Newer psoriasis therapies have shown robust responses among subgroups of patients in randomized clinical trials, yet little is known about the comparative effectiveness of biologic treatments in population subgroups receiving care in the real world.

What was learned from the study?

The Psoriasis Study of Health Outcomes (PSoHO) provides direct comparative effectiveness of different biologics across seven clinically relevant subgroups of patients with moderate-to-severe psoriasis in a real-world setting.

Patients in the anti-interleukin-17A cohort versus the other biologics cohort had significantly higher odds of achieving all outcomes across all subgroups, except the Asian subgroup.

The presence of comorbid psoriatic arthritis may affect a patient's clinical response to some treatments evidenced by the significantly higher odds of achieving skin clearance at week 12 with anti-interleukin-17A biologics compared to other biologics.

INTRODUCTION

Although randomized clinical trials (RCTs) are considered the gold standard for evaluating the efficacy and safety of potential therapies, they do

not necessarily reflect the heterogeneous patient population and complex conditions encountered in daily clinical practice [1, 2]. This is of particular relevance in routine clinical care as important outcomes among patients with moderate-to-severe plaque psoriasis (PsO) have been shown to vary according to patient demographics and disease characteristics [3–5]. Older generation biologics, in particular, are associated with less favorable clinical outcomes among patients with comorbid obesity [3, 6, 7], psoriatic arthritis (PsA) [5], failure with a prior biologic treatment [8, 9], or a longer disease duration [10]. There are also insufficient, often conflicting, real-world data on the effect on clinical effectiveness of other demographic characteristics, such as sex [11–13], age [13, 14], and race [4, 13, 15]. Direct comparative effectiveness of treatments in patient subgroups may therefore contribute to the personalization of treatment selection that accounts for both patient- and disease-related factors and may help to reduce the number of switches between treatments [16].

The Psoriasis Study of Health Outcomes (PSoHO) is an ongoing, international, prospective, non-interventional observational study that has been designed to investigate the comparative effectiveness of biologic treatments for patients with moderate-to-severe PsO within a real-world setting [17]. The primary PSoHO week 12 results provided additional evidence that the early onset skin clearance and the high efficacy of anti-interleukin (IL)-17A inhibitors observed in RCTs correlated to their effectiveness in the real-world setting compared to other biologics [17]. We aim to evaluate the real-world effectiveness of anti-IL-17A biologics versus other biologics across seven clinically relevant subgroups. We also seek to inform on the pairwise comparative effectiveness of ixekizumab (IXE) versus five other individual biologics across these patient subgroups.

METHODS

Study Design and Assessments

Details of the PSoHO study including eligibility criteria, baseline patient demographics and clinical characteristics, as well as all prescribed biologics have been previously published [17]. Briefly, the PSoHO study enrolled 1981 adult patients from 23 participating countries and with a confirmed diagnosis (at least 6 months prior to baseline) of moderate-to-severe PsO who initiated or switched biologic treatment during routine medical care. Prescribed biologics were grouped into the anti-IL-17A antibodies cohort [IXE and secukinumab (SEC)] and a second cohort of other biologics targeting the IL-17 receptor A (brodalumab [BROD]), tumor necrosis factor (TNF)-α (adalimumab [ADA], certolizumab, etanercept, infliximab), IL-12/23 p40 (ustekinumab [UST]), and IL-23 p19 (guselkumab [GUS], risankizumab [RIS], and tildrakizumab). The primary endpoint was the proportion of patients achieving at least a 90% improvement in the psoriasis area and severity index score (PASI90) and/or a static Physician Global Assessment score of clear or almost clear (sPGA 0/1 on a 6-point scale) at week 12. Secondary outcomes included in this analysis were the proportion of patients who achieved PASI100 or PASI90 at week 12.

In this study, patient subgroups were prespecified a priori in the protocol and defined according to seven clinically relevant demographic and disease variables with binary categories: (i) sex (male or female) [11, 18–20], (ii) age (< 65 or ≥ 65 years) [13, 14], (iii) body mass index (BMI [≤ 30 or > 30 kg/m^2]) [19–21], (iv) race (White or Asian) [4, 22–25], (v) PsO disease duration (< 15 or ≥ 15 years) [13, 20], (vi) PsA comorbidity (present or absent) [13, 20, 26], and (vii) prior biologic use (never or ≥ 1) [8, 20, 27, 28]. Across all subgroup categories, pairwise effectiveness comparisons were completed for the anti-IL-17A cohort versus the other biologics cohort and for IXE versus the other individual biologics. Since the statistical models did not converge for any treatment groups with fewer than 100 patients, pairwise comparisons are only shown for IXE versus SEC, GUS, RIS, ADA, and UST. For the same rationale, other races were not evaluated in this study.

The protocol, amendments, and consent documentation were approved by local institutional review boards. The study was registered at the European Network of Centers for

Pharmacoepidemiology and Pharmacovigilance (ENCEPP24207) [29] and was conducted according to International Conference on Harmonization, Good Clinical Practice guidelines and the Declaration of Helsinki. All patients were required to give informed consent for participation in the study.

Statistical Analysis

Descriptive statistics are reported as mean and standard deviation or median and quartiles 1 and 3 (Q1, Q3) for continuous variables, and proportions and percentages for categorical variables. Pairwise comparisons of baseline demographics between the anti-IL-17A versus the other biologics cohort and IXE versus individual biologics were performed using Fisher's exact test or chi-square for categorical variables and analysis of variance (ANOVA), Mood's median test or exact *P* value from median test (Monte Carlo estimate) for continuous variables. A *P* value of less than 0.05 was considered statistically significant.

The comparative effectiveness analyses were performed using a machine learning, data-driven approach, known as frequentist model averaging (FMA), with this method and its application previously described [17, 30, 31]. FMA was used for pairwise comparisons between cohorts or treatments within each subcategory of the subgroups defined. Comparative adjusted results are presented as odds ratios (OR) with 95% confidence intervals (CI), formed using the 2.5th and 97.5th percentiles derived from 100 bootstrap samples. Statistical significance is indicated when the CIs do not cross the null hypotheses (OR = 1). In a few cases, no analysis strategies converged, because of zero counts for the outcome in one group, resulting in no treatment effect estimate. Missing data were imputed using non-responder imputation. Further details are provided in the Supplementary Material.

RESULTS

Baseline Demographics and Disease Characteristics

Baseline demographics and disease characteristics of the select patient subgroups are provided in Table 1. Of the 1981 patients enrolled, 9.0% of patients were 65 years or older, 47.1% of patients had endured PsO for 15 years or longer, and 64.3% of patients were biologic-naïve. At baseline, 39.0% (n = 773) initiated an anti-IL-17A biologic and 61.0% (n = 1208) received other biologics. Patient profiles were comparable between the anti-IL-17A and other biologics cohorts, with exceptions including the proportion of patients in the two age categories ($\geq$ 65 years: 11.5% vs. 7.5%; p = 0.001), or with comorbid PsA (29.4% vs. 19.4%; p = 0.001), respectively. Across individual treatments, the greatest variation in demographic distribution was in the age, race, and PsA comorbidity subgroups (Table 1). In patients who received the European Medicines Agency-approved on-label dosing (1767/1981; 89.2%), results in those outcomes studied were comparable (Supplementary Material).

Comparative Effectiveness of Anti-IL-17A Biologics Versus Other Biologics Across Patient Subgroups

Overall, patients in the anti-IL-17A cohort had significantly higher odds of achieving the primary endpoint (sPGA 0/1 and/or PASI90), PASI100, and PASI90 at week 12 compared to patients in the other biologics cohort (Fig. 1) [17]. Patients in each of the seven subgroups achieved similar response rates to those of the overall treatment cohort, except for patients with PsA treated with other biologics, who had 7–10% lower response rates. Accordingly, patients in all subgroups had significantly higher odds of achieving these outcomes in the anti-IL-17A cohort relative to the other biologics cohort, except for the Asian subgroup ORs (primary and PASI90), which did not reach statistical significance. The most pronounced contrast between the cohorts was for patients

Table 1 Demographics and disease characteristics of patients with moderate-to-severe plaque psoriasis at baseline

	Overall (*n* = 1981)	**Anti-IL-17A (*n* = 773)**	**Other biologics (*n* = 1208)**	**IXE (*n* = 532)**	**SEC (*n* = 241)**	**GUS (*n* = 303)**	**RIS (*n* = 259)**	**ADA (*n* = 284)**	**UST (*n* = 127)**
Age, years	45.3 (13.6)	*46.8 (13.7)**	44.4 (13.5)	47.4 (14.1)	45.4 (12.8)	***44.2 (13.2)***†	***44.1 (13.7)***‡	***45.1 (13.0)***‡	46.4 (14.5)
Age, *n* (%)									
< 65 years	1802 (91.0)	*684 (88.5)**	1118 (92.5)	460 (86.5)	***224 (92.9)***‡	***284 (93.7)***†	***243 (93.8)***‡	258 (90.8)	114 (89.8)
≥ 65 years	179 (9.0)	*89 (11.5)**	90 (7.5)	72 (13.5)	***17 (7.1)***‡	***19 (6.3)***†	***16 (6.2)***‡	26 (9.2)	13 (10.2)
Sex, *n* (%)									
Male	1143 (57.7)	442 (57.2)	701 (58.0)	313 (58.8)	129 (53.5)	179 (59.1)	161 (62.2)	163 (57.4)	77 (60.6)
Female	838 (42.3)	331 (42.8)	507 (42.0)	219 (41.2)	112 (46.5)	124 (40.9)	98 (37.8)	121 (42.6)	50 (39.4)
Weight, kg	85.0 (21.1)	85.6 (20.8)	84.6 (21.2)	86.3 (20.4)	83.9 (21.6)	84.0 (21.2)	83.8 (22.6)	86.7 (21.3)	82.9 (17.1)
BMI[a], kg/m^2	29.0 (6.7)	29.2 (6.6)	28.9 (6.7)	29.4 (6.6)	28.85 (6.5)	29 (6.7)	28.6 (6.9)	29.3 (6.6)	***28 (5.6)***‡
BMI, *n* (%)									
≤ 30 kg/m^2	1233 (63.3)	468 (61.7)	765 (64.3)	316 (60.5)	152 (64.1)	188 (63.3)	167 (65.0)	179 (63.7)	***92 (74.8)***†
> 30 kg/m^2	716 (36.7)	291 (38.3)	425 (35.7)	206 (39.5)	85 (35.9)	109 (36.7)	90 (35.0)	102 (36.3)	***31 (25.2)***
Race[b], *n* (%)									
White	1441 (72.7)	576 (74.5)	865 (71.6)	394 (74.1)	182 (75.5)	***162 (53.5)***†	***169 (65.3)***‡	***248 (87.3)***†	99 (78.0)
Asian	296 (14.9)	103 (13.3)	193 (16.0)	67 (12.6)	36 (14.9)	***100 (33.0)***†	***53 (20.5)***‡	***7 (2.5)***†	***8 (6.3)***‡

Table 1 continued

	Overall (*n* = 1981)	**Anti-IL-17A (*n* = 773)**	**Other biologics (*n* = 1208)**	**IXE (*n* = 532)**	**SEC (*n* = 241)**	**GUS (*n* = 303)**	**RIS (*n* = 259)**	**ADA (*n* = 284)**	**UST (*n* = 127)**
Disease duration, median years (Q1, Q3)	14.0 (6.8, 23.8)	14.3 (6.4, 24.2)	13.8 (7.1, 23.6)	13.9 (6.7, 25.3)	14.9 (6.0, 21.8)	14.9 (7.8, 24.4)	13.7 (8.2, 23.5)	14.2 (6.3, 25.0)	12.1 (6.3, 23.7)
Disease duration, *n* (%)									
< 15 years	1047 (52.9)	401 (51.9)	646 (53.5)	279 (52.4)	122 (50.6)	154 (50.8)	144 (55.6)	151 (53.2)	71 (55.9)
≥ 15 years	934 (47.1)	372 (48.1)	562 (46.5)	253 (47.6)	119 (49.4)	149 (49.2)	115 (44.4)	133 (46.8)	56 (44.1)
PASI	14.5 (8.6)	14.6 (8.5)	14.5 (8.6)	14.4 (8.5)	15.03 (8.7)	14.6 (9.3)	15.4 (9.8)	13.3 (7.1)	14.4 (7.9)
Percentage of BSA	21.3 (17.7)	21.1 (17.5)	21.5 (17.9)	20.6 (17.2)	22.3 (18.1)	21.7 (18.5)	20.6 (18.9)	20.6 (16.6)	22.6 (17.7)
sPGA, *n* (%)									
Moderate	988 (50.7)	387 (50.7)	601 (50.8)	267 (50.6)	120 (50.8)	143 (47.7)	***102 (40.8)***[‡]	***170 (60.5)***[‡]	68 (54.8)
Severe	610 (31.3)	242 (31.7)	368 (31.1)	176 (33.3)	66 (28.0)	101 (33.7)	93 (37.2)	***69 (24.6)***[‡]	37 (29.8)
Very severe	76 (3.9)	34 (4.5)	42 (3.5)	16 (3.0)	***18 (7.6)***[‡]	14 (4.7)	15 (6.0)	5 (1.8)	2 (1.6)
DLQI[c]	12.6 (7.8)	12.9 (7.9)	12.4 (7.8)	12.6 (7.9)	13.5 (7.7)	12.3 (8.1)	11.8 (7.3)	12.9 (7.6)	12.3 (8.0)
Current comorbidities reported[d]	1.5 (1.8)	1.6 (1.8)	1.4 (1.8)	1.6 (1.8)	1.6 (1.9)	1.5 (1.7)	1.4 (1.8)	1.4 (1.7)	1.7 (2.1)

Table 1 continued

	Overall (*n* = 1981)	**Anti-IL-17A (*n* = 773)**	**Other biologics (*n* = 1208)**	**IXE (*n* = 532)**	**SEC (*n* = 241)**	**GUS (*n* = 303)**	**RIS (*n* = 259)**	**ADA (*n* = 284)**	**UST (*n* = 127)**
Psoriatic arthritis, *n* (%)[c]	461 (23.3)	*227 (29.4)**	234 (19.4)	161 (30.3)	66 (27.4)	***71 (23.4)***[‡]	***32 (12.4)***[†]	***64 (22.5)***[‡]	***19 (15.0)***[†]
Any previous conventional therapy, *n* (%)	1565 (79.0)	*573 (74.2)**	992 (82.1)	393 (74.0)	180 (74.7)	225 (74.3)	199 (76.8)	***265 (93.3)***[†]	***106 (83.5)***[†]
Prior treatment with biologics, *n* (%)[f]	706 (35.7)	291 (37.7)	415 (34.4)	204 (38.4)	87 (36.1)	***178 (58.7)***[†]	111 (42.9)	***25 (8.8)***[‡]	***35 (27.6)***[‡]

All results are expressed as mean (standard deviation) of all available data for that measure, unless otherwise indicated. Anti-IL-17A cohort includes IXE- and SEC-treated patients

In cases of *n* (%) not matching total in group, remainder is attributable to missing data for patients

Italic text signifies significant difference ($P < 0.05$) between anti-IL-17A cohort vs. the other biologics cohort

Bold italic text signifies significant difference ($P < 0.05$) vs. IXE

ADA adalimumab, *BMI* body mass index, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *GUS* guselkumab, *IXE* ixekizumab, *PASI* Psoriasis Area and Severity Index, *sPGA* Static Physician Global Assessment, *PASI* Psoriasis Area and Severity Index, *Q* quartile, *RIS* risankizumab, *SEC* secukinumab, *UST* ustekinumab

[*]$P < 0.001$ vs. the other biologics cohort

[**]$P < 0.05$ vs. the other biologics cohort

[†]$P \leq 0.001$ vs. IXE

[‡]$P < 0.05$ vs. IXE

[a]Information about BMI missing for 32 patients

[b]Some individuals selected more than one race

[c]DLQI was measured on a 0–30 scale

[d]Comorbidities were captured on the basis of a pre-defined list

[e]PsA diagnosis was recorded by the dermatologists on the basis of the medical history and/or information provided by the patient

[f]Information about prior biologic use missing for 1 patient

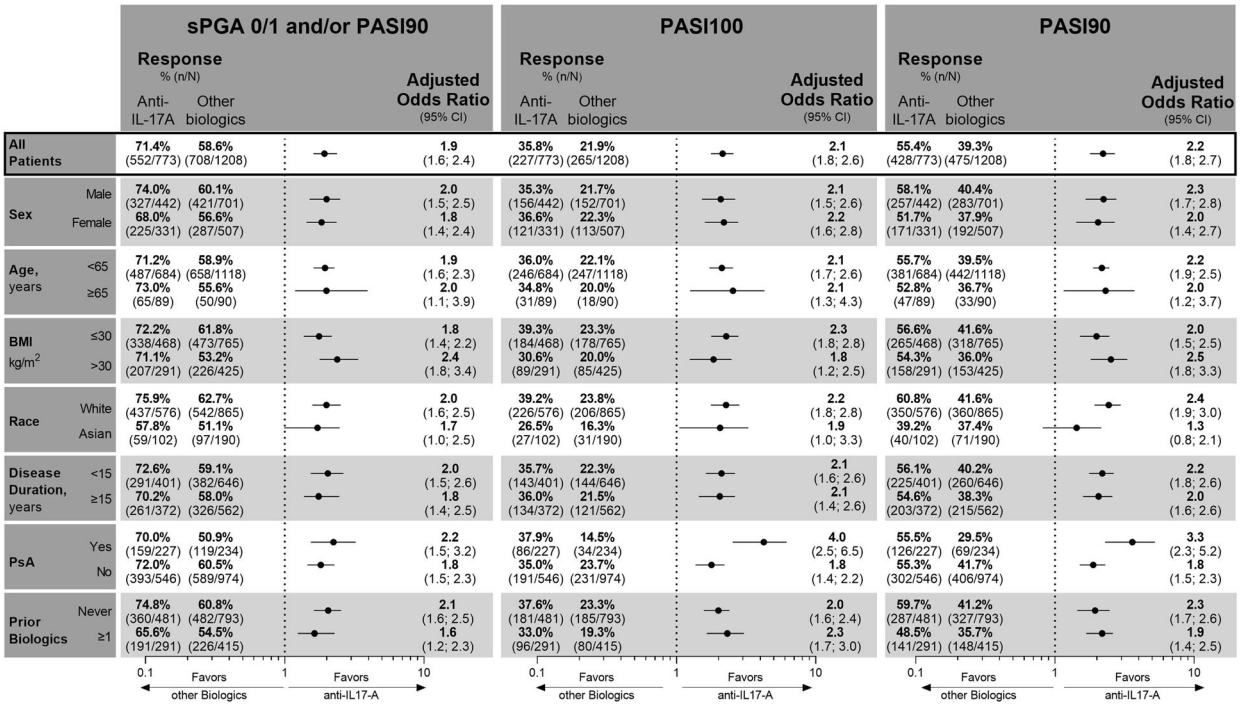

Fig. 1 Comparative effectiveness in anti-IL-17A versus other biologics cohorts across subgroups of patients with moderate-to-severe plaque psoriasis. Comparative adjusted analysis of primary (sPGA (0/1) and/or PASI90) and secondary outcomes, PASI100 and PASI90, actual responses rates, and adjusted odds ratios at week 12 for anti-IL-17A cohort and other biologics cohort across patient subgroups. Data are non-responder imputation. Results are statistically significant if 1 is not covered by the 95% CI for the odds ratios. For the Asian subgroup, the lower CI is 0.990 (primary) and 1.048 (PASI100). *BMI* body mass index, *CI* confidence interval, *IL* interleukin, *PASI* Psoriasis Area and Severity Index, *PsA* psoriatic arthritis, *sPGA* Static Physician Global Assessment

with PsA, whereby the anti-IL-17A cohort had 4.0-fold and 3.3-fold greater odds of achieving PASI100/90, respectively, versus the other biologics cohort. Moreover, the CIs associated with the OR for PASI100 were non-overlapping between patients with PsA (OR 4.0; 95% CIs 2.5, 6.5) and patients without PsA (OR 1.8; 95% CIs 1.4, 2.2; Fig. 1). Further stratification showed that patients with PsA in either treatment cohort (but not in all individual biologics) had lower unadjusted response rates when biologic-experienced compared to biologic-naïve (Supplementary Material).

Pairwise Comparisons of Ixekizumab Versus Five Individual Biologics

The unadjusted response rates for the three outcomes at week 12 were higher in the IXE cohort than the SEC cohort across all subgroup categories (Fig. 2). Compared to SEC-treated patients, IXE-treated patients had higher odds of achieving the three outcomes, with statistical significance reached for half of the subgroup categories. For the primary endpoint, statistically significant differences were not reached in the following subcategories: male, age ≥ 65 years, BMI > 30, Asian, disease duration ≥ 15 years, PsA comorbidity, or biologic-experienced (Fig. 2).

Across all subgroups, GUS-treated patients had lower response rates for the three outcomes versus IXE-treated patients, with significantly higher ORs for all subgroups in the IXE cohort, except for the 65 years or older (PASI100/90), BMI > 30 (PASI100), or Asian (primary and PASI90; Fig. 3) subgroups. Versus RIS-treated patients, IXE-treated patients had higher

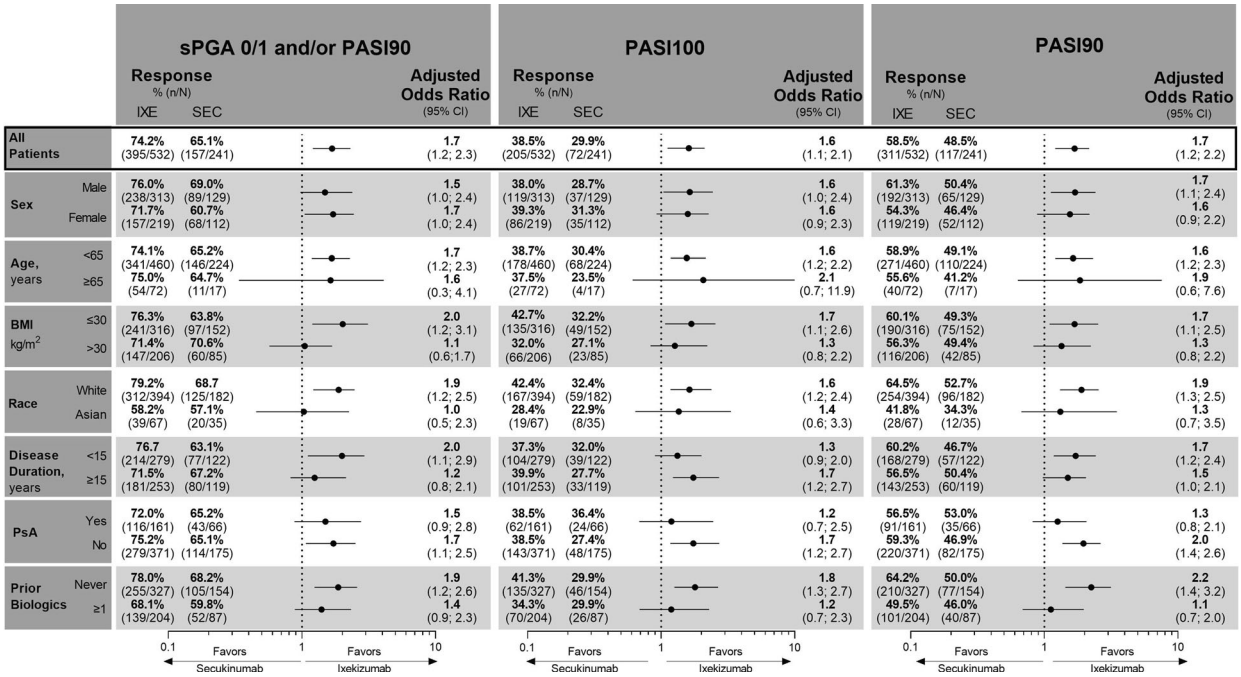

Fig. 2 Comparative effectiveness in ixekizumab versus secukinumab cohorts across subgroups of patients with moderate-to-severe plaque psoriasis. Comparative adjusted analysis of primary (sPGA (0/1) and/or PASI90) and secondary outcomes, PASI100 and PASI90, actual responses rates, and adjusted odds ratios at week 12 for ixekizumab cohort and secukinumab cohort across patient subgroups. Data are non-responder imputation. Results are statistically significant if 1 is not covered by the 95% CI for the odds ratios. For the male subgroup, the lower CI is 0.973 (primary) and 1.040 (PASI100); for the female subgroup, the lower CI is 1.049 (primary); for the ≥ 15 years subgroup, the lower CI is 0.974 (PASI90). *BMI* body mass index, *CI* confidence interval, *IXE* ixekizumab, *PASI* Psoriasis Area and Severity Index, *PsA* psoriatic arthritis, *SEC* secukinumab, *sPGA* Static Physician Global Assessment

response rates, except for ≥ 65 years (primary) and Asian subgroups, and the comparative effectiveness reached statistical significance across the subgroup categories, except for male (primary, PASI90), female (PASI90), age ≥ 65 years, BMI > 30, Asian, disease duration < 15 years, ≥ 15 years (primary), biologic-naïve (PASI100), and biologic-experienced (primary and PASI90; Fig. 4). While the ORs for each subgroup category were comparable to the OR for the overall patient group (Figs. 3 and 4), the exception was the subgroup of patients with PsA, whose odds of achieving PASI100 were considerably higher than for the overall group for IXE versus GUS (OR 3.0 vs. 2.1) and RIS (OR 2.8 vs. 1.6). This mirrors the PASI100 result of the anti-IL-17A versus the other biologics cohort for patients with PsA when compared to the overall patient group (OR 4.0 vs. 2.1) (Fig. 1).

Relative to ADA, the comparative effectiveness of IXE was significantly higher across all subgroup categories, with the IXE-treated cohort consistently demonstrating at least threefold higher odds of achieving PASI100/90 (Fig. 5). Since none of the seven Asian patients receiving ADA achieved any of the outcomes, the FMA analysis could not be conducted for this subgroup category. Likewise, none of the 19 patients with PsA who received UST achieved PASI100 (Fig. 6). Additionally, as a result of the low number of patients who received UST in the age ≥ 65 years, Asian, comorbid PsA, and biologic-experienced subgroup categories, pairwise comparisons were unviable for some outcomes. Except for patients with comorbid PsA or the

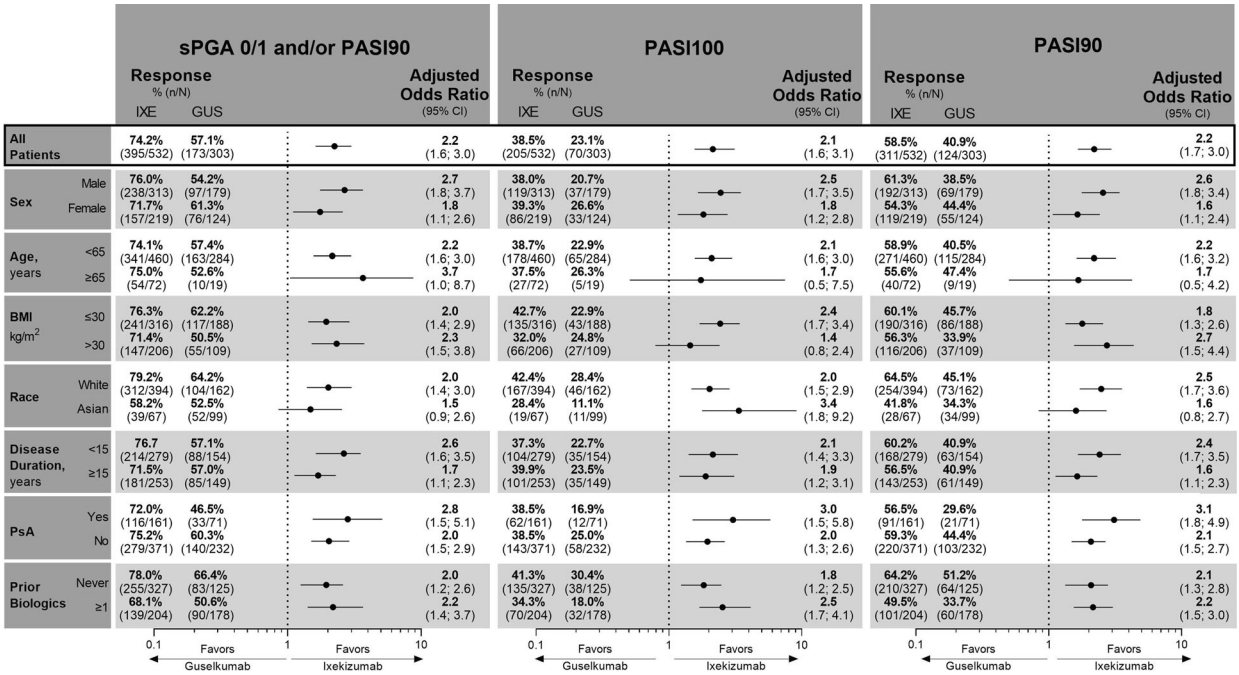

Fig. 3 Comparative effectiveness in ixekizumab versus guselkumab cohorts across subgroups of patients with moderate-to-severe plaque psoriasis. Comparative adjusted analysis of primary (sPGA (0/1) and/or PASI90) and secondary outcomes, PASI100 and PASI90, actual responses rates, and adjusted odds ratios at week 12 for ixekizumab cohort and guselkumab cohort across patient subgroups. Data are non-responder imputation. Results are statistically significant if 1 is not covered by the 95% CI for the odds ratios. For the ≥ 65 years subgroup, the lower CI is 1.043 (primary). *BMI* body mass index, *CI* confidence interval, *GUS* guselkumab, *IXE* ixekizumab, *PASI* Psoriasis Area and Severity Index, *PsA* psoriatic arthritis, *sPGA* Static Physician Global Assessment

biologic-experienced, IXE-treated patients had significantly higher odds (OR 2.1–4.0) of achieving the primary endpoint than UST-treated patients (Fig. 6). For all subgroups with viable pairwise comparisons, patients had significantly higher odds of achieving PASI100 (OR 2.6–6.6) or PASI90 (OR 2.8–6.5) when treated with IXE compared to UST.

Overall, the comparative treatment effect estimates across subgroups largely reflected the effect estimate for the overall patient group, with few exceptions (Figs. 2, 3, 4, 5, 6). Results thereby showed that patients treated with IXE had higher response rates and odds of achieving the primary endpoint, PASI100, and PASI90 at week 12 across most subgroups compared to patients treated with SEC, GUS, RIS, ADA, or UST (Figs. 2, 3, 4, 5, 6) [17].

DISCUSSION

In this subgroup analysis of week 12 data from the prospective, non-interventional PSoHO study, anti-IL-17A biologics showed consistently greater effectiveness compared to other biologics for patients with moderate-to-severe PsO, irrespective of most baseline demographics and all disease characteristics evaluated. The most pronounced difference in effectiveness between the two treatment cohorts was for patients with comorbid PsA, whereby the anti-IL-17A cohort had 19.1% (70.0/50.9), 23.4% (37.9/14.5), and 26.0% (55.5/29.5) higher primary, PASI100, and PASI90 response rates, respectively, as well as significantly higher odds of high-level skin clearance compared to the other biologics cohort. Moreover, while patients with comorbid PsA receiving other biologics had 15–40% proportionately lower response

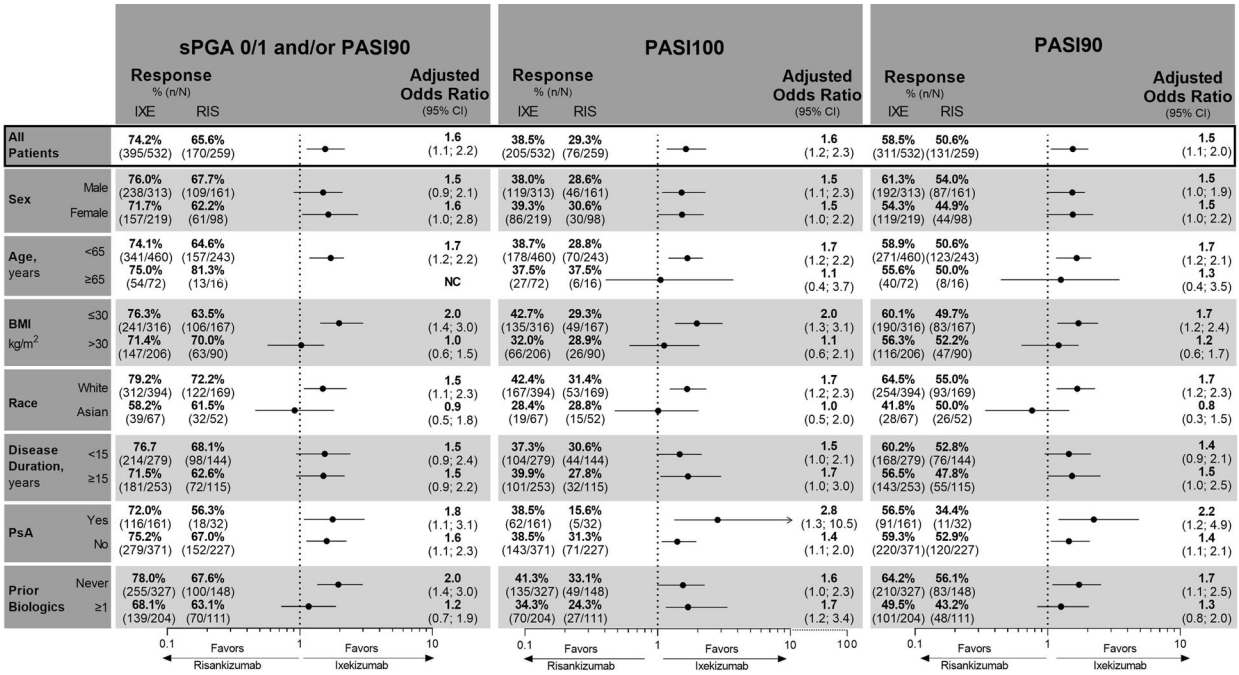

Fig. 4 Comparative effectiveness in ixekizumab versus risankizumab cohorts across subgroups of patients with moderate-to-severe plaque psoriasis. Comparative adjusted analysis of primary (sPGA (0/1) and/or PASI90) and secondary outcomes, PASI100 and PASI90, actual responses rates, and adjusted odds ratios at week 12 for ixekizumab cohort and risankizumab cohort across patient subgroups. Data are non-responder imputation. Results are statistically significant if 1 is not covered by the 95% CI for the odds ratios. For male subgroup, lower CI is 0.984 (PASI90); for female subgroup, lower CI is 1.037 (primary), 1.000 (PASI100), and 0.977 (PASI90); for < 15 years subgroup, lower CI is 0.981 (PASI100); for ≥ 15 years subgroup, lower CI is 1.046 (PASI100) and 1.000 (PASI90); for biologic naïve, lower CI is 0.992 (PASI100). Where statistical models did not converge, results are marked as non-convergence (NC). *BMI* body mass index, *CI* confidence interval, *IXE* ixekizumab, *NC* non-convergence, *PASI* Psoriasis Area and Severity Index, *PsA* psoriatic arthritis, *RIS* risankizumab, *sPGA* Static Physician Global Assessment

rates across the studied outcomes than patients without joint disease, the anti-IL-17A-treated patients had similar response rates, regardless of the presence of comorbid PsA. Proportionately lower response rates were also shown for the IL-23 treatments, GUS (23–33%) and RIS (16–50%), for patients with PsA compared to those without PsA. This indicates that patients with PsO and comorbid PsA may be more challenging to treat (and in general, even more so if biologic-experienced), and that anti-IL-17A biologics may preferentially benefit these patients compared to treatment with other biologics.

While recent real-world studies have shown that comorbid PsA is not associated with significantly increased risk for drug discontinuation [20, 26, 32, 33], there are few studies that have investigated whether the presence of PsA can affect treatment response rates and skin improvement [13, 21]. In PSoHO, no meaningful differences in skin outcomes were observed between patients with or without comorbid PsA, who were prescribed IXE, SEC, or ADA, whereas a proportionately higher treatment effectiveness across each study outcome was observed for patients unaffected by PsA who were prescribed the IL-23 biologics, RIS or GUS. This variable treatment effectiveness for patients with PsA highlights the importance of addressing the paucity of real-world studies directly comparing treatments across different patient subgroups [13]. Hence, direct comparative effectiveness data, such as those presented

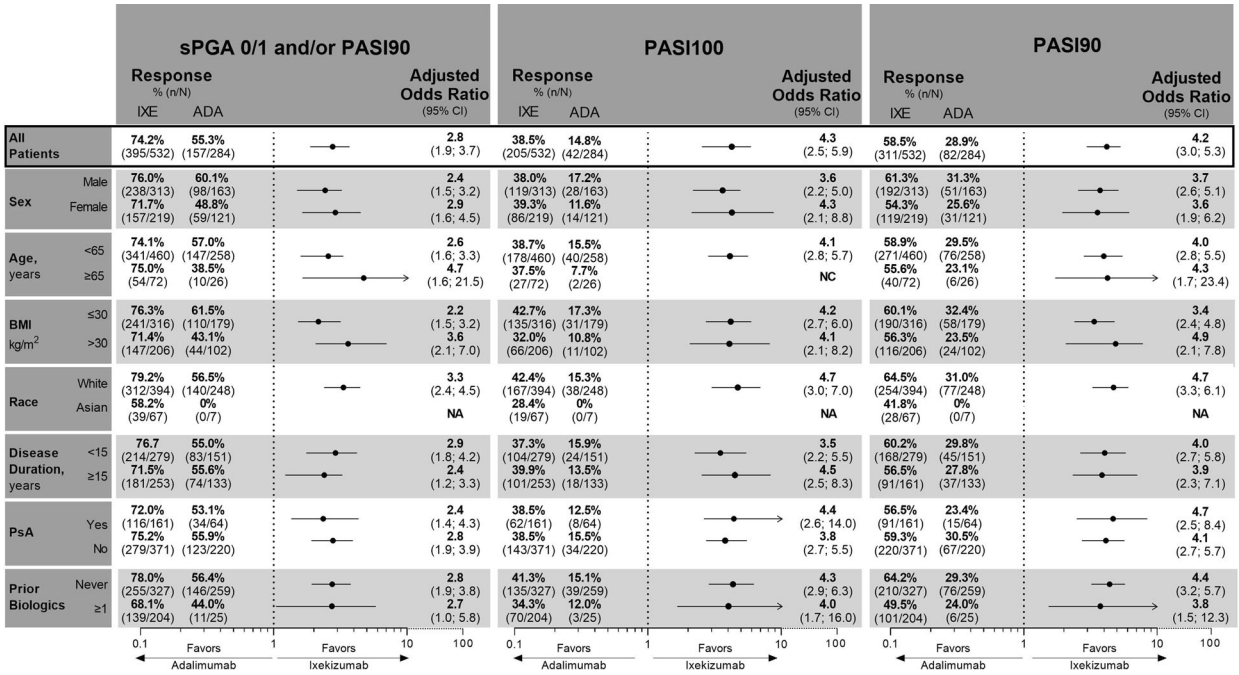

Fig. 5 Comparative effectiveness in ixekizumab versus adalimumab cohorts across subgroups of patients with moderate-to-severe plaque psoriasis. Comparative adjusted analysis of primary (sPGA (0/1) and/or PASI90) and secondary outcomes, PASI100 and PASI90, actual responses rates, and adjusted odds ratios at week 12 for ixekizumab cohort and adalimumab cohort across patient subgroups. Data are non-responder imputation. Results are statistically significant if 1 is not covered by the 95% CI for the odds ratios. For prior biologics ≥ 1 subcategory, lower CI is 1.040 (primary). Where statistical models were unviable because of low patient numbers, results are marked as not applicable (NA). *ADA* adalimumab, *BMI* body mass index, *CI* confidence interval, *IXE* ixekizumab, *NA* not applicable, *PASI* Psoriasis Area and Severity Index, *PsA* psoriatic arthritis, *sPGA* Static Physician Global Assessment

here, can assist clinicians to optimize treatment selection for individual patients with varying demographics and disease characteristics.

This study evaluated comparative biologic effectiveness across four clinically relevant patient demographic characteristics, namely sex, age, BMI, and race subgroups, and three disease- and treatment-related factors. Potential sex-specific differences have been reported in other studies, such as in the prescription pattern of systemic drugs [11, 18], disease burden [32], treatment outcomes [12], and a higher likelihood of biologic discontinuation in female patients [19, 20]. In this study, however, no sex-specific differences in treatment effectiveness after 12 weeks were identified, neither between the treatment cohorts nor between the individual treatment comparisons. These 12-week results align with the findings of a Spanish registry study that found that the treatment effectiveness of biologics was similar between male and female patients [11]. Also, in PSoHO, treatment effectiveness was comparable between patients in the < 65 and ≥ 65 years age categories, although the small sample size in the latter age category led to less stability of models and broader CIs. Prior studies investigating the comparative efficacy of biologics for patients in different age groups have shown conflicting results; one clinical trial showed that age did not significantly influence the clinical outcome at week 52 following treatment with RIS or SEC [13], while another study indicated disproportionately better clinical outcomes at week 48 for patients aged 65 or older treated with GUS compared to SEC [34].

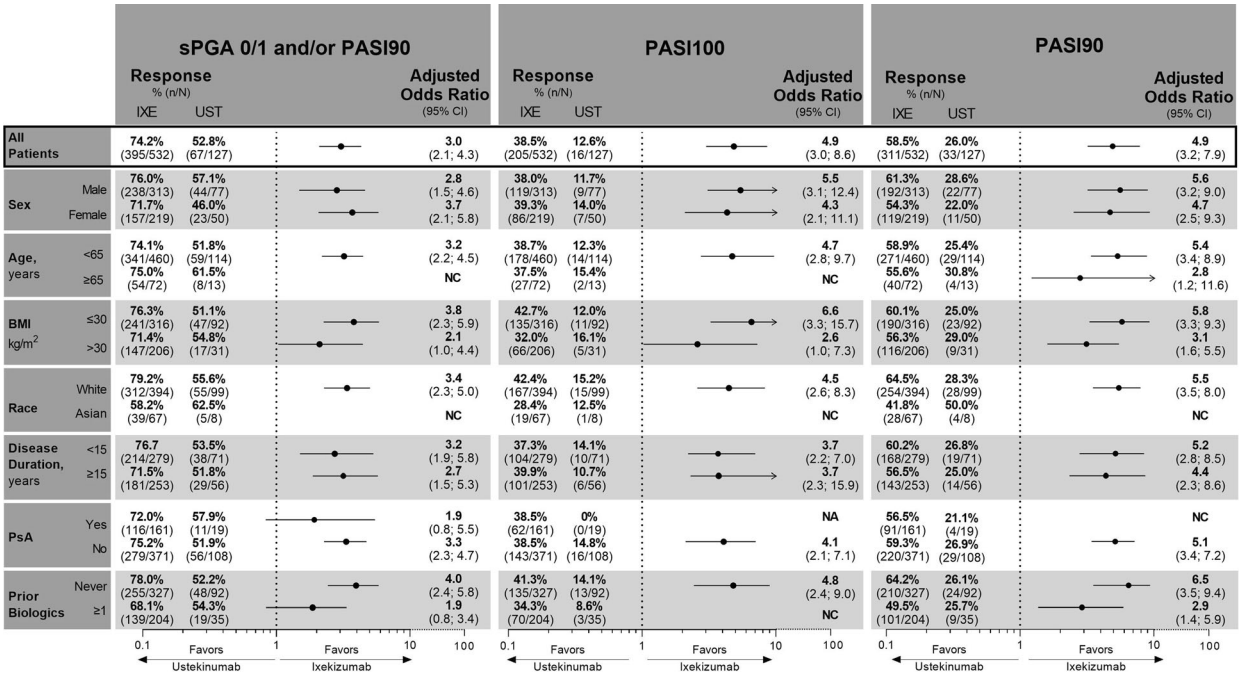

Fig. 6 Comparative effectiveness in ixekizumab versus ustekinumab cohorts across subgroups of patients with moderate-to-severe plaque psoriasis. Comparative adjusted analysis of primary (sPGA (0/1) and/or PASI90) and secondary outcomes, PASI100 and PASI90, actual responses rates, and adjusted odds ratios at week 12 for ixekizumab cohort and ustekinumab cohort across patient subgroups. Data are non-responder imputation. Results are statistically significant if 1 is not covered by the 95% CI for the odds ratios. For BMI > 30 subcategory, lower CI is 1.033 (primary) and 1.024 (PASI100). Where statistical models were unviable because of low patient numbers, results are marked as not applicable (NA). Where statistical models did not converge, results are marked as non-convergence (NC). *BMI* body mass index, *CI* confidence interval, *IXE* ixekizumab, *NA* not applicable, *NC* non-convergence, *PASI* Psoriasis Area and Severity Index, *PsA* psoriatic arthritis, *sPGA* Static Physician Global Assessment, *UST* ustekinumab

The question of whether obesity (BMI > 30 kg/m^2) affects the efficacy of biological therapies also remains controversial. In PSoHO, treatment with SEC or RIS was similarly effective as treatment with IXE in patients with a BMI > 30. Other studies have indicated that obesity is associated with lower efficacy of biologic treatment, with important consequences on drug survival [19–21]. For instance, one real-world evidence study has indicated that a higher BMI was associated with an increased risk of drug discontinuation for SEC and BROD, but not IXE, GUS, and RIS [20]. Other studies have shown that obesity has little or no impact on the efficacy of some, generally newer-generation biologics [20, 21].

There is a paucity of both RCT and real-world data evaluating psoriasis treatments across different races and ethnicities, and particularly in non-White populations [4, 22, 35]. In PSoHO, the largest proportions of patients selected White (72.7%) and Asian (14.9%) race, irrespective of their geographical location. As a result of the small numbers of patients, subgroup analyses of other race or ethnicity subgroups were unviable. High-level skin response rates were generally lower in Asian patients compared to White patients across all treatments. An explanation is not readily evident, but it should be noted that for most treatment cohorts, the Asian subgroup comprised low numbers of patients that rendered effectiveness analyses unviable for some treatment

comparisons, while others did not reach significance. Differences in PsO disease characteristics between these two subgroups have been reported previously [23, 24], but were not found to impact treatment efficacy [24]. A recent systematic review of RCT data showed that IXE provided the highest skin clearance efficacy for Asian patients compared with seven other drugs [4], and another study found no significant difference in the short-term efficacy of anti-IL-17 treatment for Caucasians [sic] and Asians [25]. Real-world data from Taiwan indicated disparate effectiveness between treatments with highest response rates with SEC, followed by UST, ADA, and etanercept, although this study did not include more recently approved biologics, such as RIS and IXE, for which data are eagerly awaited [22].

Longer PsO disease duration has been shown to be a negative predictor of clinical outcomes with IL-12/23 biologics in some studies [15], although other studies concluded that disease duration is not a significant determining factor in treatment effectiveness for patients [13, 20]. In PSoHO, whether a patient had PsO for less than 15 years or for 15 years or longer had little effect on response rates and comparative treatment effectiveness. Patients with a longer disease duration are usually more likely to have prior exposure to biologic agents and other systemic therapies [8], which may negatively affect drug efficacy and consequentially result in lower drug survival of subsequently administered biologics [8, 20, 27, 28]. Hence, treatment of biologic-experienced patients represents a significant challenge to dermatologists [27]. A recently published paper reported that patients who were biologic-naïve presented a lower hazard of discontinuation [20]. This reinforces the importance of choosing the most suitable agent *ad initium*. A lack of effectiveness is a key reason for drug switching or discontinuation and 12-week PSoHO data might provide a rationale for this finding, as biologic-experienced patients, including those with PsA comorbidity, and across cohorts and treatments, largely had lower response rates relative to biologic-naïve patients. While the ORs for IXE-treated patients who were biologic-naïve all reached statistical significance relative to patients treated with any other biologic, the significance of the comparative effectiveness for biologic-experienced patients was more variable, thus underscoring the need to tailor initial treatment selection.

The PSoHO results presented here should be interpreted in the context of the study design and its recently published primary data [17]. First, observational studies have inherent limitations, including measured and unmeasured confounding and other bias (including selection bias) compared with RCTs. The application of FMA can accommodate for some of these uncertainties in model choice through the machine learning framework [31]. Statistical analyses and strategies were pre-specified in the protocol and included the grouping of non-anti-IL-17A biologics into a single category. This study also presented an opportunity to develop and extend the initial application of FMA to the evaluation of treatment effects across patient subgroups. The execution and statistical precision of these comparative analyses were constrained by the number of representative patients in each treatment cohort, category, and the respective covariates used. There was no enrolment restriction per treatment group and although the highest proportion of patients were prescribed IXE, other key biologics are represented in sufficiently high numbers to facilitate reliable comparisons. These 12-week data provide insights into the speed of action of different biologics and will complement longer-term effectiveness data that will follow.

CONCLUSIONS

Despite evidence that clinical outcomes for patients with moderate-to-severe PsO may vary on the basis of patient demographics and disease characteristics, this study showed relative consistency between comparative treatment effectiveness, indicating that both the older and newer biologics work consistently across patient subgroups in this routine clinical care setting. Of note, our results indicate that the presence of comorbid PsA may affect a patient's clinical response to some treatments and that these patients have significantly higher odds of

achieving skin clearance at week 12 with anti-IL-17A biologics compared to other biologics.

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Compliance with Ethics Guidelines. The protocol, amendments and consent documentation were approved by local institutional review boards. The study was registered at the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCEPP24207) [29] and was conducted according to International Conference on Harmonization, Good Clinical Practice guidelines and the Declaration of Helsinki. All patients were required to give informed consent for participation in the study. We confirm that the necessary central or local IRB and/or ethics committee approvals have been obtained for this multi-site, international study by United BioSource LLC (UBC).

Data Availability. Data are available on reasonable request. Lilly provides access to all individual participant data collected during the study, after anonymization. Data are available to request after primary publication acceptance. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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