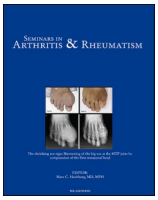
Seminars in Arthritis and Rheumatism 65 (2024) 152388

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit



Patient-reported outcomes in axial spondyloarthritis and psoriatic arthritis patients treated with secukinumab for 24 months in daily clinical practice

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https://doi.org/10.1016/j.semarthrit.2024.152388

Available online 26 January 2024

ARTICLE INFO

Keywords:
Spondyloarthritis
Biologic therapy
Cohort study
Rheumatic diseases
Clinical study in epidemiology

ABSTRACT

Objectives: In patients with axial spondyloarthritis (axSpA) or psoriatic arthritis (PsA) initiating secukinumab, we aimed to assess and compare the proportion of patients achieving 6-, 12- and 24-month patient-reported outcomes (PRO) remission and the 24-month retention rates.
Patients and methods: Patients with axSpA or PsA from 16 European registries, who initiated secukinumab in routine care were included. PRO remission rates were defined as pain, fatigue, Patient Global Assessment (PGA) ≤2 (Numeric Rating Scale (NRS) 0–10) and Health Assessment Questionnaire (HAQ) ≤0.5, for both axSpA and PsA, and were calculated as crude values and adjusted for drug adherence (LUNDEX). Comparisons of axSpA and PsA remission rates were performed using logistic regression analyses (unadjusted and adjusted for multiple confounders). Kaplan-Meier plots with log-rank test and Cox regression analyses were conducted to assess and compare secukinumab retention rates.
Results: We included 3087 axSpA and 3246 PsA patients initiating secukinumab. Crude pain, fatigue, PGA and HAQ remission rates were higher in axSpA than in PsA patients, whereas LUNDEX-adjusted remission rates were similar. No differences were found between the patient groups after adjustment for confounders. The 24-month retention rates were similar in axSpA vs. PsA in fully adjusted analyses (HR [95 %CI] = 0.92 [0.84–1.02]).
Conclusion: In this large European real-world study of axSpA and PsA patients treated with secukinumab, we demonstrate for the first time a comparable effectiveness in PRO remission and treatment retention rates between these two conditions when adjusted for confounders.

Introduction

Axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) are chronic, inflammatory conditions, which are part of the spondyloarthritis disease spectrum [1,2]. While axSpA mainly affects the axial skeleton, i.e. the sacroiliac joints and spine [1], PsA is associated with psoriasis and characterized by peripheral arthritis, dactylitis and enthesitis, although axial involvement can also be seen [2]. Both axSpA and PsA can cause structural damage in the spine and joints, and patients often experience pain, disability, fatigue, reduced work capacity, and reduced quality of life [1–4].

For patients with inadequate response to initial therapy (i.e., non-steroidal anti-inflammatory drugs (NSAIDs) for axSpA [5], or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) for PsA [6]), biologic (b) DMARDs are recommended, most often a tumour necrosis factor inhibitor (TNFi) [5,7]. In recent years, Interleukin-17 inhibitors (IL-17i), have become an alternative treatment to TNFi, also as a first-line bDMARD. The pro-inflammatory cytokine IL-17A plays a key role in the pathogenesis of axSpA and PsA. On binding to a receptor, IL-17A upregulates inflammatory gene expression by stabilizing pro-inflammatory cytokine mRNA and inducing de novo gene transcription [8]. As a result, secukinumab, a fully human IgG1 monoclonal antibody targeting interleukin-17A, has demonstrated sustained improvements in signs and symptoms of both diseases [9].

Patient-reported outcomes (PROs) are important in the evaluation of rheumatic diseases. Several PROs—including pain and fatigue—are incorporated in the respective core domain sets of axSpA and PsA [10,11], i.e., are recommended to be measured in all clinical trials [12,13]. Among the PROs, pain is considered the single most important item to patients and physicians in both axSpA and PsA [14,15]. Fatigue is also an important measure for the clinical evaluation of the disease, as it is clinically present in about 50 % of patients, and is associated with a poorer quality of life [16].

Real-world data regarding secukinumab treatment outcomes in patients with axSpA [17,18] and PsA [19,20] are limited. However, PROs have been investigated in randomised controlled trials (RCTs) in separate cohorts of patients with axSpA and PsA treated with secukinumab. Although these two diseases belong to the same spondyloarthritis spectrum, axSpA trials have reported numerically better outcomes regarding pain and fatigue than PsA trials [21–24]. However, to our knowledge, neither RCTs nor observational studies have directly compared PRO responses to secukinumab treatment in axSpA vs. PsA patients.

Therefore, the aims of this study were to assess and compare in a cohort of axSpA and PsA patients receiving secukinumab as part of routine care (1) the proportion of patients achieving 6-, 12- and 24-month remission of pain, fatigue, Patient Global Assessment (PGA) and Health Assessment Questionnaire (HAQ), and (2) the 24-month secukinumab retention rates.

Methods

European spondyloarthritis research collaboration network and data collection

This study was conducted within the European Spondyloarthritis Research Collaboration Network (EuroSpA) [25]. The EuroSpA collaboration aims to explore research questions by secondary use of prospectively collected real-life data in patients with spondyloarthritis [18]. The network was initiated in 2016 and currently consists of 16 European registries: AmSpA (Netherlands), SRQ (Sweden), ATTRA (Czech Republic), BIOBADASER (Spain), biorx.si (Slovenia), BSRBR-AS (United Kingdom), DANBIO (Denmark), ERSBR (Estonia), GISEA (Italy), ICEBIO (Iceland), NOR-DMARD (Norway), Reuma.pt (Portugal), ROB-FIN (Finland), RRBR (Romania), SCQM (Switzerland), TURKBIO (Turkey).

Based on a predefined study protocol, pseudonymized data were securely uploaded by individual registries onto the EuroSpA server. Subsequently, data were harmonized, quality checked and datasets from all registries were pooled before statistical analyses were conducted.

Patients

Patients eligible for inclusion were aged ≥ 18 years at the time of diagnosis, with a diagnosis of axSpA or PsA registered by the treating rheumatologist. Patients were required to have been followed in one of the 16 registries from the start of the first secukinumab treatment, and hence, had a registered start date of this first secukinumab treatment between January 1st 2015 and December 1st 2021.

Variables and assessments

The following baseline (i.e., secukinumab treatment start) variables were extracted from each registry (when available): demographics (age, gender), registry, HLA-B27 status (axSpA only), fulfilment of classification criteria (Modified New York criteria [26] and/or the ASAS criteria [27] for axSpA, and CASPAR criteria [28] for PsA), disease

duration, smoking status (current/non-current) and body mass index (BMI, kg/m^2), presence of comorbidities (cardiovascular disease, diabetes, kidney disease (ever/never)), presence of extra-articular manifestations (uveitis, inflammatory bowel disease (IBD), psoriasis, enthesitis, and dactylitis (ever/never)), Physician Global Assessment (PhGA, Numeric Rating Scale (NRS) 0–10), tender and/or swollen joint counts, CRP (C-reactive protein, mg/L), and ESR (erythrocyte sedimentation rate, mm/hr), secukinumab dose, number of previous targeted synthetic(ts)/bDMARD treatments, concomitant csDMARD treatment (methotrexate, leflunomide, sulfasalazine, other (yes/no)).

For each secukinumab treatment, start and if relevant stop dates of the treatment, were identified. All PROs were assessed at baseline, 6, 12, and 24 months. Pain, fatigue and PGA were reported as visual analogue scales (NRS, 0–10) and HAQ as a score (0–3).

The visits were defined according to the following time-windows: from 30 days prior to 30 days after secukinumab initiation (baseline), 90–270 days (6 months), 271–450 days (12 months) and 631–810 days (24 months) in patients still treated. Priority was given to visits with the highest number of available PROs. If several visits had equal numbers of available PROs, the visit closest to the 6-, 12-, or 24-month visit date was prioritized. Visit data collected outside of the predefined windows were not included in the data set.

PRO remission rates

Neither in axSpA nor in PsA has international consensus been achieved regarding the cut-off values for PRO remission. In axSpA, the ASAS working group in 2001 proposed a definition of partial remission in axSpA patients including a value of < 20 mm in these four domains: PGA, pain, function (represented by the BASFI score (0–100 scale)) and inflammation (represented either by the mean of the two morning stiffness–related BASDAI VAS scores, or by morning stiffness duration with a maximum of 120 min (0–100 scale)) [29].

Based on this, and adapted to a 0–10 NRS, we defined the following PRO remission rates: pain remission ≤ 2, PGA ≤ 2, fatigue ≤ 2 and HAQ ≤ 0.5 [30] for both axSpA and PsA.

Statistical analyses

Statistical analyses were performed according to a predefined statistical analysis plan. Summary statistics (mean (SD) and percentages) are reported. All analyses were stratified by diagnosis (i.e. axSpA and PsA). Sensitivity analyses according to number of previous b/tsDMARDs (0/1/$\geq$2) were performed.

Remission rates were calculated at 6-, 12-, and 24-month follow-up as both crude rates and LUNDEX-adjusted rates [31]. The LUNDEX-adjusted rates were calculated to include information on response and drug retention in one combined measure: the crude remission rate is multiplied with the fraction of patients still receiving treatment at the timepoint of interest, thus taking the drug retention into account.

Comparison of remission rates in patients still treated at 6-, 12-, and 24-month follow-up of axSpA vs. PsA patients were performed by logistic regression analyses (unadjusted, age and gender adjusted, and fully adjusted (age, gender, registry, and number of previous b/tsDMARDs)). Comparisons of PRO values and absolute changes in PROs of axSpA vs. PsA patients at 6, 12 and 24 months were performed with analysis of covariance (ANCOVA), unadjusted and adjusted for confounders, analogously to the above logistic regression models.

Drug retention rates over the 24-month follow-up were estimated using Kaplan-Meier survival analyses, with baseline defined as the secukinumab treatment start date. Observations were censored according to date of data extraction (January 1st 2015 to December 1st 2021), date of death or end of registry follow-up, whichever came first. Comparisons of the retention rates for PsA vs. axSpA patients were performed by Cox regression (unadjusted, age and gender adjusted, and fully adjusted (for age, gender, registry, and number of previous b/tsDMARDs)).

All analyses were performed on complete case data for the relevant outcome. No imputation of missing data was performed on the dependent variables and only one patient had missing data on age, while no other explanatory variables in the above models contained missing values.

Comparison of PRO remission rates were additionally performed with sensitivity analyses including additional confounders. Two models were performed in patients with available data: sensitivity model 1 (adjustment with the fully adjusted model + smoking status and baseline secukinumab dose), and sensitivity model 2 (adjustment with the fully adjusted model + smoking status, baseline secukinumab dose and cardiovascular disease).

A significance level of 0.05 was used. Statistical analyses were performed with R version 4.3.1 (R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2022) and graphs were produced with R and Excel.

Ethics

All patient data were collected in accordance with national legal and regulatory requirements in the different countries. The study was approved by the respective national Data Protection Agencies and Ethical Committees according to legal regulatory requirements in the participating countries, performed in accordance with the Declaration of Helsinki, and followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [32].

Results

In total, 3087 axSpA patients from 16 registries, and 3246 PsA patients from 14 registries were included (AmSpA and BRSBR-AS registries do not include PsA patients).

Baseline characteristics

Among the 3087 axSpA patients, 52.5 % were men and 73.1 % were HLA-B27 positive, while among the 3246 PsA patients, 56.9 % were women. AxSpA patients were younger (46.9 vs. 51.9 years old), more likely to smoke (27.3% vs. 18.5 %), and less likely to have cardiovascular disease (22.4 % vs. 29.4 %) or diabetes (8.2 % vs 12.9 %) than PsA patients. No clinically relevant differences in disease duration and BMI were found between axSpA and PsA patients. Baseline PRO and PhGA levels were quite similar in the two groups, while axSpA patients had a higher CRP level (mean 17.1 mg/L vs. 11.9 mg/L), and PsA patients had higher number of tender and swollen joints. As expected, more PsA patients received concomitant csDMARDs at secukinumab initiation compared to axSpA patients (49.4 % vs. 30.0 %). In both groups, approximately 1/4 of patients were b/tsDMARD naïve at secukinumab initiation (Table 1).

Overall, demographic characteristics, disease activity measures and PROs at baseline were similar between patients with and without available data on pain at 6 months, both in axSpA and PsA groups. (Supplementary Table 1).

Comparisons of PRO scores in axSpA vs. PsA patients

Crude comparisons

The decrease in pain, fatigue and PGA values from baseline to 24-month follow-up was greater in axSpA patients compared to PsA patients, while HAQ values were quite similar between axSpA and PsA at baseline and during follow-up (Table 2). Overall, all PRO remission rates were higher in axSpA than PsA patients, and unadjusted comparisons showed statistically significant higher remission rates in axSpA than PsA

Table 1
Baseline characteristics of axSpA and PsA patients.

Baseline characteristics*	axSpA patients (n = 3087)		PsA patients (n = 3246)	
	Value	N available	Value	N available
Age (years)	46.9 (12)	3087	51.9 (11.9)	3245
Sex (male)	1622 (52.5 %)	3087	1400 (43.1 %)	3246
HLA-B27 positive	1309 (73.1 %)	1791	–	–
BMI (kg/m^2)	27.5 (5.4)	1611	28.3 (5.9)	1443
Years since diagnosis (years)	9.0 (9.2)	2590	8.6 (7.9)	2494
Currently smoking	694 (27.3 %)	2545	447 (18.5 %)	2415
Comorbidities**				
- Cardiovascular disease	369 (22.4 %)	1651	354 (29.4 %)	1205
- Diabetes	108 (8.2 %)	1318	152 (12.9 %)	1181
- Kidney disease	50 (3.1 %)	1624	39 (3.3 %)	1190
Non-musculoskeletal manifestations**				
- History of uveitis	182 (14.1 %)	1290	36 (3.5 %)	1041
- History of IBD	43 (3.3 %)	1306	13 (1.5 %)	860
- History of psoriasis	124 (9.4 %)	1324	723 (83.1 %)	870
History of dactylitis	83 (12.2 %)	682	261 (43.6 %)	598
History of enthesis	301 (32.3 %)	931	203 (35.4 %)	574
Fulfilment of classification criteria				
- Modified New York criteria	635 (72.2 %)	879	–	–
- ASAS criteria	990 (87.5 %)	1131	–	–
Fulfilment of CASPAR Criteria	–	–	734 (94.0 %)	781
Secukinumab –150mg	1010 (49.6 %)	2036	383 (19.9 %)	1924
Secukinumab –300mg	68 (3.3 %)	2036	329 (17.1 %)	1924
Secukinumab – Unknown dose	958 (47.1 %)	2036	1212 (63.0 %)	1924
Previous b/ts DMARDs				
- b/ts DMARD naïve	805 (26.1 %)	3087	815 (25.1 %)	3246
- 1 previous b/ts DMARD	752 (24.4 %)	3087	805 (24.8 %)	3246
- ≥ 2 previous b/ts DMARDs	1530 (49.6 %)	3087	1626 (50.1 %)	3246
Concomitant csDMARDs	721 (30.0 %)	2401	1277 (49.4 %)	2587
- Methotrexate	358 (15.5 %)	2313	949 (38.5 %)	2465
- Sulfasalazine	360 (15.7 %)	2291	184 (8.3 %)	2221
- Leflunomide	38 (1.7 %)	2218	229 (10.3 %)	2222
- Others	63 (2.7 %)	2342	96 (4.1 %)	2318
No concomitant csDMARDs	1680 (70.0 %)	2401	1310 (50.6 %)	2587
PROs				
- Pain (0–10)	6.6 (2.3)	1825	6.2 (2.5)	1863
- Fatigue (0–10)	6.7 (2.4)	1533	6.6 (2.5)	1221
- PGA, (0–10)	6.6 (2.3)	1892	6.4 (2.4)	2007
- HAQ (0–3)	1.1 (0.6)	1380	1.1 (0.7)	1773
Disease activity measures				
- PhGA, (0–10)	4.4 (2.5)	1283	4.2 (2.6)	1539
- 28 tender joint counts	2.0 (4.0)	1240	5.9 (6.1)	2105
- 28 swollen joint counts	0.7 (2.1)	1316	3.0 (3.9)	2091
- CRP (mg/L)	17.1 (28.6)	2044	11.9 (21.1)	2080
- ESR (mm/hr)	25.9 (23.1)	1539	22.6 (21.4)	1739

*Values are presented as mean (SD) and n (%) for continuous and categorical variables, respectively. **Comorbidities and non-musculoskeletal manifestations were defined as ever or never present. ASAS, Assessment of Spondyloarthritis international Society; axSpA, axial spondyloarthritis; BMI, Body Mass Index; b/ts DMARD, biologic/targeted synthetic Disease-Modifying Anti-Rheumatic drug; CASPAR, ClASsification for Psoriatic Arthritists; CRP, C-reactive protein; csDMARD, conventional synthetic Disease-Modifying Anti-Rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire disability index; HLA-B27, Human Leukocyte Antigen subtypes B*2701–2759; IBD, Inflammatory Bowel Disease; PGA, Patient's global assessment of disease activity; PhGA, Physician Global assessment; PROs, Patient-reported outcomes; PsA, psoriatic arthritis.

(Table 2, Fig. 1). Regarding pain, more axSpA patients than PsA patients with high baseline pain values (≥8) were able to reach pain remission (≤2) at 6 months e.g., 26.1 % axSpA patients with high baseline pain values had pain remission after 6 months of secukinumab, while for PsA patients it was 19.9 % (Fig. 2). Similarly, overall, absolute changes in pain, fatigue and PGA were higher in axSpA than PsA patients, with statistically significant differences between the groups in unadjusted comparisons, while absolute changes in HAQ between axSpA and PsA were similar during follow-up (Table 3).

Adjusted comparisons

There were no relevant differences in pain, PGA and HAQ remission rates between the groups after adjustment for treatment retention, as 6-/12-/24-month LUNDEX-adjusted remission rates were similar (Table 2, Fig. 1). Additionally, overall, no differences were found in pain, PGA and HAQ values, remission rates and absolute changes between the groups after correction for multiple confounders in ANCOVA and logistic regression analyses (Tables 2 and 3, Fig. 1).

LUNDEX-adjusted fatigue remission rates were slightly higher in axSpA than in PsA patients but the difference between the groups tended to decrease during follow-up. After adjustment for confounders, a difference between the groups at the limit of significance was found for fatigue values and remission, with a higher OR [95 % CI] for remission in PsA (1.3 [1.01–1.6] and 1.6 [1.04–2.6], respectively at 6 and 24 months) (Table 2, Fig. 1).

Sensitivity analyses

Similarly to the above results, in sensitivity analyses further adjusted for smoking status, baseline secukinumab dose and cardiovascular disease, and performed in patients with available data, no relevant differences in pain, PGA and HAQ remission rates between axSpA and PsA patients was found. A higher fatigue remission at the limit of significance was found in PsA patients (Supplementary Table 2).

Comparisons according to b/tsDMARD status

In both axSpA and PsA patients, LUNDEX-adjusted remission rates were markedly higher in bio-naïve patients than in patients with 1 or ≥ 2 prior b/tsDMARDs. In bio-naïve patients, LUNDEX-adjusted PRO remission rates were numerically higher in axSpA than in PsA, with decreasing differences with longer follow-up. In patients who had previously received 1 or ≥2 prior bDMARDs, LUNDEX-adjusted remission rates were similar between axSpA and PsA patients at 6, 12 and 24 months (Supplementary Table 3, Supplementary Figure 1).

Table 2
Comparisons of PRO values and PRO remission rates 6, 12 and 24 months after secukinumab initiation in European axSpA and PsA patients.

PROs	Months	PRO values							PRO remission rates								
		axSpA patients (n = 3087)		PsA patients (n = 3246)		Estimated difference (CI) PsA vs. axSpA			axSpA patients (n = 3087)			PsA patients (n = 3246)			OR (CI) PsA vs. axSpA		
		Mean (sd)	N available	Mean (sd)	N available	Unadjusted	Adjusted (age + gender)	Fully adjusted*	Crude	LUNDEX-adjusted	N available	Crude	LUNDEX-adjusted	N available	Unadjusted	Adjusted (age + gender)	Fully adjusted*
Pain	0	6.6 (2.3)	1825	6.2 (2.5)	1863	–	–	–	–	–	–	–	–	–	–	–	–
	6	4.4 (2.7)	1513	4.6 (2.8)	1583	**0.2 (0.1; 0.4)**	0.1 (−0.1; 0.3)	−0.2 (−0.4; 0.0)	29.9	20.2	1513	26.5	18.8	1583	0.8 (0.7; 1.0)	0.9 (0.8; 1.1)	1.1 (0.9; 1.3)
	12	3.9 (2.6)	849	4.2 (2.7)	956	**0.3 (0.1; 0.6)**	0.2 (−0.1; 0.4)	−0.1 (−0.4; 0.1)	38.5	19.6	849	32.5	18.3	956	**0.8 (0.6; 0.9)**	0.9 (0.7; 1.1)	1.1 (0.8; 1.3)
	24	3.8 (2.7)	413	4.4 (2.7)	467	**0.6 (0.2; 0.9)**	**0.4 (0.1; 0.8)**	0.0 (−0.4; 0.4)	40.2	14.2	413	29.6	11.3	467	**0.6 (0.5; 0.8)**	**0.7 (0.5; 0.9)**	1.0 (0.7; 1.4)
Fatigue	0	6.7 (2.4)	1533	6.6 (2.5)	1221	–	–	–	–	–	–	–	–	–	–	–	–
	6	4.8 (3.0)	1326	5.3 (2.9)	1091	**0.6 (0.3; 0.8**)	**0.5 (0.2; 0.7)**	**−0.3 (−0.6; −0.1)**	28.6	19.3	1326	22.1	15.6	1091	**0.7 (0.6; 0.9)**	**0.8 (0.6; 0.9)**	**1.3 (1.02; 1.6)**
	12	4.1 (2.9)	724	5.1 (3.0)	586	1.0 (0.7; 1.3)	0.9 (0.6; 1.2)	0.0 (−0.3; 0.3)	35.8	18.2	724	26.5	14.9	586	**0.6 (0.5; 0.8)**	**0.7 (0.6; 0.9)**	1.3 (0.9; 1.7)
	24	4.2 (2.8)	338	5.1 (3.0)	295	0.9 (0.4; 1.3)	0.7 (0.3; 1.2)	−0.2 (−0.7; 0.2)	33.7	11.9	338	26.8	10.3	295	0.7 (0.5; 1.0)	0.8 (0.6; 1.1)	**1.6 (1.1; 2.6)**
PGA	0	6.6 (2.3)	1892	6.4 (2.4)	2007	–	–	–	–	–	–	–	–	–	–	–	–
	6	4.6 (2.7)	1576	4.7 (2.8)	1656	0.1 (0.0; 0.3)	0.0 (−0.2; 0.2)	**−0.3 (−0.5; −0.1)**	28.7	19.4	1576	25.9	18.3	1656	0.9 (0.7; 1.0)	1.0 (0.8; 1.1)	1.2 (1.0; 1.4)
	12	3.9 (2.6)	896	4.3 (2.7)	1085	**0.4 (0.1; 0.6)**	0.2 (−0.0; 0.5)	−0.2 (−0.4; 0.1)	38.2	19.4	896	32.2	18.1	1085	**0.8 (0.6; 0.9)**	0.9 (0.7; 1.1)	1.1 (0.9; 1.4)
	24	3.8 (2.8)	425	4.4 (2.7)	519	**0.6 (0.3; 0.9)**	**0.4 (0.1; 0.8)**	0.0 (−0.3; 0.4)	43.3	15.3	425	29.9	11.5	519	**0.6 (0.4; 0.7)**	**0.6 (0.5; 0.8)**	0.8 (0.6; 1.1)
HAQ	0	1.1 (0.6)	1380	1.1 (0.7)	1773	–	–	–	–	–	–	–	–	–	–	–	–
	6	0.9 (0.6)	1078	0.9 (0.7)	1511	0.1 (0.0; 0.1)	0.0 (0.0; 0.0)	0.0 (−0.1; 0.1)	36.2	24.4	1078	33.2	23.5	1511	0.9 (0.7; 1.0)	1.1 (0.9; 1.3)	1.1 (0.9; 1.3)
	12	0.8 (0.6)	576	0.9 (0.7)	892	0.1 (0.0; 0.1)	0.0 (−0.1; 0.1)	0.0 (−0.1; 0.1)	39.6	20.2	576	33.7	19.0	892	0.8 (0.6; 1.0)	0.9 (0.8; 1.2)	1.0 (0.8; 1.3)
	24	0.8 (0.6)	276	0.9 (0.7)	443	0.1 (0.0; 0.2)	0.1 (−0.1; 0.1)	0.0 (0.0; 0.1)	43.8	15.5	276	33.0	12.6	443	**0.6 (0.4; 0.9)**	0.7 (0.5; 1.0)	0.9 (0.6; 1.3)

*Adjustment for age, gender, registries, and number of previous b/tsDMARDS (0/1/≥2). Crude/LUNDEX, crude and LUNDEX–adjusted rates [30]. axSpA, axial spondyloarthritis; CI, Confidence Interval; HAQ, Health Assessment Questionnaire; OR, Odds Ratio; PGA, Patient's global assessment of disease activity; PROs, patient–reported outcomes; PsA, psoriatic arthritis; sd, standard deviation; Pain, fatigue, PGA, were scored on a 0–10 numeric rating scale (NRS); HAQ was scored on a scale ranging from 0 to 3; PRO remission criteria were defined as following: pain remission ≤ 2, PGA ≤ 2, fatigue ≤ 2, HAQ ≤ 0.5; Significant values are indicated by bold type.

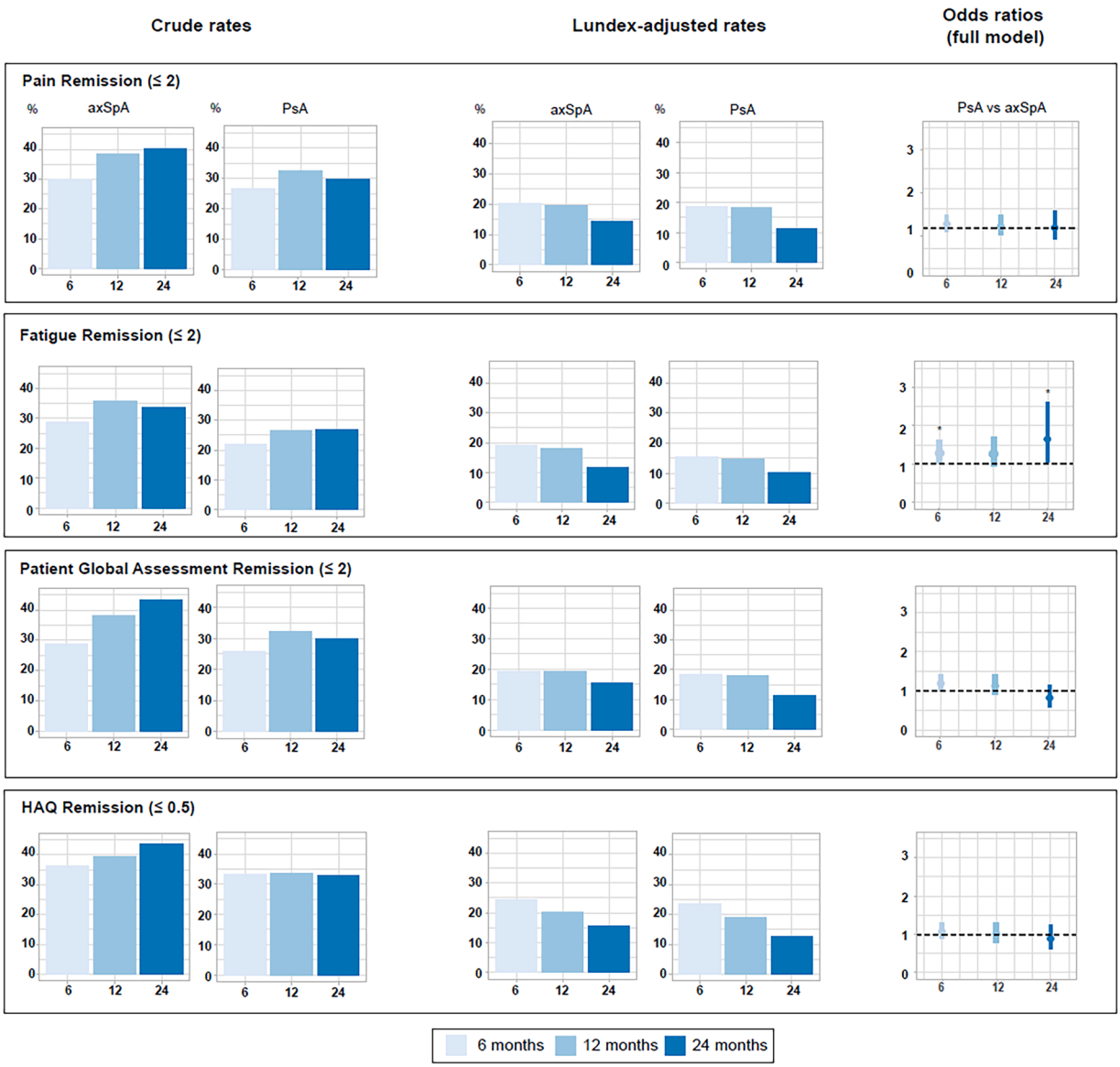


Fig. 1. PRO remission rates (crude and LUNDEX-adjusted), with fully adjusted comparisons (results of logistic regression analysis with odds ratios), in axSpA and PsA patients. *significant Odds Ratio. axSpA, axial spondyloarthritis; PsA, psoriatic arthritis; HAQ, Health Assessment Questionnaire. The full model is adjusted for age, gender, registries, and number of previous b/tsDMARDS (0/1/≥2).

PRO values and PRO remission rates across registries

Heterogeneity in PRO values and PRO remission rates across different European registries was found for both axSpA and PsA patients. Crude pain remission rates at 24 months varied from 18.9 % (Sweden) to 67.8 % (Romania) for axSpA, and from 18.0 % (Denmark) to 66.7 % (Romania) for PsA (Supplementary Table 4, Supplementary Table 5).

Secukinumab retention rates

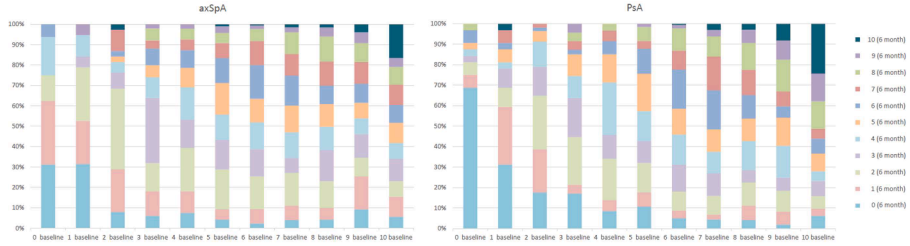
AxSpA patients had numerically lower 6-/12-/24-month secukinumab retention rates compared to PsA patients, but no statistically significant differences between the groups were demonstrated in adjusted Cox regression models (24-month adjusted HR [95 %CI] = 0.92 [0.84–1.02]) (Fig. 3).

Retention rates were significantly lower in the subgroups of patients who had received 1 prior and ≥2 prior b/tsDMARDs compared to bionaïve patients in both axSpA and PsA (Supplementary Figure 2).

Discussion

This is the first real-life comparative study of secukinumab effectiveness as assessed by PROs in axSpA vs. PsA patients. Although axSpA and PsA both belong to the spondyloarthritis spectrum, they are characterized by different clinical, laboratory and imaging hallmarks. Due to heterogeneity in the phenotypes of these two diseases, it is expected that there may be differences in the treatment response. However, the comparison of treatment effectiveness between patients with different inflammatory rheumatic disease entities are challenging due to different age and sex distributions of the patient populations. In more than 6000 patients from 16 European countries we demonstrated that while PRO values and crude PRO remission rates showed higher effectiveness of secukinumab in axSpA patients compared to PsA patients, we largely found comparable secukinumab effectiveness in axSpA and PsA patients in adjusted analyses.

To our knowledge, no RCTs have compared secukinumab effectiveness in axSpA vs. PsA patients directly. However, similarly to our crude results, RCTs have reported a numerically higher secukinumab



	axSpA Pain scores at 6 months												PsA Pain scores at 6 months											
Baseline pain scores	0	1	2	3	4	5	6	7	8	9	10	Total	0	1	2	3	4	5	6	7	8	9	10	Total
0	5 (31.3)	5 (31.3)	2 (12.5)	0 (0.0)	3 (18.75)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (100)	22 (68.8)	2 (6.3)	2 (6.3)	1 (3.1)	1 (3.1)	1 (3.1)	2 (6.3)	0 (0)	1 (3.1)	0 (0.0)	0 (0.0)	32 (100)
1	6 (31.6)	4 (21.0)	5 (26.3)	1 (5.3)	2 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	19 (100)	10 (31.2)	9 (28.1)	3 (9.4)	3 (9.4)	1 (3.1)	2 (6.3)	1 (3.1)	2 (6.3)	0 (0)	0 (0.0)	1 (3.1)	32 (100)
2	3 (7.9)	8 (21.1)	15 (39.5)	3 (7.9)	2 (5.3)	1 (2.6)	1 (2.6)	4 (10.5)	0 (0.0)	0 (0.0)	1 (2.6)	38 (100)	10 (17.5)	12 (21.1)	15 (26.3)	8 (14.0)	7 (12.3)	3 (5.2)	1 (1.8)	1 (1.8)	0 (0)	0 (0.0)	0 (0.0)	57 (100)
3	3 (6.0)	6 (12.0)	7 (14.0)	16 (32.0)	5 (10.0)	3 (6.0)	4 (8.0)	2 (4.0)	3 (6.0)	1 (2.0)	0 (0.0)	50 (100)	8 (17.0)	2 (4.3)	11 (23.4)	9 (19.2)	5 (10.6)	5 (10.6)	1 (2.1)	2 (4.3)	2 (4.3)	2 (4.2)	0 (0.0)	47 (100)
4	7 (7.5)	10 (10.6)	20 (21.3)	13 (13.8)	15 (16.0)	9 (9.6)	8 (8.5)	5 (5.3)	5 (5.3)	2 (2.1)	0 (0.0)	94 (100)	8 (8.5)	5 (5.3)	19 (20.2)	11 (11.7)	24 (25.6)	13 (13.8)	6 (6.4)	5 (5.3)	3 (3.2)	0 (0.0)	0 (0.0)	94 (100)
5	4 (4.2)	5 (5.1)	19 (19.5)	14 (14.4)	12 (12.4)	15 (15.5)	12 (12.4)	7 (7.2)	5 (5.2)	3 (3.1)	1 (1.0)	97 (100)	14 (10.7)	9 (6.9)	19 (14.5)	14 (10.7)	19 (14.5)	24 (18.3)	16 (12.2)	5 (3.8)	9 (6.9)	2 (1.5)	0 (0.0)	131 (100)
6	4 (2.2)	13 (7.2)	29 (16.0)	24 (13.3)	24 (13.3)	21 (11.6)	30 (16.6)	21 (11.6)	11 (6.1)	3 (1.6)	1 (0.5)	181 (100)	9 (4.9)	7 (3.8)	17 (9.3)	24 (13.1)	27 (14.8)	23 (12.6)	35 (19.1)	17 (9.3)	20 (10.9)	3 (1.6)	1 (0.6)	183 (100)
7	8 (3.9)	15 (7.3)	33 (16.0)	15 (7.3)	26 (12.6)	27 (13.1)	30 (14.6)	22 (10.7)	22 (10.7)	5 (2.4)	3 (1.4)	206 (100)	7 (4.3)	4 (2.5)	15 (9.2)	18 (11.0)	17 (10.4)	18 (11.0)	31 (19.0)	27 (16.6)	16 (9.8)	5 (3.1)	5 (3.1)	163 (100)
8	11 (4.1)	16 (6.0)	35 (13.0)	41 (15.2)	31 (11.5)	30 (11.2)	24 (8.9)	32 (11.9)	33 (12.3)	12 (4.4)	4 (1.5)	269 (100)	11 (4.0)	20 (7.3)	31 (11.2)	17 (6.2)	39 (14.1)	30 (10.9)	32 (11.6)	34 (12.3)	36 (13.0)	18 (6.5)	8 (2.9)	276 (100)
9	12 (9.2)	21 (16.2)	12 (9.2)	15 (11.5)	10 (7.7)	10 (7.7)	12 (9.2)	14 (10.8)	12 (9.2)	7 (5.4)	5 (3.9)	130 (100)	2 (1.8)	7 (6.4)	11 (10.1)	17 (6.4)	17 (15.6)	15 (13.8)	6 (5.5)	8 (7.3)	17 (15.6)	10 (9.2)	9 (8.3)	119 (100)
10	5 (5.5)	9 (9.9)	7 (7.7)	10 (11.0)	7 (7.7)	9 (9.9)	8 (8.8)	9 (9.9)	8 (8.8)	4 (4.4)	15 (16.4)	91 (100)	5 (6.1)	3 (3.7)	5 (6.1)	6 (7.3)	4 (4.9)	7 (8.5)	6 (7.3)	4 (4.9)	11 (13.4)	11 (13.4)	20 (24.4)	82 (100)

Fig. 2. Proportion of patients with various pain levels at month 6, stratified by baseline pain level, in European axSpA and PsA patients. Stacked bar chart showing the distribution of pain score of patients with axSpA and PsA 6 months after secukinumab initiation, dependent on how the same patients scored at start of secukinumab initiation (baseline). Table: n (%) of patients as illustrated in stacked bar chart. axSpA: axial spondyloarthritis. PsA: psoriatic arthritis.

Table 3
Comparisons of absolute changes in PROs 6, 12 and 24 months after secukinumab initiation in European axSpA and PsA patients.

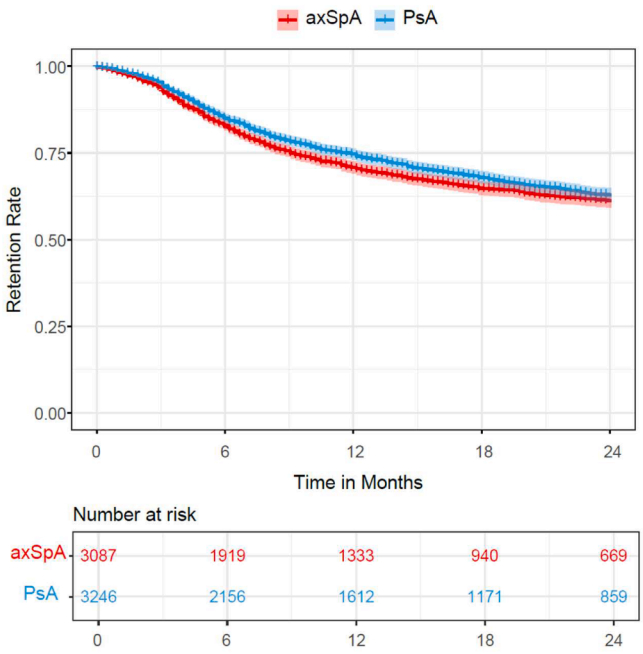
PROs	Months	Absolute changes in PROs axSpA patients ($n = 3087$) Median (IQR)	N available	PsA patients ($n = 3246$) Mean (sd)	N available	Estimated difference (CI) PsA vs. axSpA Unadjusted	Adjusted (age + gender)	Fully adjusted*
Pain	6	−2 (−4; 0)	1191	−1 (−4; 0)	1206	**0.2 (0.1; 0.4)**	0.1 (−0.1; 0.3)	−0.2 (−0.4; 0.1)
	12	−3 (−6; −1)	655	−2 (−4; 0)	732	**0.3 (0.1; 0.6)**	0.2 (−0.1; 0.4)	−0.1 (−0.4; 0.1)
	24	−3 (−5; −1)	320	−2 (−4; 0)	365	**0.6 (0.2; 0.9)**	**0.4 (0.1; 0.8)**	0.0 (−0.4; 0.4)
Fatigue	6	−2 (−4; 0)	1027	−1 (−3; 0)	790	**0.6 (0.3; 0.8)**	**0.5 (0.2; 0.7)**	−0.3 (−0.6; −0.1)
	12	−3 (−5; 0)	553	−1 (−3; 0)	431	1.0 (0.7; 1.3)	0.9 (0.6; 1.2)	0.0 (−0.3; 0.3)
	24	−2 (−5; 0)	262	−2 (−4; 0)	218	0.9 (0.4; 1.3)	0.7 (0.3; 1.2)	−0.2 (−0.7; 0.2)
PGA	6	−2 (−4; 0)	1206	−2 (−4; 0)	1236	0.1 (−0.1; 0.3)	0.1 (−0.2; 0.2)	**−0.3 (−0.5; −0.1)**
	12	−3 (−5; −1)	670	−2 (−5; 0)	793	**0.4 (0.1; 0.6)**	0.2 (−0.1; 0.5)	−0.2 (−0.4; 0.1)
	24	−3 (−5; −1)	321	−2 (−4; 0)	387	**0.6 (0.3; 0.9)**	**0.4 (0.1; 0.8)**	0.0 (−0.3; 0.4)
HAQ	6	−0.1 (−0.5; 0)	878	−0.1 (−0.5; 0)	1125	0.1 (0.0; 0.1)	0.0 (−0.1; 0.1)	0.0 (−0.1; 0.1)
	12	−0.2 (−0.6; 0)	458	−0.2 (−0.6; 0)	678	0.1 (0.0; 0.1)	0.0 (−0.1; 0.1)	0.0 (−0.1; 0.1)
	24	−0.2 (−0.6;0)	226	−0.2 (−0.6; 0)	341	0.1 (0.1; 0.2)	0.1 (0.0; 0.1)	0.0 (−0.1; 0.1)

*Adjustment for age, gender, registries, and number of previous b/tsDMARDS (0/1/≥2). axSpA, axial spondyloarthritis; CI, Confidence Interval; HAQ, Health Assessment Questionnaire; IQR, Interquartile Range; PGA, Patient's global assessment of disease activity; PROs, patient–reported outcomes; PsA, psoriatic arthritis; sd, standard deviation; Pain, fatigue, PGA, were scored on a 0–10 numeric rating scale (NRS); HAQ was scored on a scale ranging from 0 to 3; Significant values are indicated by bold type.

effectiveness in axSpA than in PsA patients for pain and fatigue [21–24]. In the MEASURE 2 study, after 16 weeks of secukinumab 150 mg, axSpA patients had a mean change in spinal/nocturnal pain of −34.6/−30.2 (patients with normal CRP), and −26.7/−31.6 (patients with elevated CRP) [21], while in the FUTURE 2 study, PsA patients had a mean change in pain at week 16 of −23.1 and −23.9 for secukinumab 150 mg and 300 mg, respectively [23]. Regarding fatigue, evaluated by FACIT-F total score, axSpA patients had a mean change at week 24 of −7.4 to −8.8 in MEASURE 1 and 2 studies, respectively [24], while PsA patients had a mean change at week 24 of −6.7 in FUTURE 1 study [22], both receiving secukinumab 150 mg. Real-world data regarding secukinumab effectiveness assessed by PROs (pain, fatigue, PGA and HAQ) in patients with axSpA and PsA are very limited. Williams *et al.* have shown in axSpA an improvement in fatigue 16 weeks after secukinumab initiation with a mean change of −10.75 in FACIT-F total score [17]. However, there are no observational studies in the literature regarding the effectiveness of secukinumab on pain and fatigue in patients with PsA. Moreover, no studies have compared TNFi effectiveness assessed by pain, fatigue, PGA and HAQ in axSpA vs. PsA.

There are no recommendations in the literature on the cut-off values for PRO remission in either axSpA or PsA. In PsA, the minimal disease activity (MDA) criteria states patients as achieving MDA when meeting 5 out of the 7 following criteria: ≤ 1 tender joints, ≤ 1 swollen joints, PASI/BSA ≤ 1/3, patient pain VAS ≤ 15, PGA ≤ 20, HAQ ≤ 0.5 and tender entheseal points ≤ 1 [33]. Therefore, we choose to use the ASAS working group's definition of partial remission in axSpA patients including a value of < 20 mm in the four domains: PGA, pain, function and inflammation [29], and we also applied these cut-off values to PsA patients to make comparisons feasible, although we have been less stringent on pain remission for PsA patients than MDA criteria.

We found a numerically higher 24-month retention rate for PsA patients compared to axSpA patients, but neither unadjusted, nor adjusted comparisons of retention rates demonstrated any clinically or statistically significant differences between the two diseases. The 24-month axSpA retention rate of the present study appears lower than the secukinumab retention rate previously reported in the literature. In the MEASURE 2 randomised clinical trial, the 3-year retention rate was 86 % [34]. Compared to patients in the MEASURE 2 trial, our population was older (mean age 47 *vs.* 42 years), fewer were TNFi-naïve (26 % vs. 61 %) and we included both radiographic (r-axSpA) and non-radiographic axSpA (nr-axSpA) patients, in contrast to only r-axSpA patients in MEASURE 2 [34]. In small epidemiologic studies, Ramonda et al. found a 24-month retention rate of 75 % in 149 axSpA patients [35], while Gentileschi et al. reported a 24-month retention rate of 78.2



	Retention rates (%)		24-month Hazard ratios [95%CI] PsA *vs.* axSpA		
	axSpA	PsA	Unadjusted	Adjusted: Age + gender	Fully adjusted*
6 months	82.9	85.0	0.94 [0.86-1.02]	0.92 [0.84-1.01]	0.92 [0.84-1.02]
12 months	70.8	74.7			
24 months	61.3	62.9			

Fig. 3. Secukinumab retention rates in axSpA and PsA patients, with unadjusted and adjusted hazard ratios. *Values adjusted for age, gender, registries, and number of previous b/tsDMARDS. (0/1/≥2). axSpA, axial spondyloarthritis; PsA, psoriatic arthritis; CI, Confidence Interval.

% in 39 axSpA patients [36]. Patients in our study were younger (mean age 47 *vs.* 51 and 54), with higher CRP level (17.4 mg/L vs. 4.5 mg/L in the Ramonda et al. study), and higher BMI (27.6 *vs.* 24.6 kg/m^2 in the Ramonda et al. study). However, the 24-month axSpA secukinumab retention rate of the present study is comparable to the 24-month TNFi retention rate reported in a previous epidemiologic ankylosing spondylitis study [37].

Among PsA patients, the secukinumab retention rate found in the present study is in line with previous findings from a smaller Italian observational study of 62 psoriasis and 90 PsA patients, which described a 24-month secukinumab retention rate of 57 % [38].

In accordance with the literature, the present study reports better secukinumab effectiveness for PROs and retention rate for b/tsDMARD-naïve patients compared with patients treated with one or more previous b/tsDMARDs, in both axSpA and PsA [20]. This pattern has also been observed for TNFi [39,40], and reflects that patients who previously failed a bDMARD treatment constitute a more treatment resistant patient group.

To date, only a few observational studies on secukinumab effectiveness in axSpA and PsA have been published [17–19]. An important strength of our study is that we describe and compare for the first time secukinumab effectiveness between axSpA and PsA patients in a large prospective observational cohort of patients initiating secukinumab in a real-life setting. From RCTs, data indicate a higher efficacy with regards to PROs in axSpA patients than in PsA patients. A key message from our study is that the effectiveness of secukinumab regarding PROs and retention rate is similar in axSpA and PsA patients when comparison are adjusted for confounders. Thus, clinically observed differences in effectiveness between axSpA and PsA may potentially be explained by other factors than the disease per se. The generalizability of results is high, due to the inclusion of 16 registries across Europe. It was also a strength that data completeness was high for drug retention.

Our study also has several limitations. Missingness of outcome data was prevalent, both at secukinumab treatment start, but also increasingly during follow-up, as follow-up of individual patients stopped at the time of withdrawal from treatment. Also, information on secukinumab dose at baseline was lacking (almost 50 % missing data), and data available on secukinumab dose at baseline showed most of axSpA patients receiving the 150 mg dose, while PsA patients received the 150 mg and 300 mg dose equally. These differences between axSpA and PsA regarding secukinumab dose reflect the real-life practice, and follow the prescription guidelines [41]. Furthermore, sensitivity analyses adjusted with baseline secukinumab dose have been performed, without showing any differences from the results of the main model. As with all observational studies, selection bias and heterogeneity of patients across registries were potentially present and may influence effectiveness measures.

In conclusion, our study supports the effectiveness of secukinumab in both axSpA and PsA, as measured by PRO remission and 24-month drug retention rates, and demonstrates a comparable secukinumab effectiveness in both axSpA and PsA patients when adjusted for confounders.

Funding

The EuroSpA collaboration was financially supported by Novartis. Novartis had no influence on the data collection, statistical analyses, manuscript preparation or decision to submit.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Sara Nysom Christiansen, Simon Horskjær Rasmussen, Lykke Midtbøll Ørnbjerg: research grant from Novartis; Marion Pons: research grant from Novartis and speaker fees from Sandoz; Brigitte Michelsen: research grant from Novartis and the centre for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY) is funded as a Centre for Clinical Treatment Research by The Research Council of Norway (project 328,657); Bente Glintborg: research grants from Pfizer, Abbvie, BMS, Sandoz; Bjorn Gudbjornsson: consulting fees from Novartis and speaker fees from Novartis, Nordic-Pharma; Gerdur Grondal: none; Jiri Vencovsky: research grant from Abbvie, consulting fees from Abbvie, Argenx, Boehringer, Eli Lilly, Gilead, Octapharma, Pfizer, UCB and speaker fees from Abbvie, Biogen, Boehringer, Eli Lilly, Gilead, MSD, Novartis, Pfizer, Roche, Sanofi, UCB, Werfen; Anne Gitte Loft: research grant from Novartis andspeaking and/or consulting fees from AbbVie, Janssen, Lilly, MSD, Novartis, Pfizer, UCB, paid instructor from Pfizer; Ziga Rotar: consulting fees from Abbvie, Novartis, Eli Lilly, Pfizer, Janssen and speaker fees from Abbvie, Amgen, Novartis, MSD, Medis, Biogen, Eli Lilly, Pfizer, Sanofi, Lek, Janssen; Katja Perdan Pirkmajer: consulting fees from Abbvie, Novartis, Medis, Eli Lilly, Pfizer, Boehringer Ingelheim and speaker fees from Abbvie, Novartis, MSD, Medis, Eli Lilly, Pfizer, Lek, Janssen; Michael J. Nissen: research grant from Pfizer andconsulting and/or speaker fees from Abbvie, Eli Lilly, Janssens, Novartis, Pfizer; Jana Baranova: none; Gary J. Macfarlane: research grant from GSK; Gareth T.Jones: research grants from Abbvie, Pfizer, UCB, Amgen, GSK and speaker fees from Janssen; Florenzo Iannone: research grant from BMS, Galapagos, Pfizer and consulting and/or speakers fees from Abbvie, Amgen, AstraZeneca, BMS, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, UCB; Roberto Caporali: consulting and/or speaker fees from Abbvie, Amgen, AstraZeneca, BMS, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, UCB; Karin Laas: research grant from Abbvie, Johnson and Johnson, Novartis, Pfizer; Sigrid Vorobjov: none; Daniella Di Giuseppe: none; Tor Olofsson: none; Sella Aarrestad Provan: Research grant from Boehringer Ingelheim and consulting fees from Boehringer Ingelheim; Karen Minde Fagerli: none; Isabel Castrejon: consulting and speaker fees from BMS, Eli-Lilly, Galapagos, Gilead, Janssen, Novartis, MSD, Pfizer, GSK; Lucia Otero-Varela: None; Marleen Van de Sande: research grants from UCB, Janssen, Novartis, Eli Lilly, consulting fees from Novartis, Abbvie, Eli Lilly UCB and speaker fees from Novartis, UCB, Janssen; Irene van der Horst-Bruinsma: Unrestricted Grants received for investigator initiated studies from MSD, Pfizer, AbbVie, UCB. Fees received for lectures from BMS, AbbVie, Pfizer, MSD, UCB, consulting fees from Abbvie, UCB, MSD, Novartis, Lilly and speaker fees from UCB; Dan Nordström: research grant from MSD, consulting fees from Abbvie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, UCB, and speaker fees from Novartis, Pfizer, UCB; Laura Kuusalo: consulting fees from Gilead, Pfizer and speaker fees from Abbvie, Lilly, Medac, Orion, Pfizer, UCB; Miguel Bernades: none; Merete Lund Hetland: Research grants from Novartis, Abbvie, Biogen, BMS, Celltrion, Eli Lilly, Janssen Biologics B.V, Lundbeck Fonden, MSD, Medac, Pfizer, Roche, Samsung Biopies, Sandoz, Novartis, Nordforsk, consulting fees from Abbvie, chaired the steering committee of the Danish Rheumatology Quality Registry (DANBIO, DRQ), which receives public funding from the hospital owners and funding from pharmaceutical companies and speaker fees from Pfizer, Medac, Sandoz; Mikkel Østergaard: Research grant from Abbvie, BMS, Merck, Novartis and UCB and consulting and/or speaker fees from Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Hospira, Janssen, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi, UCB

Acknowledgment

On behalf of the EuroSpA Scientific Committee, the authors acknowledge Novartis Pharma AG for supporting the EuroSpA collaboration.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152388.

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