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ARTICLE

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Secukinumab demonstrates improvements in absolute and relative psoriasis area severity indices in moderate-to-severe plaque psoriasis: results from a European, multicentric, retrospective, real-world study

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ABSTRACT

Objective: This European, multicentric, retrospective study aimed to collect data on secukinumab effectiveness in a real-world setting.

Research design and methods: All psoriatic patients starting secukinumab between January 2016 and February 2017 in 11 European centers were followed until February 2018 and retrospectively evaluated.

Main outcome measures: Secukinumab effectiveness was assessed by relative improvement from baseline of the Psoriasis Area Severity Index (PASI) and absolute PASI score modifications throughout 52 weeks of therapy. Additionally measures assessing effectiveness were used, including improvements of body surface area (BSA) and Dermatology Life Quality Index (DLQI).

Results: Out of the 330 patients with potentially 52-week treatment duration, naïve to biologics patients showed greater probability to achieve PASI score of $\leq$1, $\leq$2, $\leq$3, and $\leq$5 at week 12, compared to bio-experienced patients (45.86% vs. 27.17%, 62.42% vs. 42.42%, 73.89% vs. 57.80%, and 84.08% vs. 74.57%, respectively). The greater effectiveness of secukinumab treatment in bio-naïve patients was confirmed at week 24 and 52.

Conclusions: In this real-world experience, secukinumab was proven effective in treating psoriasis patients throughout a 52-weeks observation period, with higher response in bio-naïve patients. This study may contribute to defining the clinical profile of secukinumab best-responders.

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KEYWORDS
Secukinumab; IL-17; psoriasis; effectiveness; absolute PASI; DLQI

Introduction

Plaque psoriasis is a chronic inflammatory skin disorder which causes substantial physical, psychological, and quality of life impairments (1–4). Among the multiple cytokines contributing to the pathogenesis of psoriasis, interleukin (IL)-17A is considered a key pro-inflammatory mediator of psoriatic inflammation and tissue damage as it induces the expression of keratinocyte-derived products such as chemokines, cytokines, and anti-microbial peptides, creating feed-forward loops that sustain and amplify skin inflammation (5,6).

Secukinumab, a recently approved fully human monoclonal antibody targeting IL-17A, neutralizes IL-17A as both homodimer and heterodimer dimeric ligands of IL-17. Secukinumab has demonstrated high efficacy and a favorable safety profile in clinical trials (7–9). However, these encouraging results have largely been obtained in patient cohorts selected for clinical trials, poorly reflecting the more complex psoriatic patient population observed in a real-world setting (10).

Recently, some real-world studies describing the effectiveness and safety of secukinumab have been published, but only one study included data on the absolute residual PASI score (11–24). Indeed, the effectiveness of antipsoriatic treatments is usually reported as the relative 75%, 90%, or 100% improvement from baseline on the Psoriasis Area Severity Index (PASI 75, PASI 90, PASI 100), though there is emerging interest in the evaluation of absolute PASI score reduction as a better benchmark of therapeutic response and the higher clinical relevance of the remaining absolute PASI score as therapeutic target (i.e. PASI score 0–1, PASI score $\leq$2, PASI score $\leq$3, and PASI $\leq$5) (25–27). A recent analysis of data from the CLEAR study found that PASI ranges strongly correlated with Dermatology Life Quality Index (DLQI) score (28). When patients were grouped by absolute PASI score, those with a constantly lower residual PASI score (PASI score 0–1 or PASI score $>$1–3) had a longer duration of time spent with a DLQI score $\leq$1 than those with higher residual PASI values or with absolute PASI scores that did not fluctuate.

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This European multicentric retrospective study aimed to collect data on the effectiveness of secukinumab in a real-world setting, including a large population of 508 patients treated with secukinumab and evaluating relative PASI improvement as well as absolute PASI score modifications throughout 52 weeks of secukinumab therapy.

Materials and methods

This multicenter retrospective observational study comprised 11 European centers, one based in Switzerland, three in Portugal, and seven in Italy. All patients affected by moderate-severe plaque psoriasis with or without arthritis and treated with secukinumab at the labeled posology of 300 mg at the baseline, at week 1, 2, 3, 4, and then every 4 weeks, after appropriate screening tests were included in this study. All patients were treated out of any clinical trial. Due to the great variability of the marketization process across European Countries, we assumed that by January 2016, secukinumab was available in all abovementioned European countries. Patients treated with at least 3-month secukinumab therapy were included in the study. As clinically meaningful patient subcohort, we selected those patients who started secukinumab therapy between January 2016 and February 2017 and were followed until February 2018 in order to assure the assessment of effectiveness over a minimum observation period of 52 weeks (potentially with at least one year of observation period). Temporary treatment interruptions (e.g. due to surgery or logistic issues) of less than 3 months duration were allowed.

Patient demographic characteristics and clinical/anamnestic data were collected from the database of each dermatology unit: age, gender, height, weight, and body mass index (BMI), smoking habit, family history of psoriasis, comorbidities, disease duration (defined as the time from psoriasis diagnosis to start of secukinumab treatment), age at diagnosis, baseline PASI score and body surface area (BSA), presence of comorbidities (i.e. psoriatic arthritis (PsA), obesity, etc.). Previous systemic and/or biologic antipsoriatic therapies, concomitant medications for eventual comorbidities, and reasons of secukinumab discontinuation were also collected.

The present study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983, on Ethical Principles for Medical Research Involving Human Subjects and after approval by the local ethical committee of each University clinic. All eligible patients provided written informed consent.

Statistical analysis

Descriptive statistics were calculated for each variable, using frequencies and percentage for categorical variables and mean ± standard deviation (SD) for continuous ones. Categorical variables were compared with the Chi-square test, while continuous with the *t*-test or Wilcoxon's test based on data distribution. An ANCOVA model on ranks was used to compare PASI score between biologic naïve cohort (in the manuscript referred as bio-naïve patients) vs. prior biologic experienced (referred as bio-experienced patients) cohort, taking into account the following variables: age, PASI at baseline, the presence of PsA, BMI, duration of psoriasis, naïve to systemic therapy and drug association. Determinant to PASI response was analyzed by means of a logistic regression model, using the stepwise selection method, taking into account the following factors: naïve to biologic treatment vs. prior exposed, PASI class at baseline (<20 vs. ≥ 20), age (<65 vs. ≥ 65), BMI class (<30 vs. ≥ 30), naive or prior exposed to systemic therapy and presence of PsA. The comparison between biologic naïve cohort vs. biologic experienced cohort of the proportion of patients with mean absolute PASI scores ≤ 1, ≤ 2, ≤ 3, and ≤ 5 was analyzed by means of a logistic regression model with the covariates described above.

Beside the 'as-observed' approach, the non-responder imputation (NRI) and last observation carried forward (LOCF) methods were used to manage missing value in PASI score, for the proportion of patients with mean absolute PASI scores of ≤ 1, ≤ 2, ≤ 3, and ≤ 5 as well as for PASI 90/PASI 100.

All statistical analyses were done with SAS v9.4 (SAS Inc., Cary, NC), and, due to the nature of the study, a $p < .05$ was considered statistically significant.

Results

Baseline characteristics and subject disposition

Overall, 508 patients were collected and their baseline characteristics can be found in Table 1.

To assess the effectiveness of secukinumab over a minimum period of 52 weeks, 330 patients who started treatment from January 2016 to January 2017 were selected and were eligible for analysis. The mean observation period for this subcohort consisted of 492.52 ± 223.87 days (70.36 ± 31.98 weeks).

The demographic features of this patient subcohort mostly reflected those observed in the overall population, but differ in

Table 1. Demographics and baseline characteristics of the overall study population.

Characteristics	Overall patient cohort ($N = 508$)	1-year cohort ($N = 330$)	<1-year cohort ($N = 178$)	*p* Value†
Age (years), mean (SD)	51.96 (14.39)	51.94 (14.64)	52.01 (13.96)	.9788
Gender, male, *n* (%)	336 (66.14)	225 (68.18)	111 (62.36)	.1858
Bodyweight (kg), mean (SD)	78.91 (16.19)	78.30 (15.87)	79.99 (16.74)	.3975
BMI (kg/m^2), mean (SD)	26.84 (4.80)	26.55 (4.79)	27.35 (4.79)	.0315
Disease duration (years), mean (SD)	18.49 (12.43)	16.93 (10.82)	21.41 (14.57)	.0016
Age at diagnosis (years), mean (SD)	33.48 (16.72)	35.02 (16.99)	30.58 (15.85)	.0059
PASI score, mean (SD)	15.28 (8.10)	16.65 (8.25)	12.75 (7.18)	<.0001
BSA affected, mean (SD)	21.66 (16.23)	23.00 (16.79)	19.74 (15.23)	.0718
DLQI, mean (SD)	18.48 (6.41)	18.16 (5.87)	18.79 (6.90)	.4914
Weeks of therapy at last observation, mean (SD), weeks	71.29 (47.93)	–	–	–
Presence of PsA, *n* (%), yes	143 (28.26)	71 (21.52)	72/176 (40.91)	<.0001
Family history of psoriasis, *n* (%), yes	213 (43.83)	122/312 (39.10)	91/174 (52.30)	.0049
Former smoker, *n* (%), yes	107 (33.13)	–	–	–
Naïve to systemic therapies, *n* (%), yes	57 (11.24)	31 (9.39)	26/177 (14.69)	.0720
Naïve to biologic therapies, *n* (%), yes	228 (45.97)	157 (47.58)	71 (42.77)	.3110

BMI: body mass index; BSA: body surface area; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; SD: standard deviation.

p Values were computed by means of a chi-square test (for proportion) or Wilcoxon's test (for continuous data).

†Between cohort for whom one-year data were available, vs. the not-one-year cohort.

some characteristics (Table 1). The mean baseline PASI score was significantly higher than those observed in patients not included in this analysis (16.65 ± 8.25 vs. 12.75 ± 7.18, $p < .0001$), while the presence of PsA was lower (21.52% vs. 40.91%).

However, in this patient population, there were some baseline differences between bio-naïve and bio-experienced patients. Bio-naïve patients were younger (mean 50.20 ± 15.89 vs. 53.51 ± 13.24 years, $p = .0439$), with a lower BMI (26.02 ± 4.60 vs. 27.07 ± 4.93 kg/m^2, $p = .0333$) and lower number of obese subjects (14.29% vs. 24.84%, $p = .0191$), they had a shorter disease duration (15.14 ± 10.74 vs. 18.56 ± 10.67 years, $p = .0014$), a higher baseline PASI score (18.58 ± 8.72 vs. 14.90 ± 7.40, $p < .0001$), with a higher number of patients having a PASI score >20 (41.40% vs. 22.54%, $p = .0002$), a lower rate of PsA (6.37% vs. 35.26%, $p < .0001$), a higher number of patients naïve to any systemic conventional therapy (15.92% vs. 3.47%, $p = .0001$), and a lower association with other drugs (7.01% vs. 16.18%, $p = .0099$) (Table 2).

Efficacy outcomes

In the subcohort consisting of 330 patients with potential 52-week observation, a marked reduction in PASI score with secukinumab therapy was detected, with a mean absolute PASI score that decreased to 4.87 ± 5.31 (Figure 1) at week 4, 2.68 ± 3.55 at week 12, and 1.57 ± 2.34 at week 52. This progressive reduction was also confirmed using the LOCF approach. These findings were consistent with PASI score reductions detected in patients in the overall study population for whom a post-baseline PASI score evaluation was available ($N = 508$). At week 12, absolute PASI scores of ≤1, ≤2, ≤3, and ≤5 were achieved by 36.06%, 51.81%, 65.45%, and 79.09% of patients, respectively (according to NRI approach). These percentages increase over time for absolute PASI scores of ≤1, ≤2, reaching 45.15% and 56.36% at week 52 (Figure 2).

One determinant factor affecting clinical response (i.e. absolute PASI score ≤2) was to be naïve to biologic therapies (odds ratio (OR) (95% confidence interval (CI)) at week 52: 0.106 (0.048–0.235); $p < .0001$). A significantly lower mean PASI score was detected in bio-naïve vs. bio-experienced patients at weeks 12 (2.15 ± 3.02 vs. 3.21 ± 3.94; $p = .0003$), 24 (1.28 ± 2.29 vs. 2.64 ± 3.01; $p \leq .0001$), and 52 (1.03 ± 2.20 vs. 2.15 ± 2.35; $p \leq .0001$). The proportion of patients in bio-naïve vs. bio-experienced subcohorts achieving absolute PASI scores of ≤1, ≤2, ≤3, and ≤5 is reported in Figure 2. At week 12, higher rates of bio-naïve patients compared to bio-experienced patients achieved absolute PASI score of ≤1, ≤2, ≤3, and ≤5, in 45.86% vs. 27.17%, 62.42% vs. 42.42%, 73.89% vs. 57.80%, and 84.08% vs. 74.57%, respectively, as detected by NRI imputation analysis (Figure 2).

Similarly, more bio-naïve patients achieved an absolute PASI score of ≤1, ≤2, ≤3, and ≤5 at week 24 and at week 52,

Table 2. Demographic features and baseline characteristics distinguishing bio-naïve from bio-experienced patients, with potential 52-week observational period ($N = 330$).

Characteristics	Bio-naïve patients ($N = 157$)	Bio-experienced patients ($N = 173$)	*p* Value
Age (years), mean (SD)	50.20 (15.89)	53.51 (13.24)	.0439
Bodyweight (kg), mean (SD)	78.30 (15.87)	79.99 (16.74)	.3975
BMI (kg/m^2), mean (SD)	26.55 (4.79)	27.35 (4.79)	.0315
Disease duration (years), mean (SD)	16.93 (10.82)	21.41 (14.57)	.0016
Age at diagnosis (years), mean (SD)	35.02 (16.99)	30.58 (15.85)	.0059
PASI score, mean (SD)	16.65 (8.25)	12.75 (7.18)	<.0001
BSA affected, mean (SD)	23.00 (16.79)	19.74 (15.23)	.0718
DLQI, mean (SD)	18.16 (5.87)	18.79 (6.90)	.4914
Weeks of therapy at last observation, mean (SD), weeks	–	–	–
Presence of PsA, *n* (%), yes	71 (21.52)	72/176 (40.91)	<.0001
Family history of psoriasis, *n* (%), yes	122/312 (39.10)	91/174 (52.30)	.0049
Former smoker, *n* (%), yes	–	–	–
Naïve to systemic therapies, *n* (%), yes	31 (9.39)	26/177 (14.69)	.0720
Naïve to biologic therapies, *n* (%), yes	157 (47.58)	71 (42.77)	.3110

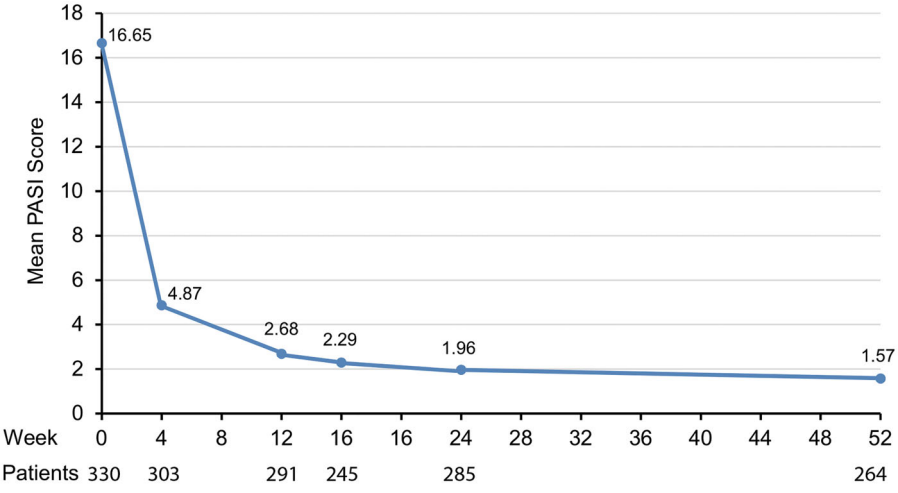

Figure 1. Change in Psoriasis Area Severity Index (PASI) score over time ('as observed' approach) in the subcohort of patients with potential 52-week observation ($N = 330$).

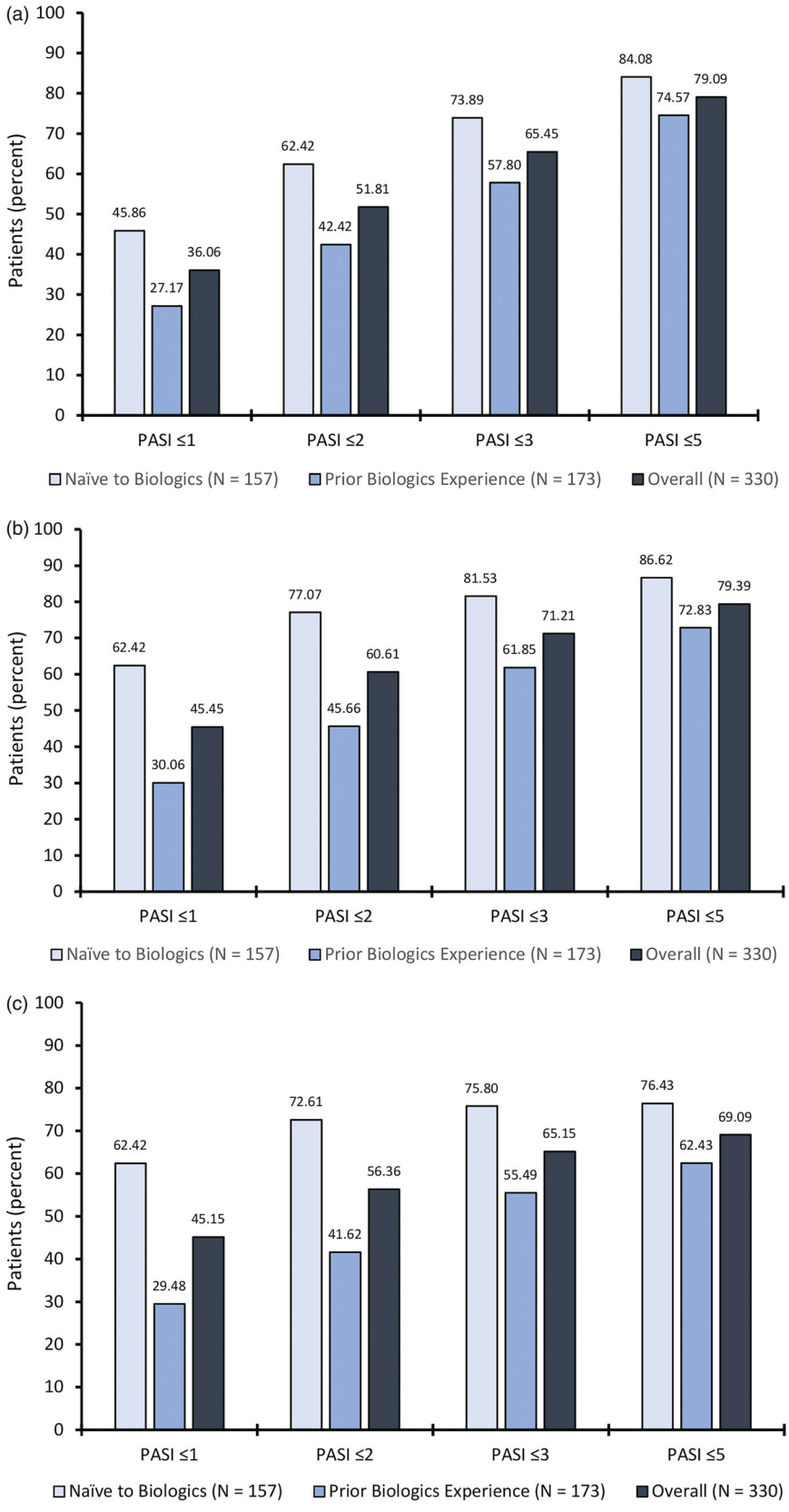

Figure 2. Proportion of patients with a Psoriasis Area Severity Index (PASI) score of $\leq$1, $\leq$2, $\leq$3, and $\leq$5 at week 12 (a), 24 (b), and 52 (c) of secukinumab treatment. Non-responder imputation (NRI) approach was applied.

compared to bio-experienced patients (week 52: 62.42% vs. 29.48%, 72.61% vs. 41.62%, 75.80% vs. 55.49%, and 76.43% vs. 62.43%, respectively) (Figure 2).

Percentages of patients with PASI 75/90/100 responses over time for the NRI population are shown in Table 3. As observed for absolute PASI score, multivariate analysis identified bio-naïve

Table 3. Relative improvements in PASI over time in patients with potential 52-week observation ($N = 330$).

Visit	PASI	Naïve to biologics $N = 157$	Prior experience of biologics $N = 173$	Overall $N = 330$	p Value†
Week 12	PASI 75	129 (82.17)	114 (65.90)	243 (73.64)	.3284
	PASI 90	79 (50.32)	48 (27.75)	127 (38.48)	.0048
	PASI 100	46 (29.30)	25 (14.45)	71 (21.52)	.0316
Week 24	PASI 75	135 (86.99)	114 (65.90)	249 (75.45)	.0186
	PASI 90	107 (68.15)	57 (32.95)	164 (49.70)	<.0001
	PASI 100	76 (48.41)	37 (21.39)	113 (34.24)	<.0001
Week 52	PASI 75	121 (77.07)	102 (58.96)	223 (67.58)	.1371
	PASI 90	108 (68.79)	52 (30.06)	160 (48.48)	<.0001
	PASI 100	75 (47.77)	31 (17.92)	106 (32.12)	<.0001

BMI: body mass index; PASI: Psoriasis Area and Severity Index.
Data are *n* (%).
†Calculated by means of a regression model taking into account the following variables: age, PASI at baseline, psoriatic arthritis, BMI, duration of psoriasis, naïve to systemic therapy and association with drug.

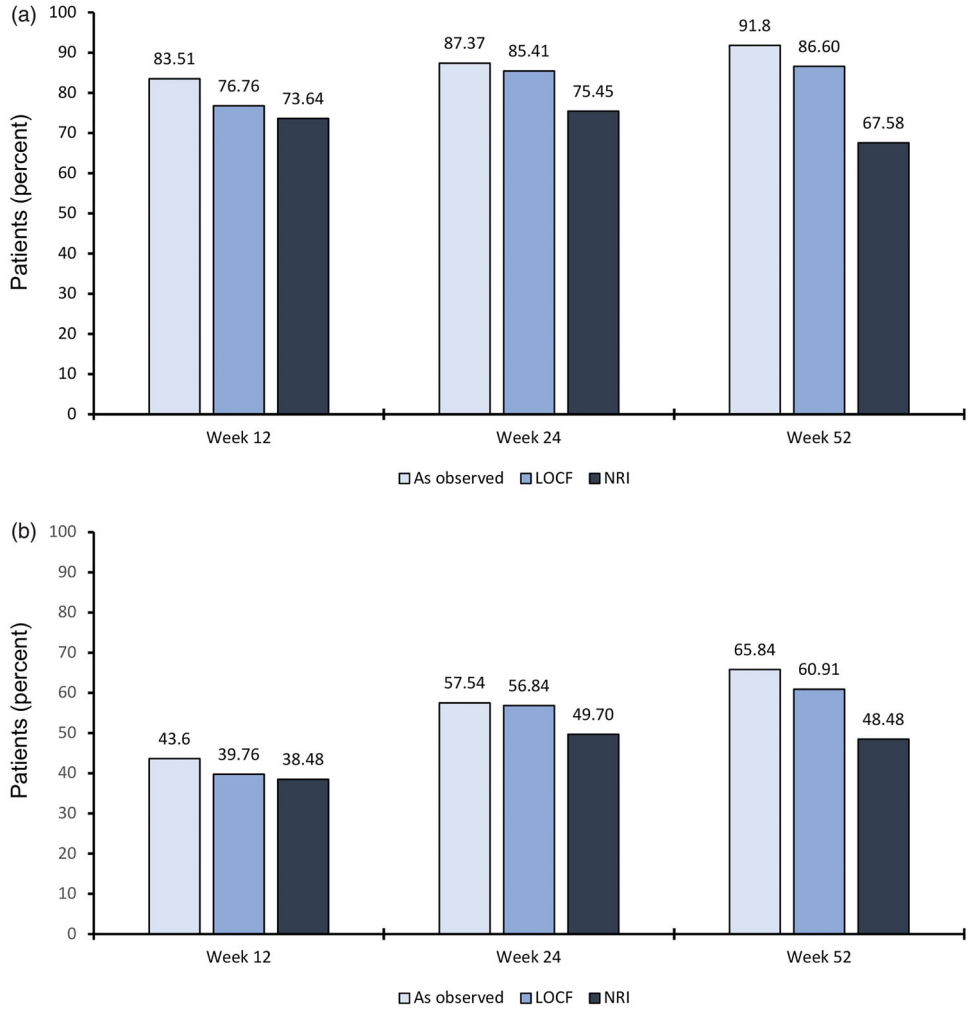

Figure 3. Proportion of (a) Psoriasis Area Severity Index (PASI) 75 and (b) PASI 90 responses over time by statistical approach. Abbreviations: LOCF: last observation carried forward; NRI: non-responder imputation.

condition as an independent predictor of high PASI reduction, with patients naïve to biologics showing greater improvements of relative PASI score over time (Table 3). In particular, at week 12, 82.17% vs. 65.90%, 50.32% vs. 27.75%, and 29.30% vs. 14.45%, of bio-naïve vs. bio-experienced patients, respectively, achieved PASI 75, 90, and 100, respectively, considering the NRI approach. Corresponding PASI responses at weeks 24 and 52 were 85.99% vs. 65.90%, 68.15% vs. 32.95%, and 48.41% vs. 21.39%, respectively, for PASI 75, 90, and 100 at week 24, and 77.07% vs. 58.96%, 68.79% vs. 30.06%, and 47.77% vs. 17.92%, respectively, for PASI 75, 90, and 100 at week 52 (Table 3).

Similar differences in treatment outcome between bio-naïve and bio-experienced patients were seen when LOCF and 'as observed' analyses were conducted (Figure 3).

In this patient subcohort ($N = 330$), the drop-out rate was 20.0% at week 52, resulting from treatment interruption caused

by inefficacy ($N = 22$, 6.7%), due to adverse events ($N = 1$, 0.3%), and by patient decision ($N = 2$, 0.6%). An additional 41 patients (12.4%) were lost to follow-up.

Discussion

Although secukinumab has been shown to be well tolerated and effective in treating patients with plaque psoriasis and PsA in multiple clinical trials (7–9,29–34) with up to 5-year follow up (35), randomized controlled trials are likely to enroll patient populations with more stringent inclusion/exclusion criteria and generally the study design allows a short-term observation compared to the real-world setting.

A variety of real-world studies have been recently published: some of them analyzed secukinumab drug survival (36–39), whereas others assessed its efficacy in psoriasis patient populations with peculiar features, or assessing its effectiveness as improvement of DLQI, BSA, PGA, and PASI scores (11–24). Nevertheless, they reported favorable secukinumab safety and effectiveness in terms of mean reduction of PASI value over time, as patient rates achieving PASI 75, PASI 90, and PASI 100 responses at different timepoints, Investigator's Global Assessments or improvements in quality of life measures (11–19,22). No data on the residual absolute PASI scores of ≤ 1, ≤ 2, ≤ 3, ≤ 5 achieved by secukinumab-treated patients were reported, with the exception of Notario et al. (12). These studies confirmed secukinumab as an important treatment option for patients with moderate-to-severe plaque psoriasis confirming the solid evidence base established from randomized clinical trials. Nevertheless, greater clinical relevance has been recently attributed to the absolute PASI score compared to the relative PASI score (25–28). Different absolute PASI scores have been suggested as clinical endpoints, useful to assess clinical response to treatments (27,28). Moreover, absolute PASI values have been identified and increasingly reported as therapeutic targets in a treat-to-target strategy (25–27).

In our study, that included 11 European dermatology centers, we evaluated the effectiveness of secukinumab in a real-world setting that included a large population of patients with plaque psoriasis treated for up to 52 weeks. The study confirmed the high effectiveness of secukinumab in treating psoriasis, as demonstrated by the reduction of PASI score, in terms of both absolute and relative PASI. Currently, absolute PASI is emerging as a relevant index for assessing therapeutic response. Absolute PASI is likely to become accepted as more clinically meaningful than improvement in relative PASI score, particularly because it may better reflect the real-world evaluation of effectiveness and it could represent an important treatment goal.

In the 330 patients evaluated over an observation period of 52 weeks, mean PASI score lowered from 16.65 at baseline to 2.68, 1.96, and 1.57, after 12, 24, and 52 weeks.

These outcomes are slightly higher compared to those reported from another multicentric study assessing the effectiveness of secukinumab in terms of absolute PASI score (12). This discrepancy could be accounted for the difference in patient characteristics, as our study population showed higher proportion of bio-naïve patients (47.6% vs. 27.9% in our population vs. the population in the Notario et al. study (12)) and patients naïve to any systemic therapy (9.4% vs. 2.9%), lower rate of patients with PsA (21.5% vs. 33.1%), lower rate of obese subjects (19.6% vs. 44.9%), and lower mean BMI value (26.55 ± 4.8 vs. 30.06 ± 6.8) and a lower baseline PASI compared to those usually observed in a clinical trial. Moreover, in the Spanish multicentric study, a proportion of patients (14%, 19/136) was treated with 150 mg secukinumab, a dose that is labeled for the treatment of PsA, but that might be associated with a lower clinical response.

In our study, the multivariate analysis identified the bio-naïve condition as independent variable predicting a superior therapeutic response to secukinumab. Additionally, bio-naïve patients also presented some demographic characteristics and baseline disease features that might favorably impact on secukinumab efficacy. Indeed, in this best-responder patient subcohort, BMI was slightly lower (26.0 vs. kg/m^2), disease duration was shorter, arthritis was less observed, age was slightly lower, compared to bio-experienced (Table 2). This is in line with other reports, showing a greater and faster response to secukinumab in patients bio-naïve, younger, and with lower BMI (11,12,15). Notably, in this study, treatment response in bio-naïve patients was higher compared to bio-experienced patients who showed lower response rates, notwithstanding a higher proportion of patients with baseline PASI score ≥ 20.

In conclusion, the relevance of this study was derived from a deeper analysis of secukinumab effectiveness including both absolute PASI values and relative PASI improvements observed during secukinumab therapy. Our findings may also contribute to better characterize the patient profile of the optimal secukinumab responder as we expanded and detailed demographic features and disease characteristics that can positively affect clinical response, highlighting the relevance of patient selection in enhancing drug performance. However, there are some limitations. First, it is retrospective and can suffer from the effects of bias in the treatment and the rate of patients lost-to-follow up. Second, the observation period was limited to 52 weeks whereas other studies had longer observational periods (14,15). Third, relatively small cohort of patients was included (17,19,23).

As no single therapy can suit all psoriatic patients, as even highly effective biologic agents could fail in treating a complex disease such as psoriasis, it is crucial to identify the potentially best-responder patients in order to personalize the therapeutic approach. Future prospective studies, such as the PROSPECT study (23), may provide highly valuable outcomes to confirm these findings that could be considered are preliminary.

Disclosure statement

Dr. Chiricozzi served as advisory board member and consultant, and has received fees and speaker's honoraria or has participated in clinical trials for Abbvie, Biogen, Fresenius Kabi, Leo Pharma, Lilly, Novartis, UCB-Pharma, Sanofi, and Janssen. Dr. Piaserico served as advisory board member and has received fees and speaker's honoraria or has participated in clinical trials for Abbvie, Almirall, Fresenius Kabi, Galderma, Leo Pharma, Lilly, Novartis, UCB-Pharma, and Janssen. Dr. Conti served as advisory board member and consultant, and has received fees and speaker's honoraria or has participated in clinical trials for Abbvie, Leo Pharma, Eli Lilly, Novartis, UCB-Pharma, Pfizer, Sandoz and Janssen Cilag. Dr. Torres served as scientific consultant/speaker/clinical study investigator for AbbVie, Amgen, Boehringer Ingelheim, Biogen, Celgene, Janssen, LEO-Pharma, Eli-Lilly, MSD, Novartis, Pfizer, Samsung Bioepis, Sanofi Dr. Conrad served as scientific consultant/speaker/clinical study investigator for AbbVie, Actelion, Amgen, Celgene, Janssen, LEO Pharma, Lilly, MSD, Novartis, and Pfizer. Dr. Ferreira served as scientific consultant/speaker/clinical study investigator for AbbVie, Janssen, LEO-Pharma, Eli-Lilly, Novartis, Pfizer Dr. Leite served as scientific consultant/speaker/clinical study investigator AbbVie, Janssen, Eli-Lilly, Novartis Dr.

Mendes-Bastos served as scientific consultant/speaker/clinical study investigator for AbbVie, Pfizer, Janssen, LEO Pharma, Novartis, Sanofi, Teva, Bayer and L'Oreal. The remaining Authors stated no conflict of interests.

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