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Real-World Six- and Twelve-Month Drug Retention, Remission, and Response Rates of Secukinumab in 2,017 Patients With Psoriatic Arthritis in Thirteen European Countries

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Objective. There is a lack of real-life studies on interleukin-17 (IL-17) inhibition in psoriatic arthritis (PsA). We assessed real-life 6- and 12-month effectiveness (i.e., retention, remission, low disease activity [LDA], and response rates) of the IL-17 inhibitor secukinumab in PsA patients overall and across 1) number of prior biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), 2) years since diagnosis, and 3) European registries.

Methods. Thirteen quality registries in rheumatology participating in the European Spondyloarthritis Research Collaboration Network provided longitudinal, observational data collected as part of routine care for secondary use. Data were pooled and analyzed with Kaplan-Meier plots, log rank tests, Cox regression, and multiple linear and logistic regression analyses.

Results. A total of 2,017 PsA patients started treatment with secukinumab between 2015 and 2018. Overall secukinumab retention rates were 86% and 76% after 6 and 12 months, respectively. Crude (LUNDEX adjusted) 6-month remission/LDA (LDA including remission) rates for the 28-joint Disease Activity Index for Psoriatic Arthritis, the Disease Activity Score in 28 joints using the C-reactive protein level, and the Simplified Disease Activity Index (SDAI) were 13%/46% (11%/39%), 36%/55% (30%/46%), and 13%/56% (11%/47%), and 12-month rates were 11%/46% (7%/31%), 39%/56% (26%/38%), and 16%/62% (10%/41%), respectively. Clinical Disease Activity Index remission/LDA rates were similar to the SDAI rates. Six-month American College of Rheumatology 20%/50%/70% improvement criteria responses were 34%/19%/11% (29%/16%/9%); 12-month rates were 37%/21%/11% (24%/14%/7%). Secukinumab effectiveness was significantly better for b/tsDMARD-naive patients, similar across time since diagnosis (<2/2–4/>4 years), and varied significantly across the European registries.

Conclusion. In this large real-world study on secukinumab treatment in PsA, 6- and 12-month effectiveness was comparable to that in previous observational studies of tumor necrosis factor inhibitors. Retention, remission, LDA, and response rates were significantly better for b/tsDMARD-naive patients, were independent of time since diagnosis, and varied significantly across the European countries.

INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous inflammatory rheumatic disease affecting, e.g., peripheral joints, axial spine, skin, and entheses, with significant impact on health-related quality of life (1–3). The treatment options for PsA have improved during the last few decades with the introduction of biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) (4). Nevertheless, a recent real-world study of >14,000 patients with PsA, who started treatment with a tumor

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SIGNIFICANCE & INNOVATIONS

- Secukinumab retention, remission, low disease activity (LDA), and response rates were significantly better for biologics-naive patients after 6 as well as 12 months of treatment.
- Overall 6- and 12-month secukinumab retention rates were high; remission, LDA, and response rates were good; and overall effectiveness was comparable to that in previous observational studies of tumor necrosis factor inhibitors.
- This study is to date the largest real-world study on secukinumab effectiveness in patients with psoriatic arthritis, including 2,017 patients from 13 European national registries.
- The study documents the effectiveness of secukinumab for treatment of psoriatic arthritis in clinical practice and shows significantly better outcomes for biologics-naive patients. This may be taken into consideration in treatment decisions in routine clinical care.

necrosis factor inhibitor (TNFi), showed that less than one-half of the patients had achieved clinical remission after 6 months (5). Thus, there is an unmet need for other treatment options in patients with PsA (2,6).

The fully human IgG monoclonal interleukin-17A (IL-17A) inhibitor secukinumab was approved for use in PsA patients in the European Union in 2015 (7). Secukinumab has demonstrated good efficacy and safety in randomized controlled trials (RCTs) (8–10), whereas large observational studies on its effectiveness in patients with PsA are lacking.

Hence, the main objective of this study was to assess the overall real-life 12-month retention rate of secukinumab in PsA patients in Europe. Secondary objectives were to assess the overall 6-month secukinumab retention rate and 6- and 12-month remission, low disease activity (LDA), and response rates. These aims were assessed overall, as well as compared across number of previous b/tsDMARD treatments, time since diagnosis, and the European registries.

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PATIENTS AND METHODS

The European Spondyloarthritis Research Collaboration Network (EuroSpA RCN). The EuroSpA RCN currently includes 15 European quality registries of spondyloarthritis patients (5,11,12). The collaboration was initiated in 2016, but data collection had started as early as 1999 in some of the registries. The main aim of the collaboration is to investigate clinically relevant research questions by secondary use of prospectively collected real-life data (5,11,12). All data are anonymized in the different registries before upload to a secured central server. The data are quality checked and pooled prior to statistical analyses.

Patients. The studies in the EuroSpA collaboration are based on secondary use of real-world data already collected in the different registries, i.e., independently of the current study. In this study, we included data from PsA patients starting secukinumab for the first time between May 2015 and December 2018 in 13 countries in the EuroSpA RCN (ranked by number of patients): ARTIS (Sweden), DANBIO (Denmark), SCQM (Switzerland), GISEA (Italy), BIOBADASER (Spain), ATTRA (Czech Republic), biorx.si (Slovenia), Reuma.pt (Portugal), NOR-DMARD (Norway), ROB-FIN (Finland), ICEBIO (Iceland), RRBR (Romania), and TURKBIO (Turkey). Inclusion criteria for the current analyses were age ≥18 years at treatment initiation, a diagnosis of PsA as judged by the treating rheumatologist, and a registered start and, if relevant, stop date of secukinumab. The exclusion criterion was patients with no available clinical data.

Assessments. We included data on age, sex, time since diagnosis, current smoking status (yes/no), body mass index (kg/m^2), start and stop dates of secukinumab, previous b/tsDMARD treatment, evaluator's global assessment, patient's global assessment, pain and fatigue, C-reactive protein (CRP) level (mg/liter), erythrocyte sedimentation rate (ESR, mm/hour), 28-joint Disease Activity Index for Psoriatic Arthritis (DAPSA28) score (13), Disease Activity Score in 28 joints using the CRP level (DAS28-CRP) score (14), Clinical Disease Activity Index (CDAI) score (15), and Simplified Disease Activity Index (SDAI) score (15). The following remission/LDA and response measures were calculated at 6 and 12 months treatment: DAPSA28 remission (≤4) (13), DAPSA28 LDA (≤14) (13), DAS28-CRP remission (<2.6) (16), DAS28-CRP LDA (≤3.2) (17), CDAI remission (≤2.8) (15), CDAI LDA (≤10) (15), SDAI remission (≤3.3) (15), SDAI LDA (≤11) (15), American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) Boolean remission (18), change in DAPSA28, DAS28-CRP, CDAI, and SDAI, ACR 20%/50%/70% improvement criteria (ACR20/50/70) response (19), and EULAR response (moderate/good) (17).

Primary and secondary outcomes. Primary outcome was the overall 12-month secukinumab retention rate. Secondary outcomes were the overall 6-month secukinumab retention rate and 6- and 12-month remission, LDA, and response rates.

Statistical analyses. All statistical analyses were performed according to a predefined statistical analysis plan developed by the researchers in the EuroSpA collaboration. Descriptive statistics were performed for demographic data and baseline disease activity measures. All effectiveness analyses were compared across 1) the number of previous b/tsDMARDs (0/1/≥2), 2) years since diagnosis (<2/2–4/>4), and 3) the individual registries. Drug retention was explored by Kaplan-Meier analyses with log rank test and by Cox regression analyses adjusted for age, sex, and time since diagnosis (comparisons 1 and 3 above), or age and sex (comparison 2 above).

Remission, LDA, response rates, and change measures were compared by chi-square test, Fisher's exact test, and Kruskal-Wallis test, as appropriate, as well as by multiple linear and logistic regression analyses adjusted for age, sex, and time since diagnosis (comparisons 1 and 3 above), or age and sex (comparison 2 above), as appropriate. Multiple comparisons for the number of previous b/tsDMARDs (0/1/≥2) were performed by log rank test, chi-square test, Fisher's exact test, and Kruskal-Wallis with post hoc Dunn test, as appropriate, where *P* values were adjusted by applying the Holm's correction.

Significance of relevant groups was tested through likelihood ratio test or Wald test, as appropriate, by comparing 2 nested models. A significance level of 0.05 was used for all statistical tests. In adjusted analyses, multivariate imputation by chained equations (including 50 imputed data sets) was used for 463 patients with missing data for time since diagnosis (no missing data for age and sex). The variables used for imputing time since diagnosis were age, sex, country, and b/tsDMARD treatment series number. None of the other variables including outcome was imputed. To avoid inflating remission and response rates, these were provided both as crude values and with LUNDEX (20) adjustment, i.e., integrating clinical response and adherence to therapy in a composite value. In the Kaplan-Meier and Cox regression analyses, observations were censored by first occurrence of 1 of the following: end of registry follow-up or date of data extraction. Patients who stopped treatment due to remission or other reasons (e.g., pregnancy) were censored at the stop date to reflect that their withdrawal was not due to lack of effectiveness or adverse events. The baseline date was defined as the secukinumab treatment start date. To assess the robustness regarding the main outcomes, sensitivity analyses for patients 1) having ≥1 swollen joints (of 28) at baseline and 2) having date of data extraction at least 12 months after secukinumab treatment start were performed. Competing risk analysis was performed for a cumulative incidence curve showing withdrawal due to adverse events and lack of effectiveness. Numbers available for each of the analyses are shown in Supplementary Tables 1–7,

available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24560. Statistical analyses were performed with R, version 3.6.1.

Ethics. Approval of the study was obtained from the respective national data protection agencies and research ethical committees according to the individual legal regulatory requirements in the different registries/countries. The study was performed in accordance with the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (21).

RESULTS

We included a total of 2,017 PsA patients who started secukinumab for the first time (Table 1). The number of patients included from the different European registries varied from 30 (TURKBIO) to 657 (ARTIS). Significant heterogeneity in demographic data and baseline disease activity across the European registries was found (see Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24560). Information on doses was not registered systematically. Of 745 patients in whom doses were registered, 42% of the patients initiated secukinumab 150 mg, and 58% initiated secukinumab 300 mg.

Secukinumab retention rates. The crude 95% confidence interval secukinumab retention rates were overall 76% (74–78%) after 12 months and 86% (85–88%) after 6 months of treatment (Table 2). Secukinumab retention rates after 6 as well as 12 months of treatment were significantly higher in biologics-naive patients compared with patients previously treated with ≥2 b/tsDMARDs (Table 2 and Figure 1A). The findings were similar in 6- and 12-month adjusted Cox regression analyses (see Supplementary Table 8, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24560).

Secukinumab retention was not significantly associated with time since diagnosis, either in unadjusted or in adjusted analyses

Table 1. Demographic characteristics and baseline disease activity measures*

	All patients (n = 2,017)	b/tsDMARD naive (n = 441)	1 prior b/tsDMARD (n = 461)	≥2 prior b/tsDMARDs (n = 1,115)	*P*†
Age, years	52 (44–60)	50 (41–58)	51 (44–59)	53 (45–60)	<0.001
Men, %	43	51	46	39	<0.001
Years since diagnosis	7 (3–13)	4 (1–10)	6 (2–12)	8 (5–14)	<0.001
Current smokers, %	19	18	22	18	0.356
BMI, kg/m^2	27.5 (24.3–31.2)	28.1 (24.1–31.8)	27.3 (24.1–30.1)	27.3 (24.5–31.6)	0.309
B/tsDMARD treatment, % first (% last previous)					<0.001 (<0.001)
Adalimumab	29 (21)	–	30 (30)	28 (18)	
Certolizumab	5 (8)	–	5 (5)	5 (10)	
Etanercept	28 (22)	–	25 (25)	29 (20)	
Golimumab	10 (12)	–	9 (9)	10 (13)	
Infliximab	22 (13)	–	15 (15)	25 (12)	
Other‡	7 (24)	–	15 (15)	3 (27)	
CRP, mg/liter	5 (2–12)	7 (2–19)	4 (2–9)	5 (2–12)	<0.001
ESR, mm/hour	16 (7–31)	20 (8–36)	13 (6–27)	16 (7–30)	0.002
TJC28	4 (1–9)	5 (1–10)	3 (1–8)	4 (1–9)	<0.001
SJC28	1 (0–4)	2 (0–6)	1 (0–3)	2 (0–4)	<0.001
Patient global score	70 (50–83)	70 (51–84)	67 (42–80)	70 (50–85)	<0.001
Pain score	66 (46–80)	65 (45–78)	62 (40–78)	68 (48–81)	<0.001
Fatigue score	70 (50–85)	65 (50–80)	65 (41–80)	73 (55–87)	<0.001
Evaluator global score	40 (20–60)	57 (30–75)	35 (20–50)	35 (20–50)	<0.001
HAQ score	1.1 (0.6–1.6)	1.0 (0.5–1.5)	1.0 (0.5–1.4)	1.2 (0.8–1.8)	<0.001
DAPSA28 score	25.9 (17.4–37.6)	29.1 (19.1–41.9)	22.3 (13.5–32.4)	26.2 (18.0–37.6)	<0.001
DAS28-CRP score	4.2 (3.2–5.0)	4.5 (3.6–5.4)	3.8 (2.7–4.6)	4.2 (3.3–5.0)	<0.001
SDAI score	19.5 (12.9–28.9)	24.4 (15.3–35.4)	16.9 (10.0–24.3)	18.9 (13.0–27.5)	<0.001
CDAI score	18.0 (12.0–26.7)	22.6 (14.3–33.9)	16.0 (8.9–23.6)	17.5 (12.0–25.4)	<0.001

* Values are the median (interquartile range) unless indicated otherwise. Numbers available for each of the analyses are shown in Supplementary Table 5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24560. b/tsDMARD = biologic/targeted synthetic disease-modifying antirheumatic drug; BMI = body mass index; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAPSA28 = 28-joint Disease Activity Index for Psoriatic Arthritis; DAS28-CRP = Disease Activity Score in 28 joints using the CRP level; ESR = erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire; SDAI = Simplified Disease Activity Index; SJC28 = Swollen joint count in 28 joints; TJC28 = Tender joint count in 28 joints.
† Comparisons between b/tsDMARD-naive patients and 1 prior and ≥2 prior b/tsDMARD-treated patients were performed with Kruskal-Wallis or chi-square test, as appropriate.
‡ Other previous b/tsDMARDs include ustekinumab, rituximab, abatacept, tocilizumab, apremilast, anakinra, and additionally (never as first b/tsDMARD) baricitinib and tofacitinib. Patients were included between May 2015 and December 2018.

Table 2. Treatment effectiveness after 6 and 12 months of secukinumab treatment (unadjusted analyses)*

	All patients (n = 2,017)	b/tsDMARD naive (n = 441)	1 prior b/tsDMARD (n = 461)	≥2 prior b/tsDMARDs (n = 1,115)	P†
Secukinumab drug retention rate, % (95% CI)					
6 months	86 (85–88)	90 (87–93)	86 (83–90)	85 (83–87)	0.045§
12 months	76 (74–78)	82 (78–86)	78 (74–82)	72 (70–75)	0.001§
Time in weeks to secukinumab withdrawal before 12 months due to the following‡					
Primary and secondary lack of effectiveness	24 (17, 33)	24 (17, 35)	24 (17, 30)	24 (17, 34)	0.691
Adverse events	14 (6, 28)	22 (13, 28)	15 (7, 25)	12 (5, 29)	0.395
Remission	21 (20, 43)	20 (19, 20)	–	43 (32, 43)	0.236
Other reasons	21 (12, 32)	27 (15, 40)	10 (4, 36)	21 (15, 27)	0.161
DAPSA28 score					
6 months	15.1 (8.2, 25.0)	10.1 (5.2, 17.5)	15.7 (9.0, 22.0)	16.9 (9.6, 27.1)	<0.001¶
12 months	14.9 (8.1, 24.8)	10.2 (4.1, 16.3)	15.2 (8.4, 23.6)	16.3 (10.0, 26.0)	<0.001¶
DAS28-CRP score					
6 months	3.0 (2.2, 4.0)	2.5 (1.9, 3.3)	3.1 (2.2, 3.9)	3.2 (2.4, 4.2)	<0.001#
12 months	3.0 (2.2, 4.0)	2.5 (1.7, 3.3)	3.0 (2.1, 3.9)	3.2 (2.4, 4.2)	<0.001¶
SDAI score					
6 months	10.2 (5.4, 16.7)	6.9 (3.5, 11.0)	10.4 (6.3, 15.3)	11.4 (6.6, 18.5)	<0.001¶
12 months	9.2 (5.2, 15.2)	5.7 (2.5, 9.5)	9.3 (5.8, 16.2)	10.5 (6.8, 16)	<0.001¶
CDAI score					
6 months	9.3 (4.9, 15.9)	6.2 (3.4, 10.5)	9.4 (5.5, 14.4)	10.9 (6.0, 17.8)	<0.001#
12 months	8.5 (4.4, 14.2)	5.1 (2.1, 9.3)	8.7 (5.2, 14.6)	9.8 (5.8, 14.9)	<0.001¶
Change in DAPSA28 score from baseline					
6 months	−9.5 (−20.7, −0.2)	−17.2 (−27.5, −8.3)	−8.5 (−17.6, −0.1)	−6.6 (−18.3,0.3)	<0.001¶
12 months	−10.3 (−21.9, −1.3)	−16.2 (−28.0, −8.3)	−5.0 (−10.6,1.0)	−10.3 (−21.9, −0.2)	<0.001#
Change in DAS28-CRP score from baseline					
6 months	−0.9 (−1.9, −0.1)	−2.0 (−3.0, −1.1)	−0.8 (−1.7, 0.1)	−0.6 (−1.6, 0.01)	<0.001¶
12 months	−1.1 (−2.0, −0.1)	−1.9 (−3.1, −1.0)	−0.5 (−1.3, 0.03)	−1.0 (−1.9, −0.02)	<0.001#
Change in SDAI score from baseline					
6 months	−8.9 (−17.4, −2.0)	−16.9 (−26.1, −9.3)	−7.5 (−13.5, −1.1)	−6.0 (−13.4, −0.2)	<0.001¶
12 months	−9.7 (−18.6, −2.4)	−15.0 (−24.2, −7.5)	−4.9 (−10.4, 1.3)	−9.6 (−17.9, −2.2)	<0.001#
Change in CDAI score from baseline					
6 months	−8.0 (−16.1, −1.6)	−15.1 (−24.6, −8.0)	−6.0 (−13.1, −1.4)	−5.3 (−12.2, −0.1)	<0.001¶
12 months	−8.8 (−16.0, −2.0)	−13.9 (−21.5, −7.3)	−5.0 (−10.4, 0.8)	−8.1 (−15.9, −1.5)	<0.001#
DAPSA28 score ≤4, %					
6 months					
Crude	13	23	13	10	<0.001§
LUNDEX adjusted‡	11	20	11	8	<0.001¶
12 months					
Crude	11	22	11	8	<0.001¶
LUNDEX adjusted‡	7	17	7	5	<0.001§
DAPSA28 score ≤14, %					
6 months					
Crude	46	64	45	41	<0.001¶
LUNDEX adjusted‡	39	57	37	34	<0.001¶
12 months					
Crude	46	70	46	40	<0.001¶
LUNDEX adjusted‡	31	52	30	26	<0.001¶
DAS28-CRP score <2.6, %					
6 months					
Crude	36	53	35	30	<0.001¶
LUNDEX adjusted‡	30	47	29	25	<0.001¶
12 months					
Crude	39	55	41	34	<0.001¶
LUNDEX adjusted‡	26	41	27	21	<0.001¶
DAS28-CRP score ≤3.2, %					
6 months					
Crude	55	71	57	49	<0.001¶
LUNDEX adjusted‡	46	63	47	40	<0.001¶
12 months					
Crude	56	72	55	51	<0.001¶
LUNDEX adjusted‡	38	54	37	33	<0.001¶

(Continued)

Table 2. (*Cont'd*)

	All patients (n = 2,017)	b/tsDMARD naive (n = 441)	1 prior b/tsDMARD (n = 461)	≥2 prior b/tsDMARDs (n = 1,115)	*P*†
SDAI score ≤3.3, %					
6 months					
Crude	13	24	13	9	<0.001¶
LUNDEX adjusted‡	11	21	11	8	<0.001¶
12 months					
Crude	16	32	11	11	<0.001¶
LUNDEX adjusted‡	10	24	8	7	<0.001¶
SDAI score ≤11, %					
6 months					
Crude	56	75	56	48	<0.001¶
LUNDEX adjusted‡	47	66	47	39	<0.001¶
12 months					
Crude	62	81	58	56	<0.001¶
LUNDEX adjusted‡	41	61	39	36	<0.001¶
CDAI score ≤2.8, %					
6 months					
Crude	13	19	12	10	0.004§
LUNDEX adjusted‡	10	17	10	8	0.002§
12 months					
Crude	16	32	14	11	<0.001¶
LUNDEX adjusted‡	11	24	10	7	<0.001¶
CDAI score ≤10, %					
6 months					
Crude	55	74	58	46	<0.001¶
LUNDEX adjusted‡	46	66	48	38	<0.001¶
12 months					
Crude	59	79	58	53	<0.001¶
LUNDEX adjusted‡	40	59	39	34	<0.001¶
ACR/EULAR Boolean remission, %					
6 months					
Crude	9	20	8	6	<0.001¶
LUNDEX adjusted‡	8	18	6	5	<0.001¶
12 months					
Crude	9	17	9	6	<0.001§
LUNDEX adjusted‡	6	12	6	4	<0.001§
ACR20 response, %					
6 months					
Crude	34	59	26	27	<0.001¶
LUNDEX adjusted‡	29	52	22	22	<0.001¶
12 months					
Crude	37	63	16	33	<0.001¶
LUNDEX adjusted‡	24	47	10	21	<0.001¶
ACR50 response, %					
6 months					
Crude	19	41	11	13	<0.001¶
LUNDEX adjusted‡	16	36	9	11	<0.001¶
12 months					
Crude	21	45	4	16	<0.001¶
LUNDEX adjusted‡	14	34	3	10	<0.001¶
ACR70 response, %					
6 months					
Crude	11	26	7	6	<0.001¶
LUNDEX adjusted‡	9	23	6	5	<0.001¶
12 months					
Crude	11	28	4	6	<0.001¶
LUNDEX adjusted‡	7	21	3	4	<0.001¶
EULAR good/moderate response, %					
6 months					
Crude	59	83	57	50	<0.001¶
LUNDEX adjusted‡	49	74	48	41	<0.001¶

(Continued)

Table 2. (*Cont'd*)

	All patients (n = 2,017)	b/tsDMARD naive (n = 441)	1 prior b/tsDMARD (n = 461)	≥2 prior b/tsDMARDs (n = 1,115)	*P*†
12 months					
Crude	60	79	44	59	<0.001¶
LUNDEX adjusted‡	40	59	30	38	<0.001¶

* Values are the median (interquartile range) unless indicated otherwise. Numbers available for each of the analyses are shown in Supplementary Table 6, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24560. 95% CI = 95% confidence interval; ACR = American College of Rheumatology; ACR20/50/70 = ACR 20%/50%/70% improvement criteria; b/tsDMARD = biologic/targeted synthetic disease-modifying antirheumatic drug; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAPSA28 = 28-joint Disease Activity Index for Psoriatic Arthritis; DAS28-CRP = Disease Activity Score in 28 joints using the CRP level; EULAR = European Alliance of Associations for Rheumatology; SDAI = Simplified Disease Activity Index.
† Drug retention rates were compared across the 3 groups with Kaplan-Meier with log rank test, continuous measures by Kruskal-Wallis test, and proportions by chi-square test or Fisher's exact test, as appropriate. Multiple comparisons between groups were conducted by log rank test, Kruskal-Wallis with post hoc Dunn test, chi-square test, or Fisher's exact test, as appropriate, with *P* values to be adjusted by applying the Holm's correction.
‡ Patients with at least 12 months from secukinumab start to date of data extraction. Patients who stopped treatment due to remission or other reasons (e.g., pregnancy) were censored at the stop date to reflect that their withdrawal was not due to lack of effectiveness or adverse events.
§ Statistically significant difference between b/tsDMARD-naive patients and patients treated with ≥2 prior b/tsDMARDs.
¶ Statistically significant difference between b/tsDMARD-naive patients and patients treated with 1 prior b/tsDMARD. Statistically significant difference between b/tsDMARD-naive patients and patients treated with ≥2 prior b/tsDMARDs.
# Statistically significant difference between b/tsDMARD-naive patients and patients treated with 1 prior b/tsDMARD. Statistically significant difference between b/tsDMARD-naive patients and patients treated with ≥2 prior b/tsDMARDs. Statistically significant difference between patients treated with 1 prior b/tsDMARD and ≥2 prior b/tsDMARDs. Significance level for all tests is 0.05.

(see Supplementary Tables 2 and 8). The number of included patients varied considerably across the European registries (from 30 to 657 patients). Significant differences in retention rates across the registries were observed, with 6-month retention rates varying between 80% (DANBIO) and 97% (TURKBIO), and 12-month retention rates varying from 51% (ROB-FIN) to 92% (RRBR and ATTRA) (Table 3 and Figure 2). Similar differences were found in adjusted analyses (see Supplementary Table 8).

Remission. Crude and LUNDEX-adjusted proportions of patients achieving DAPSA28, DAS28-CRP, SDAI, and CDAI remission after 6 and 12 months are presented in Table 2. DAPSA28, SDAI, and CDAI remission rates were similar (~10–15%), whereas approximately one-third of the patients achieved DAS28-CRP remission.

The proportion of patients achieving remission was significantly higher in biologics-naive patients than in patients previously treated with 1 and ≥2 b/tsDMARDs (Table 2, Figure 3, and Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24560). Adjusted analyses gave similar results (see Supplementary Table 9, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24560).

Crude and adjusted remission rates at 6 and 12 months of treatment were independent of time since diagnosis (see Supplementary Tables 2 and 9). Overall, heterogeneity in crude and adjusted remission rates across the European registries was found (Table 3 and Supplementary Table 7).

LDA (including remission). Crude and LUNDEX-adjusted proportions of patients achieving DAPSA28, DAS28-CRP, SDAI, and CDAI LDA after 6 and 12 months of treatment are presented in Table 2, Figure 3, and Supplementary Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24560/abstract. Overall, crude and LUNDEX-adjusted LDA rates were significantly higher in biologics-naive patients, also in adjusted analyses (see Supplementary Table 9).

For all outcomes, achievement of LDA was independent of time since diagnosis (see Supplementary Table 2), also after adjustment (see Supplementary Table 9). Significant heterogeneities in crude (Table 3) and adjusted (see Supplementary Table 9) LDA rates were seen between the registries.

Response rates. ACR20/50/70 responses were achieved by 34%/19%/11% of the patients, and EULAR moderate/good response by 59% of the patients after 6 months. After 12 months, numbers were largely the same (Table 2). Changes in outcome measures from baseline to 6 months (and 12 months, respectively) were as follows: DAPSA28 –9.5 (–10.3), DAS28-CRP –0.9 (–1.1), SDAI –8.9 (–9.7), and CDAI –8.0 (–8.8).

Significantly better outcomes for ACR20/50/70 and EULAR moderate/good responses were observed for biologics-naive patients (Table 2, Figure 3, and Supplementary Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24560/abstract), also after adjustment (see Supplementary Table 9).

Response rates were independent of time since diagnosis (see Supplementary Table 2), also in adjusted analyses (see Supplementary Table 9). Significant heterogeneity in response rates between the European registries was found in crude as well as adjusted analyses (Table 3 and Supplementary Table 9).

Safety. Of the 2,017 patients starting secukinumab, 1,543 patients started treatment at least 12 months before date of data

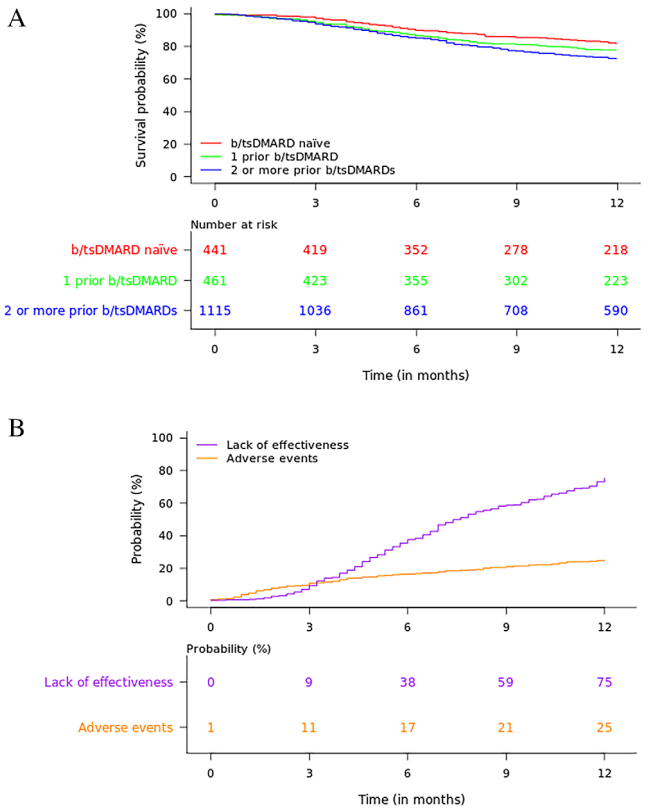

Figure 1. **A**, Pooled 12-month secukinumab retention rates stratified by number of previous biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) (Kaplan-Meier curve with log rank test; $P = 0.001$). **B**, Cumulative incidence curve for withdrawal of secukinumab due to adverse events and lack of effectiveness.

extraction. Of these 1,543 patients, 602 patients withdrew from secukinumab before 12 months, of whom 107 patients withdrew due to adverse events. Time in weeks to secukinumab withdrawal for these 107 patients was similar across number of previous b/tsDMARDs (0/1/≥2) (Table 2). More patients withdrew from secukinumab due to lack of effectiveness than due to adverse events (Table 2). The cumulative incidence curve, which estimates the cumulative probabilities of treatment withdrawal over time, shows that the cumulative probability of withdrawal due to lack of effectiveness is higher than adverse events after ~4 months of treatment (Figure 1B).

Sensitivity analyses. Sensitivity analyses of 976 patients with ≥1 swollen joint (of 28) at the start of secukinumab treatment showed largely similar results to the analyses in Table 2 (see Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24560). Sensitivity analyses of patients with secukinumab initiation at least 12 months before date of data extraction also showed largely similar results but did not reach significance for the 6-month comparison of retention rates across number of previous b/tsDMARDs (b/tsDMARD naive: 89% [86–93%]; 1 prior b/tsDMARD: 85% [81–89%]; ≥2 prior b/tsDMARDs: 85% [82–87%]; $P = 0.107$ [see Supplementary Table 4]).

DISCUSSION

This large real-life study of secukinumab effectiveness (i.e., drug retention, remission, LDA, and response rates) included 2,017 patients with PsA treated as part of routine care in 13 countries across Europe. Overall, high 6-month (86%) and 12-month (76%) secukinumab retention rates were found. Secukinumab effectiveness was significantly better for biologics-naive patients after 6 as well as 12 months of treatment, was independent of time since diagnosis, and differed significantly across the European countries. Remission, LDA, and response rates were overall comparable to previous real-life observations in patients treated with a TNFi (5). Hence, this large observational study documents the effectiveness of secukinumab in the treatment of PsA patients.

Secukinumab effectiveness has previously been reported in one observational study of 76 Spanish PsA patients, in which 12-month retention rates were somewhat higher than in our study; for biologics-naive patients, it was 91%, and for non-naive patients, it was 82% (22). Good 1-year secukinumab effectiveness has also been reported in an Italian observational study of 130 PsA patients (23). In the FUTURE 1 RCT, 89% of the patients in the 150-mg secukinumab group reached 52 weeks, and ACR20/50 responses at week 24 and 52 were achieved by 50%/35% and 60%/43% of the patients, respectively (24). In our observational study, ACR20/50 responses at week 26 and 52 were lower than in the FUTURE 1 study (34%/19% and 37%/21%), probably reflecting that the study designs differed substantially (longitudinal observational study with 22% biologics-naive patients versus RCT with 71% biologics-naive patients). In the FUTURE 5 RCT, 91% of the patients treated with 150 mg of secukinumab completed 52 weeks of treatment, with ACR20/50/70 responses of 64%/41%/26%, thus substantially higher than in our study (10).

Interestingly, the overall secukinumab retention rates in this real-life study were similar to the retention rates of TNFi in a recently published observational study of 14,261 European biologics-naive PsA patients (86% versus 86% at 6 months; 76% versus 77% at 12 months, respectively) and numerically slightly higher for biologics-naive secukinumab than TNFi starters (90% versus 86% at 6 months, and 82% versus 77% at 12 months, respectively) (5). Overall, remission and response rates for patients treated with secukinumab were fairly similar to what was reported for TNFi (5) as well as to the effectiveness of TNFi reported in other, smaller observational studies (25–28).

Similar to findings in observational studies on TNFi, and in the FUTURE 2 and 5 trials, the current study demonstrated that effectiveness of secukinumab declines with increasing previous use of

Table 3. Retention, remission, low disease activity (including remission), and response rates after 6 and 12 months of secukinumab treatment across European observational registries (unadjusted analyses)*

	ARTIS (n = 657)	ATTRA (n = 151)	BIO-BADASER (n = 154)	Biorx.si (n = 79)	DANBIO (n = 313)	GISEA (n = 180)	ICEBIO (n = 38)	NOR-DMARD (n = 60)	Reuma.pt (n = 68)	ROB-FIN (n = 47)	RRBR (n = 37)	SCQM (n = 203)	TURKBIO (n = 30)	P†
Drug retention rate, % (95% CI)														
6 months	82 (79–85)	94 (90–98)	93 (89–97)	92 (87–98)	80 (75–84)	96 (93–99)	87 (77–98)	83 (74–94)	91 (84–98)	83 (73–94)	92 (83–100)	90 (85–94)	97 (90–100)	<0.001
12 months	66 (62–70)	92 (88–97)	84 (78–91)	89 (82–96)	70 (65–76)	88 (82–93)	77 (64–93)	72 (61–86)	86 (78–96)	51 (39–68)	92 (83–100)	82 (77–88)	–	<0.001
DAPSA28 score ≤4														
6 months														
Crude	8	22	–	11	12	–	0	14	14	19	–	35	21	<0.001
LUNDEX	6	21	–	10	9	–	0	12	13	16	–	31	–	<0.001
12 months														
Crude	6	23	–	10	14	–	NC	16	16	NC	–	15	NC	0.004
LUNDEX	3	20	–	9	9	–	NC	11	14	NC	–	12	–	0.002
DAPSA28 score ≤14														
6 months														
Crude	37	61	–	53	44	–	42	61	54	54	–	58	74	<0.001
LUNDEX	30	58	–	49	33	–	35	50	49	45	–	51	–	<0.001
12 months														
Crude	35	79	–	48	46	–	NC	68	63	NC	–	59	NC	<0.001
LUNDEX	19	67	–	42	29	–	NC	49	55	NC	–	47	–	<0.001
DAS28-CRP score <2.6														
6 months														
Crude	27	46	50	40	33	–	29	54	45	42	60	49	63	<0.001
LUNDEX	21	44	44	37	25	–	24	44	41	35	52	43	–	<0.001
12 months														
Crude	25	62	49	46	41	–	50	63	50	NC	NC	41	NC	<0.001
LUNDEX	14	53	36	41	26	–	37	45	44	NC	NC	33	–	<0.001
DAS28-CRP score ≤3.2														
6 months														
Crude	45	62	69	64	53	–	64	79	64	73	73	60	74	<0.001
LUNDEX	36	58	60	59	40	–	54	64	58	61	64	53	–	<0.001
12 months														
Crude	43	80	73	60	54	–	75	68	80	NC	NC	76	NC	<0.001
LUNDEX	23	69	54	52	34	–	55	49	70	NC	NC	61	–	<0.001
SDAI score ≤3.3														
6 months														
Crude	6	21	–	16	12	–	0	10	18	21	24	21	21	0.003
LUNDEX	5	20	–	15	9	–	0	8	16	17	21	18	–	0.003
12 months														
Crude	8	32	–	23	14	–	NC	25	5	NC	NC	15	NC	0.002
LUNDEX	4	27	–	20	8	–	NC	18	4	NC	NC	12	–	<0.001

(Continued)

Table 3. (*Cont'd*)

	ARTIS (n = 657)	ATTRA (n = 151)	BIO-BADASER (n = 154)	Biorx.si (n = 79)	DANBIO (n = 313)	GISEA (n = 180)	ICEBIO (n = 38)	NOR-DMARD (n = 60)	Reuma.pt (n = 68)	ROB-FIN (n = 47)	RRBR (n = 37)	SCQM (n = 203)	TURKBIO (n = 30)	*P*†
SDAI score ≤11														
6 months														
Crude	42	68	–	58	54	–	46	67	64	67	76	65	74	<0.001
LUNDEX	33	64	–	53	41	–	39	54	58	55	66	57	–	<0.001
12 months														
Crude	50	88	–	56	55	–	NC	83	85	NC	NC	67	NC	<0.001
LUNDEX	27	75	–	49	35	–	NC	59	74	NC	NC	53	–	<0.001
CDAI score ≤2.8														
6 months														
Crude	6	18	–	12	14	–	0	9	11	12	20	23	21	0.007
LUNDEX	5	17	–	11	10	–	0	7	10	10	17	21	–	0.008
12 months														
Crude	8	31	–	19	14	-	14	25	10	NC	NC	23	NC	0.003
LUNDEX	4	27	–	17	9	–	10	18	9	NC	NC	18	–	<0.001
CDAI score ≤10														
6 months														
Crude	41	68	–	60	53	–	41	59	64	62	76	64	74	<0.001
LUNDEX	33	64	–	55	40	–	35	48	58	52	66	56	–	<0.001
12 months														
Crude	44	88	–	58	56	–	57	83	80	NC	NC	63	NC	<0.001
LUNDEX	24	75	–	51	35	–	42	59	70	NC	NC	50	–	<0.001
ACR/EULAR Boolean remission														
6 months														
Crude	5	22	18	9	9	0	0	8	6	12	23	15	16	<0.001
LUNDEX	4	21	15	8	7	0	0	7	6	10	20	13	–	<0.001
12 months														
Crude	5	24	15	7	9	0	5	10	8	15	NC	7	NC	<0.001
LUNDEX	3	21	11	7	6	0	4	7	7	8	NC	5	–	<0.001
ACR20 response														
6 months														
Crude	24	55	–	59	25	–	NC	NC	56	–	–	NC	22	<0.001
LUNDEX	20	51	–	54	19	–	NC	NC	51	–	–	18	–	<0.001
12 months														
Crude	27	67	–	50	24	–	NC	NC	NC	–	–	NC	NC	<0.001
LUNDEX	14	58	–	44	15	–	NC	NC	NC	–	–	24	–	<0.001
ACR50 response														
6 months														
Crude	11	36	–	38	12	–	NC	NC	31	–	–	NC	11	<0.001
LUNDEX	9	34	–	35	9	–	NC	NC	28	–	–	NC	–	<0.001
12 months														
Crude	15	45	–	35	11	–	NC	NC	NC	–	–	NC	NC	<0.001
LUNDEX	8	39	–	30	7	–	NC	NC	NC	–	–	NC	–	<0.001

(Continued)

Table 3. (*Cont'd*)

	ARTIS (n = 657)	ATTRA (n = 151)	BIO-BADASER (n = 154)	Biorx.si (n = 79)	DANBIO (n = 313)	GISEA (n = 180)	ICEBIO (n = 38)	NOR-DMARD (n = 60)	Reuma.pt (n = 68)	ROB-FIN (n = 47)	RRBR (n = 37)	SCQM (n = 203)	TURKBIO (n = 30)	*P*†
ACR70 response														
6 months														
Crude	6	21	–	21	7	–	NC	NC	19	–	–	NC	11	0.010
LUNDEX	4	20	–	19	6	–	NC	NC	17	–	–	NC	–	0.001
12 months														
Crude	5	24	–	31	5	–	NC	NC	NC	–	–	NC	NC	0.002
LUNDEX	3	20	–	27	3	–	NC	NC	NC	–	–	NC	–	0.001
EULAR good/moderate response														
6 months														
Crude	50	88	69	83	50	–	NC	55	62	47	93	NC	39	<0.001
LUNDEX	40	82	61	76	38	–	NC	45	56	39	81	NC	–	<0.001
12 months														
Crude	48	93	63	77	60	–	NC	43	83	NC	NC	64	NC	<0.001
LUNDEX	26	79	47	68	37	–	NC	30	73	NC	NC	50	–	<0.001

* Values are the percentage unless indicated otherwise. Numbers available for each of the analyses are shown in Supplementary Table 7. Registries and countries are as follows: ARTIS (Sweden), DANBIO (Denmark), SCQM (Switzerland), GISEA (Italy), BIOBADASER (Spain), ATTRA (Czech Republic), biorx.si (Slovenia), Reuma.pt (Portugal), NOR-DMARD (Norway), ROB-FIN (Finland), ICEBIO (Iceland), RRBR (Romania), and TURKBIO (Turkey). 95% CI = 95% confidence interval; ACR = American College of Rheumatology; ACR20/50/70 = ACR 20%/50%/70% improvement criteria; CDAI = Clinical Disease Activity Index; DAPSA28 = 28-joint Disease Activity Index for Psoriatic Arthritis; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; EULAR = European Alliance of Associations for Rheumatology; NC = not calculated (because data from <10 patients available); SDAI = Simplified Disease Activity Index.

† Comparisons between the registries were performed with Kaplan-Meier with log rank test for retention rates and chi-square test or Fisher's exact test for remission and response rates, as appropriate.

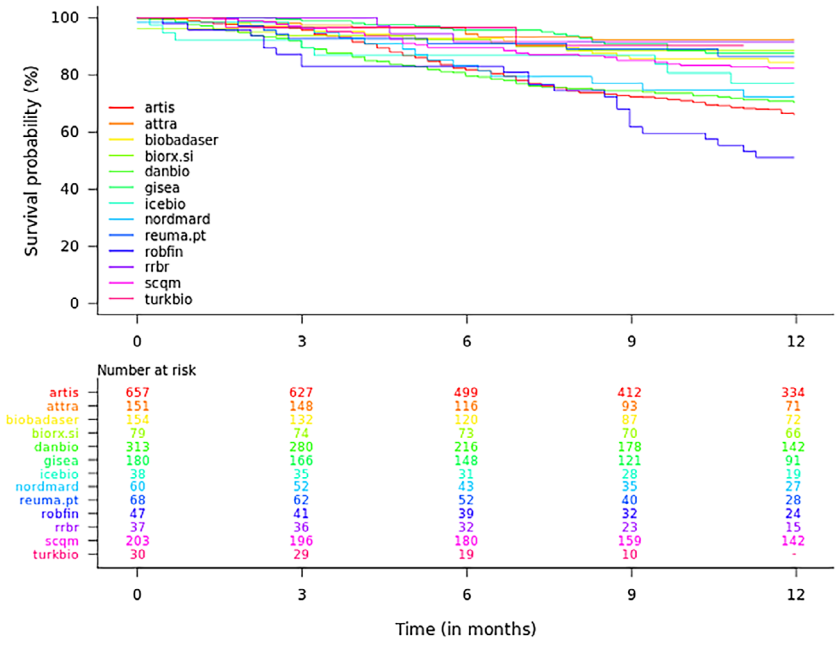

Figure 2. Twelve-month secukinumab retention rates compared across the European registries (Kaplan-Meier curve with log rank test; $P < 0.001$). Registries and countries are as follows: ARTIS (Sweden), DANBIO (Denmark), SCQM (Switzerland), GISEA (Italy), BIOBADASER (Spain), ATTRA (Czech Republic), biorx.si (Slovenia), Reuma.pt (Portugal), NOR-DMARD (Norway), ROB-FIN (Finland), ICEBIO (Iceland), RRBR (Romania), and TURKBIO (Turkey).

b/tsDMARDs, possibly reflecting confounding by indication (9,27,29,30). The similar secukinumab effectiveness for patients with different disease durations found in this study is also in accordance with previous findings for TNFi in patients with PsA (31–33).

In the 2017 updated treat-to-target recommendations for PsA, the DAPSA and minimal disease activity (MDA) are the preferred measures to define treatment target in PsA patients (34). In our study, the DAPSA (including a 66 swollen/68 tender joint count) (35) was only available in a minority of patients. Instead, we used the DAPSA28, which only requires a 28-joint count (13). The DAPSA28 has shown good criterion, correlational, and construct validity, as well as sensitivity to change, although the original DAPSA should be preferred when available (13). MDA was not assessed in the study due to lack of data on enthesitis and psoriasis in the majority of registries.

We chose the DAS28-CRP over the DAS28-ESR due to less missing data for the DAS28-CRP. Overall, the DAS28-CRP was a more liberal remission criterion than the SDAI, the CDAI, and the DAPSA28 in our study, which is consistent with previous reports (5,12,36,37). In the DAPSA28, SDAI, and CDAI LDA measures, we chose to include remission in accordance with the DAS28 LDA, as we believe that rheumatologists will be mainly interested in knowing how many patients at least were in LDA (i.e., in LDA or remission).

The major strength of this study is the 12-month longitudinal, observational study design with inclusion of a high number of PsA patients from 13 different countries. Furthermore, the data included in the study were collected independently of commercial interests as part of standard care. Hence, although Novartis supports the EuroSpA collaboration, Novartis had no influence on data collection, statistical analyses, manuscript preparation, or the decision to submit. Major limitations of the study include lack of data on extraarticular inflammatory involvement and the fact that data on the optimal number of joints (66/68) were generally not available, which may have led to underestimation of disease activity. Furthermore, the DAS28, the CDAI, and the SDAI are composite scores originally developed for RA and not PsA.

Heterogeneity in baseline characteristics and secukinumab effectiveness across the registries was found. Importantly, the number of included patients (from 30 to 657) and proportions of biologics-naive patients (from 5% to 97%) varied considerably across the registries and may explain some of the heterogeneity in effectiveness measures, e.g., a higher proportion of biologics-naive patients may positively impact upon treatment outcomes. Moreover, low patient numbers in some registries will lead to more uncertain estimates, i.e., single patients will have a higher influence on outcomes. Also, the influence of different treatment guidelines and access to treatment in the different European countries were not accounted for in this study. Hence, interpretation of the pooled analyses should be done with caution. Of note, however, consistent results in prespecified unadjusted and adjusted analyses were found.

Furthermore, as is often the case in observational studies, some missing data on disease states and response rates were observed, challenging the generalizability of the findings.

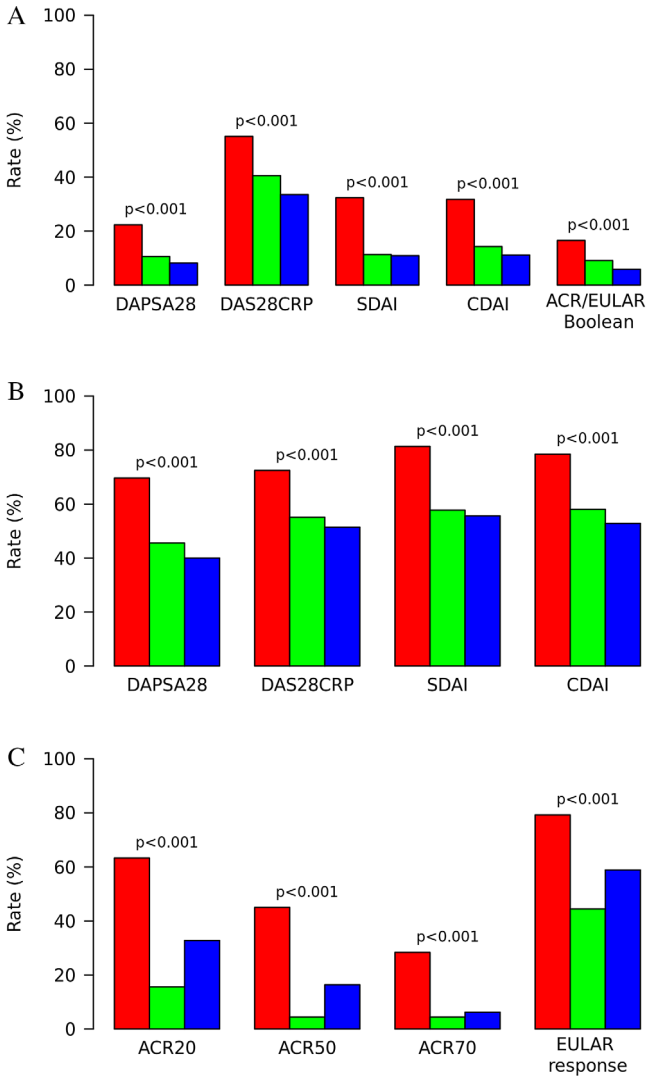

Figure 3. Bar charts of crude proportions of patients achieving remission (**A**), LDA (including remission) (**B**), and response rates (**C**) after 12 months of secukinumab treatment compared across number of previous biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) for b/tsDMARDs naive (red), 1 prior b/tsDMARD (green), and ≥2 prior b/tsDMARDs (blue). ACR = American College of Rheumatology; CDAI = Clinical Disease Activity Index; DAPSA28 = 28-joint Disease Activity Index for Psoriatic Arthritis; DAS28-CRP = Disease Activity Score in 28 joints using the CRP level; EULAR = European Alliance of Associations for Rheumatology; SDAI = Simplified Disease Activity Index.

However, the study is by far the largest real-life study to date on secukinumab effectiveness in patients with PsA.

In conclusion, in this longitudinal observational study of >2,000 patients with PsA treated with secukinumab, we found high retention rates after 6 and 12 months of treatment and good remission, LDA, and response rates. Secukinumab effectiveness was significantly better for biologics-naive patients, was independent of time since diagnosis, and varied across European registries.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Michelsen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Michelsen, Georgiadis, Di Giuseppe, Loft, Nissen, Iannone, Pombo-Suarez, Mann, Rotar, Eklund, Kvien, Santos, Gudbjornsson, Codreanu, Yilmaz, Wallman, Brahe, Möller, Favalli, Sánchez-Piedra, Nekvindova, Tomsic, Trokovic, Kristianslund, Santos, Löve, Ionescu, Pehlivan, Jones, van der Horst-Bruinsma, Ørnbjerg, Østergaard, Hetland.

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ROLE OF THE STUDY SPONSOR

Novartis had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Novartis.

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