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ORIGINAL RESEARCH

Effectiveness of secukinumab in radiographic and non-radiographic axial spondyloarthritis: a European routine-care observational study

Sara Nysom Christiansen ,[1] Simon Horskjær Rasmussen,[1] Mikkel Ostergaard,[1,2] Marion Pons,[1] Brigitte Michelsen ,[1,3,4] Karel Pavelka,[5] Catalin Codreanu,[6] Adrian Ciurea ,[7] Bente Glintborg ,[1,2] Maria Jose Santos ,[8,9] Ismail Sari,[10] Ziga Rotar ,[11,12] Bjorn Gudbjornsson ,[13,14] Gary J Macfarlane ,[15] Heikki Relas,[16] Florenzo Iannone ,[17] Karin Laas,[18] Johan K Wallman,[19,20] Marleen van de Sande,[21,22] Sella Aarrestad Provan ,[3,23] Isabel Castrejon,[24,25] Jakub Zavada,[5] Corina Mogosan,[6] Michael J Nissen ,[26] Anne Gitte Loft,[27,28] Anabela Barcelos,[29,30] Yesim Erez,[31] Katja Perdan Pirkmajer,[11,12] Gerdur Grondal,[14,32] Gareth T Jones ,[15] Anna-Mari Hokkanen,[33] Maria Sole Chimenti ,[34] Sigrid Vorobjov,[35] Daniela Di Giuseppe,[36] Tore K Kvien ,[3,37] Lucia Otero-Varela,[38] Irene van der Horst-Bruinsma ,[39] Merete Lund Hetland ,[1,2] Lykke Midtbøll Ørnbjerg [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Sara Nysom Christiansen; sara.nysom.christiansen@regionh.dk

ABSTRACT

Objectives To compare the treatment effectiveness of secukinumab in radiographic (r) versus non-radiographic (nr) axial spondyloarthritis (axSpA) patients treated in routine care across Europe.

Methods Prospectively collected data on secukinumab-treated axSpA patients with known radiographic status were pooled from nine countries.

Remission rates based on patient-reported outcomes (PROs; Numeric Rating Scale (0–10), for example, pain ≤2/Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≤2 and Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (ID) <1.3 after 6/12/24 months of secukinumab treatment were calculated.

Remission and drug retention rates in r-axSpA versus nr-axSpA patients were compared by logistic and Cox regression models (unadjusted/adjusted for age+sex/adjusted for multiple confounders).

Results Overall, 1161 secukinumab-treated patients were included (r-axSpA/nr-axSpA: 922/239). At baseline, r-axSpA patients had longer disease duration and higher C reactive protein, were more often male and HLA-B27 positive and had received fewer prior biological or targeted synthetic disease-modifying antirheumatic drugs compared with nr-axSpA patients, whereas PROs were largely similar.

During follow-up, crude PRO remission rates were significantly higher in r-axSpA compared with nr-axSpA patients (6 months: pain≤2: 40%/28%, OR=1.7; BASDAI≤2: 37%/25%, OR=1.8), as were drug retention rates (24 months: 66%/58%, HR 0.73 (ref: r-axSpA)). Proportions of patients achieving ASDAS ID were low for both groups, particularly nr-axSpA (6 months: 11%/8%).

However, when adjusting for age+sex, these differences diminished, and after adjusting for multiple confounders, no significant between-group differences remained for either remission or drug retention rates.

Conclusion Crude remission/drug retention rates in European secukinumab-treated patients were higher

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Real-world comparisons of treatment retention, remission and response rates in radiographic (r-axSpA) versus non-radiographic (nr-axSpA) axial spondyloarthritis (axSpA) patients have so far only been performed for TNF-inhibitor treatment, with varying findings.

WHAT THIS STUDY ADDS

⇒ Our study demonstrated similar secukinumab treatment effectiveness in r-axSpA and nr-axSpA patients in adjusted analyses.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Observed differences in secukinumab treatment effectiveness between r-axSpA and nr-axSpA patients seem to be explained by factors other than radiographic status per se. The inclusion of additional factors such as C reactive protein level and the number of previous biological or targeted synthetic disease-modifying antirheumatic drugs could prove beneficial for informing clinical decision-making compared with radiographic status alone.

in r-axSpA compared with nr-axSpA patients. In adjusted analyses, secukinumab effectiveness was similar in both groups, suggesting that observed differences were related to factors other than radiographic status.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic, inflammatory disease that mainly affects the axial skeleton, that is, the sacroiliac joints (SIJ) and spine.[1] The inflammation causes inflammatory back pain, reduced physical function and frequently structural damage.[1 2] The primary treatment goals in axSpA are to maximise health-related quality of life through control of symptoms and inflammation, to prevent progressive structural damage and to maintain physical function and ability to work.[3 4]

The spectrum of axSpA includes non-radiographic axSpA (nr-axSpA) and radiographic axSpA (r-axSpA), that is, without and with SIJ structural damage as determined by conventional radiography.[1 5 6] The nature of nr-axSpA has caused some controversy in recent years, with some arguing that it represents an earlier and/or milder disease stage that may progress to r-axSpA in a significant proportion of patients while others believe that it represents a separate entity.[7]

Independently of radiographic status, initial treatment of axSpA consists of non-steroidal anti-inflammatory drugs combined with regular exercise. In case of insufficient effectiveness of these interventions, biological or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), most often a tumour necrosis factor inhibitor (TNFi), are added.[3 4] Since 2015, secukinumab—a fully human IgG1 monoclonal antibody targeting interleukin 17A[8 9]—has been approved by the European Medicines Agency for use in r-axSpA, and since 2020 also for active nr-axSpA with objective signs of inflammation judged by elevated C reactive protein (CRP) and/or inflammation on MRI.[10]

Patient-reported outcomes (PROs) are increasingly considered of importance in the evaluation of rheumatic diseases and several PROs—including pain, morning stiffness and fatigue—are incorporated in the updated Assessment of Spondyloarthritis International Society (ASAS)/Outcome Measures in Rheumatology (OMERACT) core set for axSpA.[11 12] Of these core domains, pain has consistently been reported to be the most important item across r-axSpA and nr-axSpA patients, across countries and across sex, and around 80% of all patients report pain to be causing recurrent limitation to their normal daily activities.[13]

To date, limited real-world evidence on outcomes of secukinumab treatment in patients with axSpA exists,[14–17] and the effect on PROs has only been investigated in randomised controlled trials[18 19] with strict inclusion and exclusion criteria and thus limited generalisability.[20] Furthermore, real-world comparisons of treatment retention, remission and response rates in r-axSpA versus nr-axSpA patients have only been investigated in TNFi[21–27] and not in secukinumab-treated patients.

The aim of this study was to compare the treatment effectiveness of secukinumab in patients with r-axSpA versus nr-axSpA managed in routine care across European countries with a special focus on pain and other PROs.

Table 1 Secukinumab-treated patients in the nine registries in the EuroSpA collaboration including numbers of radiographic and non-radiographic axSpA patients included in the current study

Registry/country	Radiographic axSpA patients	Non-radiographic axSpA patients	Patients treated with secukinumab but no data on radiographic status (not included)
ATTRA (Czech Republic)	243	32	59
biorx.si (Slovenia)	77	13	0
BSRBR-AS (UK)	19	7	14
DANBIO (Denmark)	76	33	237
ICEBIO (Iceland)	4	0	12
reuma.pt (Portugal)	92	16	49
RRBR (Romania)	247	18	0
SCQM (Switzerland)	95	112	0
TURKBIO (Turkey)	69	8	165
All	922	239	536

axSpA, axial spondyloarthritis.

METHODS

The European Spondyloarthritis Research Collaboration Network and data collection

This study was conducted within the European Spondyloarthritis Research Collaboration Network (EuroSpA).[28] The EuroSpA collaboration investigates research questions by use of prospectively collected real-life data on patients with spondyloarthritis.[17 29–31] The network was initiated in 2016, and currently, 16 European registries are participating. Of these, nine registries record data separately regarding patients with r-axSpA and nr-axSpA and were included in this study: ATTRA (Czech Republic), biorx.si (Slovenia), BSRBR-AS (United Kingdom), DANBIO (Denmark), ICEBIO (Iceland), Reuma.pt (Portugal), RRBR (Romania), SCQM (Switzerland) and TURKBIO (Turkey) (table 1).

In the individual registries, available data were structured according to a prespecified variable list, anonymised and securely uploaded to the EuroSpA server. Subsequently, data were harmonised, quality checked and pooled before statistical analyses were conducted.

Patients

Inclusion criteria in this study were IL-17A inhibitor naïve patients with a registered axSpA diagnosis and age ≥18 years at the time of diagnosis, who initiated secukinumab

treatment in one of the nine relevant EuroSpA registries between January 2015 and June 2021 and were registered as either fulfilling the radiographic criterion of the modified New York criteria set (r-axSpA) or registered as not fulfilling this (nr-axSpA).[6] Patients with no registration of either fulfilling or not fulfilling the criteria were not included in the study. Patients were required to have been followed in the registry since secukinumab treatment initiation, and thus with a registered start date of secukinumab treatment.

Demographics and clinical characteristics

Assessments included demographics, time from diagnosis to secukinumab initiation, start and (if relevant) stop dates of secukinumab treatment, initial secukinumab dosing, numbers of previous b/tsDMARDs, concomitant conventional synthetic DMARDs (csDMARDs), current smoking (yes/no), body mass index (kg/m^2), human leucocyte antigen B27 (HLA-B27) status and the presence of comorbidities (cardiovascular disease, diabetes, kidney disease, all ever/never during disease course).

PROs included Visual Analogue Scales (VAS 0–100) or Numerical Rating Scales (NRS 0–10) of patient's global assessment of disease activity (PGA), VAS/NRS pain and VAS/NRS fatigue, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI, 0–100 or 0–10) with separate registration of back pain (BASDAI question 2 (Q2)), joint pain (BASDAI question 3 (Q3)) and stiffness (BASDAI question 5 (Q5)) and Bath Ankylosing Spondylitis Functional Index (BASFI 0–100 or 0–10).

The disease activity measures and functional indices collected were Physician's global assessment of disease activity (PhGA, VAS, 0–100 or NRS, 0–10), Bath Ankylosing Spondylitis Metrology Index (BASMI), 28 tender/swollen joint counts, (CRP, mg/L), erythrocyte sedimentation rate (ESR, mm/hour) and Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP/ESR.

Scores on a VAS 0–100 scale were converted to 0–10 by dividing with 10 and rounding to the nearest integer and therefore scores were harmonised on a common 0–10 integer scale. HAQ was collected on a 0–3 scale. Three registries (RRBR, biorx.si and SCQM) used a 0–10 NRS for pain, fatigue, PGA and PhGA while the remaining registries used a VAS 0–100 scale. For RRBR, VAS pain was not collected separately but registered from BASDAI question 2 (Q2, back pain).

Remission rates

There is no international consensus on cut-off values for PRO remission in axSpA patients, but in 2001, the ASAS working group proposed a definition of partial remission in axSpA patients including a value of ≤2 in the four domains: PGA, pain, function and inflammation.[32] Based on this, the following PRO remission criteria were used in this study: pain remission ≤2, PGA remission ≤2, fatigue remission ≤2 and BASFI remission ≤2. Furthermore, we evaluated BASDAI remission ≤2,[33] including separate registration of back pain remission (BASDAI Q2) ≤2, stiffness (BASDAI Q5) ≤2 and joint pain (BASDAI Q3) ≤2. Regarding composite scores, we used the ASDAS inactive disease (ID) (<1.3) as remission cut-off.[34]

All remission rates were assessed at 6, 12 and 24 months. The 6, 12 and 24 months visits were defined as available visits 90–270 days, 271–450 days and 631–810 days from secukinumab initiation 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 in time to 6, 12 or 24 months was prioritised.

Statistical analyses

Statistical analyses were performed according to a predefined statistical analysis plan (see online supplemental materials). Continuous data are presented as median with IQR and categorical variables as numbers with percentages.

Remission and response rates were calculated as both crude rates and LUNDEX adjusted rates.[35] LUNDEX correction[35] was applied to integrate information on response and drug retention in one combined measurement and thereby resembles the 'intention-to-treat' strategy ((fraction of patients adhering to therapy)×(fraction of patients fulfilling remission/response criteria)).

Comparison of remission and response rates at 6, 12 and 24 months follow-up of r-axSpA versus nr-axSpA patients were performed by unadjusted logistic regression analyses (model 1), with adjustment for age and sex (model 2) and in a model with adjustments for age, sex, registry, CRP at time of secukinumab initiation (baseline CRP), time from diagnosis to secukinumab initiation, and the number of previous b/tsDMARDs (0/1/≥2) (model 3). The analyses were performed on patients with available 6/12/24 months follow-up on secukinumab treatment, thus patients who had stopped secukinumab prior to respective assessment timepoint were not taken into account. In addition, analyses with stepwise introduction of individual covariates were performed to assess the contribution of each covariate. Multivariate imputation by chained equations (MICE) was used for imputation of baseline CRP in the relevant models. No other imputations were performed. All other covariates in the adjusted analyses had complete data. 100 data sets were imputed by predictive mean matching and parameter estimates were pooled by Rubin's rules implemented in the MICE R-package.[36] Comparisons of disease activity and changes (from secukinumab start) at 6, 12 and 24 months were performed with analysis of covariance, unadjusted and adjusted for confounders, analogously to the above logistic regression models. Drug retention rates at 6, 12 and 24 months were estimated using Kaplan-Meier survival analyses. Comparisons of the retention rates for r-axSpA versus nr-axSpA patients were performed by unadjusted Cox regression, adjusted for age and sex and adjusted for all confounders as for the above models. CRP at secukinumab initiation was imputed following

the same procedure as for the remission/response rate comparisons.

As sensitivity analyses, comparisons of PRO remission rates were additionally performed including additional potential confounders. Two models were performed in patients with available data: sensitivity model 1 (adjustment with the fully adjusted model+smoking status) and sensitivity model 2 (adjustment with the fully adjusted model+HLA-B27).

Observations were censored according to date of data extraction, date of death or end of registry follow-up, whichever came first. The baseline date was defined as the secukinumab treatment start date. A significance level of 0.05 was used. Statistical analyses were performed with R V.4.3.1.[37]

RESULTS

From the 9 registries (table 1), a total of 922 r-axSpA and 239 nr-axSpA patients initiating a first secukinumab treatment were identified.

Comparison of baseline characteristics

Patients with nr-axSpA differed numerically from those with r-axSpA in the majority of the registered baseline characteristics (table 2). Patients with nr-axSpA had shorter disease duration (4 vs 7 years) and fewer were male (36% vs 61%) and HLA-B27 positive (55% vs 80%) compared with r-axSpA patients. No relevant differences regarding comorbidities and tender/swollen joint counts were observed between the two groups. CRP and ASDAS-CRP scores were higher in r-axSpA. PROs were largely similar between the two groups, while PhGA was higher in r-axSpA patients.

A higher percentage of nr-axSpA patients had received at least one previous b/tsDMARD compared with r-axSpA patients (74% vs 61%) and slightly more nr-axSpA than r-axSpA patients were initiated on the higher secukinumab dose (300 mg) (7% vs 3%) while similar percentages of nr-axSpA and r-axSpA patients were registered as receiving concomitant csDMARD (table 2).

Unadjusted comparisons of PROs and disease activity measures during follow-up

While pain, fatigue and PGA were similar at baseline in the two groups, 6/12/24 months values were markedly lower in r-axSpA patients compared with nr-axSpA patients (pain: 3/3/2 vs 5/4/4, fatigue: 3/3/3 vs 5/4/4, PGA: 3/3/2 vs 5/4/4) (table 3). Similarly, remission rates at 6/12/24 months for these three PROs were significantly higher for r-axSpA patients compared with nr-axSpA patients (eg, crude 6/12/24 months pain remission rates: 40%/48%/51% for r-axSpA vs 28%/31%/36% for nr-axSpA) (table 3, figure 1).

BASDAIs were also significantly lower (at 6 and 12 months) and remission rates significantly higher (6, 12 and 24 months) in r-axSpA compared with nr-axSpA (table 3, figure 1). BASDAI questions relating to back pain (Q2), joint pain (Q3) and stiffness (Q5) similarly showed comparable baseline values but lower follow-up values and higher remission rates in the r-axSpA group compared with the nr-axSpA group (table 3).

Unadjusted logistic regression analyses showed an odds ratio (OR (CI)) of 1.7 (1.1 to 2.7) for obtaining 6 months pain remission and an OR of 1.8 (1.2 to 2.8) for obtaining 6 months BASDAI remission in r-axSpA compared with nr-axSpA patients (table 3, figure 2 (model 1)). Similar pattern of results was found for most remaining PROs, although not all significant (table 3).

Although ASDAS values were largely similar across the two groups at baseline, the ASDAS ID rates were very low during follow-up for both groups, but with numerically higher values for r-axSpA patients (6/12/24 months values: 11%/13%/18% for r-axSpA vs 8%/6%/13% for nr-axSpA) (table 3, figure 1).

Adjusted comparison of PROs and disease activity measures during follow-up

Adjustment for drug retention (LUNDEX adjustment) generally resulted in lower remission rates—compared with crude values—with decreasing values over time in both r-axSpA and nr-axSpA patients, but the adjustments did not affect the between-group differences, as LUNDEX-adjusted remission rates were still markedly higher in r-axSpA patients compared with nr-axSpA patients (table 3, figure 1).

When analyses regarding differences between r-axSpA and nr-axSpA patients (logistic regression analyses) were adjusted for age and sex, the differences in PROs diminished (figure 2, model 2), and the between-group differences disappeared after adjustment for multiple possible confounders (figure 2, MODEL 3). Subanalyses investigating the effect of the individual confounders showed that these changes were mainly a result of adjustments for registry and for some outcomes adjustments for previous b/tsDMARDs (online supplemental table 3).

Changes in values from baseline for all parameters, including estimated between-group differences, can be seen in online supplemental table 3.

Sensitivity analyses

Similarly to the above results, in sensitivity analyses further adjusted for smoking status and HLA-B27 and performed in patients with available data, no relevant differences in pain, PGA and HAQ remission rates between r-axSpA and nr-axSpA patients were found (online supplemental table 3).

Comparison of secukinumab retention rates up to 24 months

Secukinumab retention rates were higher in r-axSpA patients (87%/75%/66% at 6/12/24 months) than in nr-axSpA patients (78%/69%/58%) (figure 3). Fewer nr-axSpA patients remained on secukinumab treatment at 24 months when compared with r-axSpA patients, with an HR (95% CI) of 0.73 (0.56 to 0.94). When adjusting for age and sex, the difference in retention rates between the two groups diminished (HR 0.77, 95% CI 0.59 to 0.99),

Table 2 Baseline characteristics for radiographic and non-radiographic axial spondyloarthritis (axSpA) patients initiating secukinumab treatment between January 2015 and June 2021

	Radiographic axSpA* (n=922)		Non-radiographic axSpA† (n=239)	
	Value	N available	Value	N available
Age, years, median (IQR)	47 (38–55)	922	46 (37–55)	239
Sex (male), %	60.6	922	36.4	239
HLA-B27 positive, %	80.2	776	54.8	217
BMI, kg/m^2, median (IQR)	27 (24–31)	823	27 (23–30)	201
Years since diagnosis, median (IQR)	7 (3–14)	909	4 (2–8)	234
Current smoking, %	31.8	883	25.8	221
Comorbidities,‡ %				
Cardiovascular disease	26.6	842	22.2	212
Diabetes	10.2	617	6.0	182
Kidney disease	3.4	835	2.9	207
Extra-articular manifestations				
Uveitis (ever/never), %	14.7	740	5.9	188
IBD (ever/never), %	2.7	820	3	199
Psoriasis (ever/never, %	7.9	826	11.9	202
Enthesitis (ever/never), %	26.4	666	64.1	181
Dactylitis (ever/never), %	11.9	430	15.2	164
Secukinumab 150 mg, %	73.4	809	70.2	181
Secukinumab 300 mg, %	3.0	809	7.2	181
Secukinumab, other/unknown dose, %	23.6	809	22.7	181
Number of previous b/tsDMARDs				
No previous b/tsDMARDs, %	38.8	922	25.9	239
1 previous b/tsDMARD, %	26.1	922	23.4	239
≥2 previous b/tsDMARDs, %	35.1	922	50.7	239
Concomitant csDMARD	32.2	793	29.1	206
Concomitant—MTX, %	12.6	788	15.2	204
Concomitant—SSZ, %	22.1	789	14.9	201
Concomitant—LEF, %	1.2	770	2.0	199
PROs and disease activity measures, median (IQR)				
Pain	7 (6–8)	649	7 (6–8)	132
Fatigue	7 (5–8)	583	8 (6–8)	118
PGA	7 (5–8)	651	7 (6–8)	133
BASDAI	6.4 (5.0–7.6)	698	6.7 (4.9–7.6)	141
BASFI	5.6 (3.6–7.3)	489	5.5 (2.9–7.2)	120
PhGA	6 (3–7)	431	4 (3–7)	124
BASMI	1 (0.2–4)	84	1 (0.2–2)	49
28 tender joint counts	0 (0–2)	292	0 (0–2)	49
28 swollen joint counts	0 (0–0)	331	0 (0–0)	100
CRP, mg/L	16 (5—31)	719	5 (2–14)	157
CRP>10 mg/L, %	61.5	719	33.8	157
ESR, mm/hour	29 (14–47)	602	14 (8–32)	121
ASDAS-CRP	4.0 (3.2–4.7)	627	3.6 (2.9–4.3)	123

Pain, fatigue, PGA, BASDAI, BASFI and PhGA were scored on a 0–10 Numeric Rating Scale.
*Patients registered as fulfilling the radiographic criterion of the modified New York criteria set.[5]
†Patients registered as not fulfilling the radiographic criterion of the modified New York criteria set.[5]
‡Comorbidities were defined as ever or never present.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Function Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMI, body mass index; b/ts/csDMARD, biological/targeted synthetic/conventional synthetic disease-modifying antirheumatic drugs; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; LEF, leflunomide; MTX, methotrexate; PGA, patient's global assessment; PhGA, physician global assessment; PROs, patient-reported outcomes; SLZ, sulfasalazine.

Table 3 Patient-reported outcomes (PROs) and disease activity measures at baseline and 6, 12 and 24 months after secukinumab initiation in radiographic and non-radiographic axSpA patients

		PROs and disease activity measures							Remission rates								
		Radiographic axSpA*		Non-radiographic axSpA†		Estimated difference (CI)			Radiographic axSpA*			Non-radiographic axSpA†			OR (95% CI)		
	Months	Median (IQR)	N available	Median (IQR)	N available	Unadjusted model 1	Adjusted‡ model 2	Adjusted§ model 3	Crude (%)	LUNDEX adj. (%)	N available	Crude (%)	LUNDEX adj. (%)	N available	Unadjusted model 1	Adjusted‡ model 2	Adjusted§ model 3
Pain	0	7 (6–8)	649	7 (6–8)	132	0.0 (–0.4 to 0.4)	**–0.1 (0.5 to 0.3)**	–0.4 (–0.8 to 0.1)	–	–	–	–	–	–	–	–	–
	6	3 (2–5)	574	5 (2–7)	108	**–0.9 (–1.4 to –0.4)**	**–0.9 (–1.4 to –0.3)**	–0.1 (–0.7 to 0.5)	40	30	574	28	18	108	**1.7 (1.10 to 2.74)**	**1.7 (1.04 to 2.63)**	1.3 (0.77 to 2.16)
	12	3 (2–5)	388	4 (2–6)	71	**–0.7 (–1.3 to –0.1)**	**–0.7 (–1.3 to –0.01)**	0.1 (–0.6 to 0.8)	48	28	388	31	15	71	**2.1 (1.21 to 3.56)**	**2.0 (1.15 to 3.45)**	1.5 (0.82 to 2.81)
	24	2 (1–4)	185	4 (2–6)	31	–0.8 (–1.7 to 0.1)	–0.7 (–1.7 to 0.2)	0.1 (–0.9 to 1.1)	51	22	185	36	12	31	1.9 (0.85 to 4.16)	1.8 (0.78 to 3.94)	0.8 (0.30 to 2.26)
Fatigue	0	7 (5–8)	583	8 (6–8)	118	–0.3 (–0.8 to 0.1)	–0.3 (–0.8 to 0.1)	–0.3 (–0.8 to 0.2)	–	–	–	–	–	–	–	–	–
	6	3 (2–5)	516	5 (2–8)	97	**–1.2 (–1.8 to –0.6)**	**–1.0 (–1.6 to –0.4)**	0.2 (–0.5 to 0.9)	39	29	516	29	19	97	1.6 (0.99 to 2.55)	1.5 (0.92 to 2.42)	1.0 (0.58 to 1.74)
	12	3 (2–5)	348	4 (2–7)	61	**–0.8 (–1.5 to –0.1)**	–0.7 (–1.4 to 0.01)	0.3 (–0.5 to 1.1)	45	27	348	33	16	61	1.7 (0.99 to 3.03)	1.6 (0.88 to 2.86)	1.0 (0.49 to 1.92)
	24	3 (2–5)	166	4 (2–6)	24	–0.7 (–1.8 to 0.5)	–0.4 (–1.5 to 0.8)	1.0 (–0.2 to 2.3)	45	20	166	29	10	24	2.0 (0.78 to 5.11)	1.7 (0.66 to 4.51)	0.6 (0.17 to 2.02)
PGA	0	7 (5–8)	651	7 (6–8)	133	–0.1 (–0.5 to 0.3)	–0.2(–0.6 to 0.2)	–0.3(–0.7 to 0.1)	–	–	–	–	–	–	–	–	–
	6	3 (2–6)	601	5 (2–7)	115	**–0.9 (–1.4 to –0.4)**	**–0.7(–1.2 to –0.2)**	0.2 (–0.4 to 0.8)	37	27	601	26	17	115	**1.6 (1.05 to 2.58)**	1.5 (0.95 to 2.93)	1.0 (0.58 to 1.64)
	12	3 (1–5)	402	3 (2–6)	73	**–0.8 (–1.4 to –0.2)**	**–0.7 (–1.3 to –0.1)**	0.3 (–0.4 to 0.9)	48	28	402	36	18	73	1.6 (0.97 to 2.75)	1.5 (0.90 to 2.57)	0.9 (0.49 to 1.67)
	24	2 (1–4)	193	3 (2–7)	31	**–1.3 (–2.2 to –0.3)**	**–1.2 (–2.2 to –0.3)**	–0.1 (–1.1 to 1.0)	53	23	193	36	12	31	2.1 (0.94 to 4.60)	1.9 (0.86 to 4.32)	0.6 (0.22 to 1.81)
BASDAI	0	6.4 (5–7.6)	698	6.7 (4.9–7.6)	141	–0.1 (–0.4 to 0.3)	–0.1 (–0.5 to 0.3)	–0.1 (–0.5 to 0.2)	–	–	–	–	–	–	–	–	–
	6	2.9 (1.5–5)	658	4.2 (2.1–6.3)	124	**–0.9 (–1.3 to –0.4)**	**–0.7 (–1.2 to –0.3)**	0.2 (–0.4 to 0.7)	37	28	658	25	16	124	**1.8 (1.15 to 2.75)**	**1.6 (1.05 to 2.55)**	1.1 (0.64 to 1.74)
	12	2.5 (1.2–4.2)	437	3.8 (2.2–5.3)	79	**–0.8 (–1.4 to –0.3)**	**–0.8 (–1.3 to –0.2)**	0.1 (–0.5 to 0.6)	41	24	437	23	11	79	**2.4 (1.37 to 4.20)**	**2.4 (1.34 to 4.16)**	1.5 (0.77 to 2.75)
	24	2.2 (1–4.4)	210	3.2 (1.6–4.9)	33	–0.6 (–1.5 to 0.2)	–0.5 (–1.4 to 0.4)	0.6 (–0.3 to 1.5)	49	21	210	27	9	33	**2.5 (1.11 to 5.70)**	**2.4 (1.05 to 5.53)**	1.0 (0.36 to 2.96)
Back pain (BASDAI Q2)	0	8 (6–9)	698	7 (6–8)	141	0.1 (–0.3 to 0.6)	0.1 (–0.3 to 0.5)	0.0 (–0.5 to 0.4)	–	–	–	–	–	–	–	–	–
	6	3 (2–6)	658	5 (2–7)	124	**–0.9 (–1.4 to –0.4)**	**–0.8 (–1.3 to –0.2)**	0.2 (–0.4 to 0.8)	37	27	658	29	19	124	1.4 (0.93 to 2.15)	1.3 (0.87 to 2.06)	0.9 (0.54 to 1.39)
	12	3 (2–5)	437	5 (2–7)	79	**–1.0 (–1.6 to –0.3)**	**–0.9 (–1.6 to –0.3)**	0.1 (–0.6 to 0.8)	41	24	437	23	13	79	**1.9 (1.10 to 3.21)**	**1.9 (1.08 to 3.21)**	1.3 (0.69 to 2.35)
	24	3 (1–5)	210	4 (2–6)	33	–0.7 (–1.7 to 0.3)	–0.6 (–1.6 to 0.4)	0.6 (–0.5 to 1.6)	50	22	210	36	12	33	1.7 (0.80 to 3.68)	1.7 (0.77 to 3.64)	0.9 (0.36 to 2.20)
Joint pain (BASDAI Q3)	0	6 (3–8)	698	6 (3–8)	141	–0.3(–0.8 to 0.3)	–0.2(–0.8 to 0.3)	–0.2 (–0.8 to 0.4)	–	–	–	–	–	–	–	–	–
	6	2 (1–5)	658	4 (1–6)	124	**–1.0 (–1.5 to –0.5)**	**–0.8 (–1.3 to –0.3)**	0.0 (–0.6 to 0.6)	54	40	658	36	23	124	**2.2 (1.45 to 3.21)**	**2.0 (1.31 to 2.97)**	**1.3 (0.81 to 2.03)**
	12	2 (0–4)	437	3 (1–5)	79	–0.6 (–1.2 to 0.0)	–0.5 (–1.1 to 0.1)	0.2 (–0.5 to 0.8)	61	36	437	46	22	79	**1.9 (1.17 to 3.07)**	**1.8 (1.10 to 2.93)**	**1.1 (0.64 to 1.98)**
	24	2 (0–4)	210	3 (1–6)	33	**–1.2 (–2.1 to –0.2)**	**–1.0 (–2.0 to –0.1)**	0.3 (–0.7 to 1.3)	65	29	210	39	13	33	**2.9 (1.35 to 6.16)**	**2.6 (1.18 to 5.55)**	**1.1 (0.43 to 2.94)**
Stiffness (BASDAI Q5)	0	7 (5–9)	698	7 (5–8)	141	0.1 (–0.4 to 0.6)	0.0 (–0.5 to 0.4)	–0.1 (–0.7 to 0.3)	–	–	–		–	–	–	–	–
	6	3 (1–5)	658	4 (2–6)	124	**–0.6 (–1.1 to –0.1)**	**–0.5 (–1.1 to –0.01)**	0.1 (–0.5 to 0.7)	44	33	658	34	22	124	**1.5 (1.02 to 2.28)**	1.5 (0.99 to 2.26)	1.1 (0.69 to 1.70)
	12	2 (1–5)	437	4 (1–6)	79	**–0.7 (–1.3 to –0.03)**	**–0.7 (–1.3 to –0.05)**	0.1 (–0.6 to 0.8)	50	29	437	41	20	79	1.5 (0.91 to 2.43)	1.5 (0.91 to 2.46)	1.1 (0.63 to 1.90)
	24	2 (1–5)	210	3 (1–4)	33	–0.2 (–1.1 to 0.8)	–0.1 (–1.1 to 0.8)	0.8 (–0.2 to 1.9)	58	25	210	49	16	33	1.5 (0.70 to 3.08)	1.4 (0.67 to 3.06)	0.6 (0.23 to 1.59)

Continued

Table 3 Continued

		PROs and disease activity measures							Remission rates								
		Radiographic axSpA*		Non-radiographic axSpA†		Estimated difference (CI)			Radiographic axSpA*			Non-radiographic axSpA†			OR (95% CI)		
	Months	Median (IQR)	N available	Median (IQR)	N available	Unadjusted model 1	Adjusted‡ model 2	Adjusted§ model 3	Crude (%)	LUNDEX adj. (%)	N available	Crude (%)	LUNDEX adj. (%)	N available	Unadjusted model 1	Adjusted‡ model 2	Adjusted§ model 3
BASFI	0	5.6 (3.6–7.3)	489	5.5 (2.9–7.2)	120	0.2 (–0.3 to 0.7)	0.1 (–0.4 to 0.6)	0.0 (–0.5 to 0.6)	–	–	–	–	–	–	–	–	–
	6	3.3 (1.6–5.9)	428	4.4 (2–6)	105	–0.4 (–0.9 to 0.2)	–0.4 (–0.9 to 0.2)	0.0 (–0.7 to 0.7)	32	24	428	29	18	105	1.2 (0.74 to 1.88)	1.2 (0.74 to 1.98)	1.0 (0.59 to 1.74)
	12	3.2 (1.3–5.8)	262	3.2 (1.6–4.8)	67	0.2 (–0.4 to 0.9)	0.2 (–0.5 to 0.9)	0.4 (–0.3 to 1.2)	36	21	262	31	15	67	1.2 (0.68 to 2.15)	1.3 (0.69 to 2.28)	1.2 (0.63 to 2.44)
	24	2.8 (1.3–5.9)	122	2.7 (1.2–4.5)	29	0.4 (–0.7 to 1.4)	0.6 (–0.4 to 1.7)	0.8 (–0.3 to 2.0)	41	18	122	38	13	29	1.1 (0.49 to 2.63)	1.0 (0.42 to 2.49)	0.8 (0.30 to 2.26)
ASDAS–CRP	0	4.0 (3.2–4.7)	627	3.6 (2.9–4.3)	123	**0.3 (0.1 to 0.5)**	**0.3 (0.1 to 0.5)**	0.0 (–0.1 to 0.2)	–	–	–	–	–	–	–	–	–
	6	2.3 (1.7–3.1)	570	2.6 (2.0–3.2)	102	–0.1 (–0.3 to 0.1)	–0.1 (–0.3 to 0.2)	0.1 (–0.1 to 0.4)	11	8	570	8	5	102	1.5 (0.68 to 3.15)	1.5 (0.68 to 3.28)	1.4 (0.58 to 3.18)
	12	2.1 (1.5–2.8)	385	2.4 (1.9–3.0)	67	–0.2 (–0.4 to 0.1)	–0.2 (–0.4 to 0.1)	0.1 (–0.2 to 0.3)	13	7	385	6	3	67	2.3 (0.80 to 6.61)	2.1 (0.73 to 6.25)	1.9 (0.58 to 5.97)
	24	2.0 (1.5–2.8)	191	2.1 (1.6–2.9)	24	–0.2 (–0.6 to 0.2)	–0.2 (–0.6 to 0.3)	0.3 (–0.2 to 0.7)	18	8	191	13	4	24	1.6 (0.44 to 5.60)	1.3 (0.36 to 4.86)	0.8 (0.15 to 3.74)

Pain, fatigue, PGA, BASDAI and BASFI are presented on a 0–10 integer scale. Remission rates were defined as pain ≤2, fatigue ≤2, PGA ≤2, BASDAI (including subquestions) ≤2 and BASFI≤2. ASDAS remission was defined as ASDAS inactive disease (<1.3). Significant values are indicated by bold type.
*Patients registered as fulfilling the radiographic criterion of the modified New York criteria set.[5]
†Patients registered as not fulfilling the radiographic criterion of the modified New York criteria set.[5]
‡P values were adjusted for age and sex.
§P values were adjusted for age, sex, registry, baseline CRP, time from diagnosis to secukinumab initiation and numbers of previous b/tsDMARDs (0/1/≥2).
ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; b/tsDMARDs, biological or targeted synthetic disease-modifying antirheumatic drugs; CRP, C reactive protein; PGA, Patient's global assessment of disease activity.

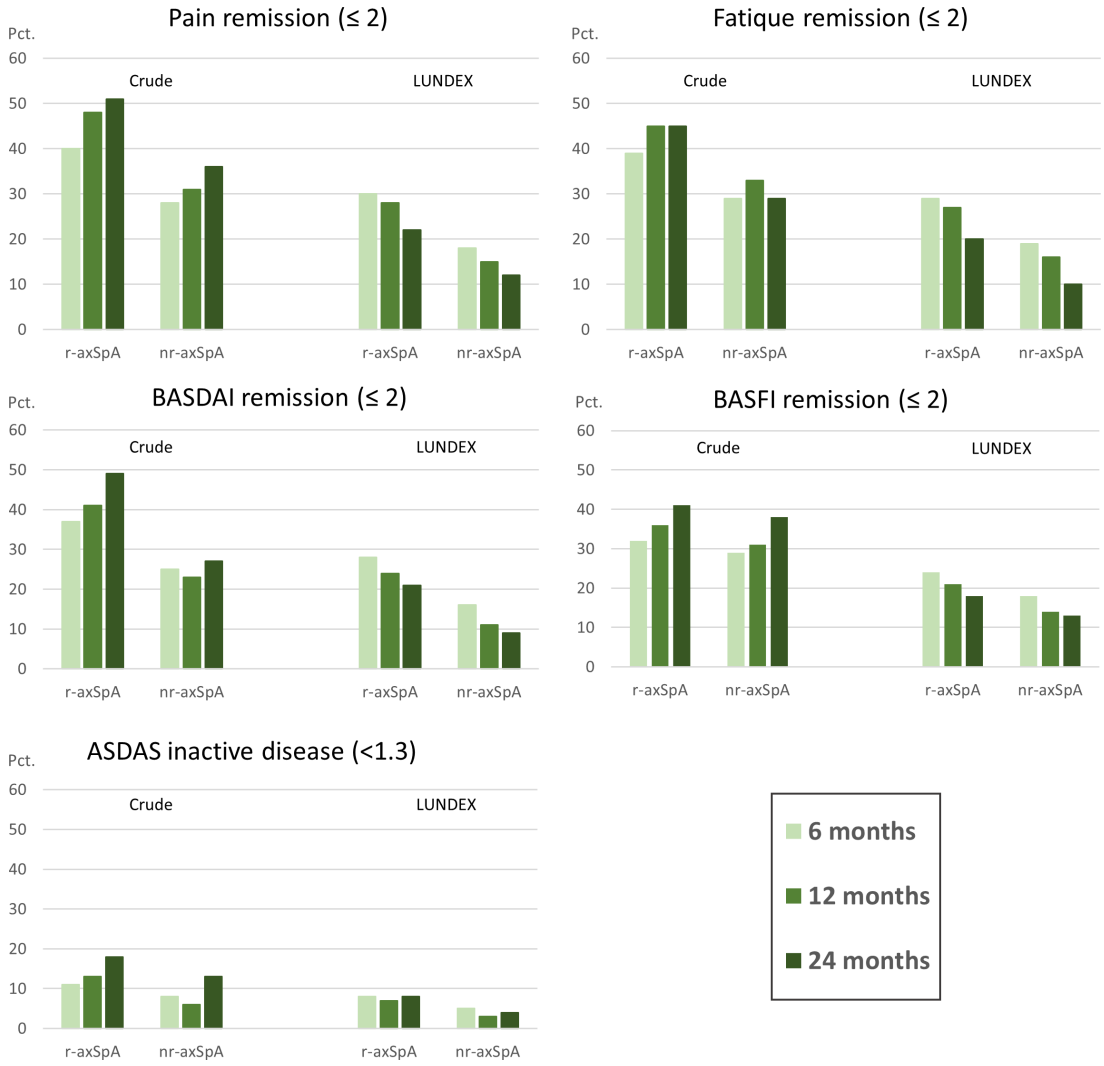


Figure 1 Crude-adjusted and LUNDEX-adjusted remission rates at 6, 12 and 24 months after secukinumab initiation in radiographic and non-radiographic axial spondyloarthritis (r- and nr-axSpA) patients. Pain, fatigue, BASDAI and BASFI are presented on a 0–10 integer scale. ASDAS, Ankylosing Spondylitis Disease Activity Score; pct, percentage; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index. LUNDEX; LUNDEX-adjusted remission rates (fraction of patients adhering to therapy)×(fraction of patients fulfilling remission/response criteria).[35]

and when adjusting for multiple confounders (model 3), no differences remained (HR 0.98, 95% CI 0.69 to 1.38) (figure 3).

DISCUSSION

Our study is the first to evaluate differences between secukinumab-treated r-axSpA and nr-axSpA patients followed in routine clinical practice across Europe. We found that although baseline PROs were similar in the two groups, crude PRO remission rates during follow-up were lower in nr-axSpA patients compared with r-axSpA patients. However, these differences disappeared after adjustments for baseline confounders, mainly registry and numbers of previous b/tsDMARDs. Secukinumab retention rates were also lower in nr-axSpA patients compared with r-axSpA patients, but again the observed differences disappeared after adjustments. In line with previous studies,[21–23 25 26] we found differences in demographic and clinical baseline characteristics, as more r-axSpA patients were males, HLA-B27 positive and had elevated baseline CRP, whereas nr-axSpA patients generally had received more previous b/tsDMARDs. Altogether, our study implies, that although nr-axSpA may generally appear to represent a more difficult-to-treat patient group compared with r-axSpA, this seems to be explained by factors other than radiographic status per se since we found secukinumab treatment effectiveness after adjustments to be similar in the two groups.

Previous studies focusing on r-axSpA versus nr-axSpA have only been performed in TNFi-treated patients.[21–27] Results regarding TNFi-treated patients may not be directly comparable to secukinumab-treated patients since the latter are more commonly biological experienced.[38] However, secukinumab and TNFi have been shown to perform similarly in axSpA patients, who have failed a first biologic.[38] Studies in TNFi-treated patients found higher overall treatment

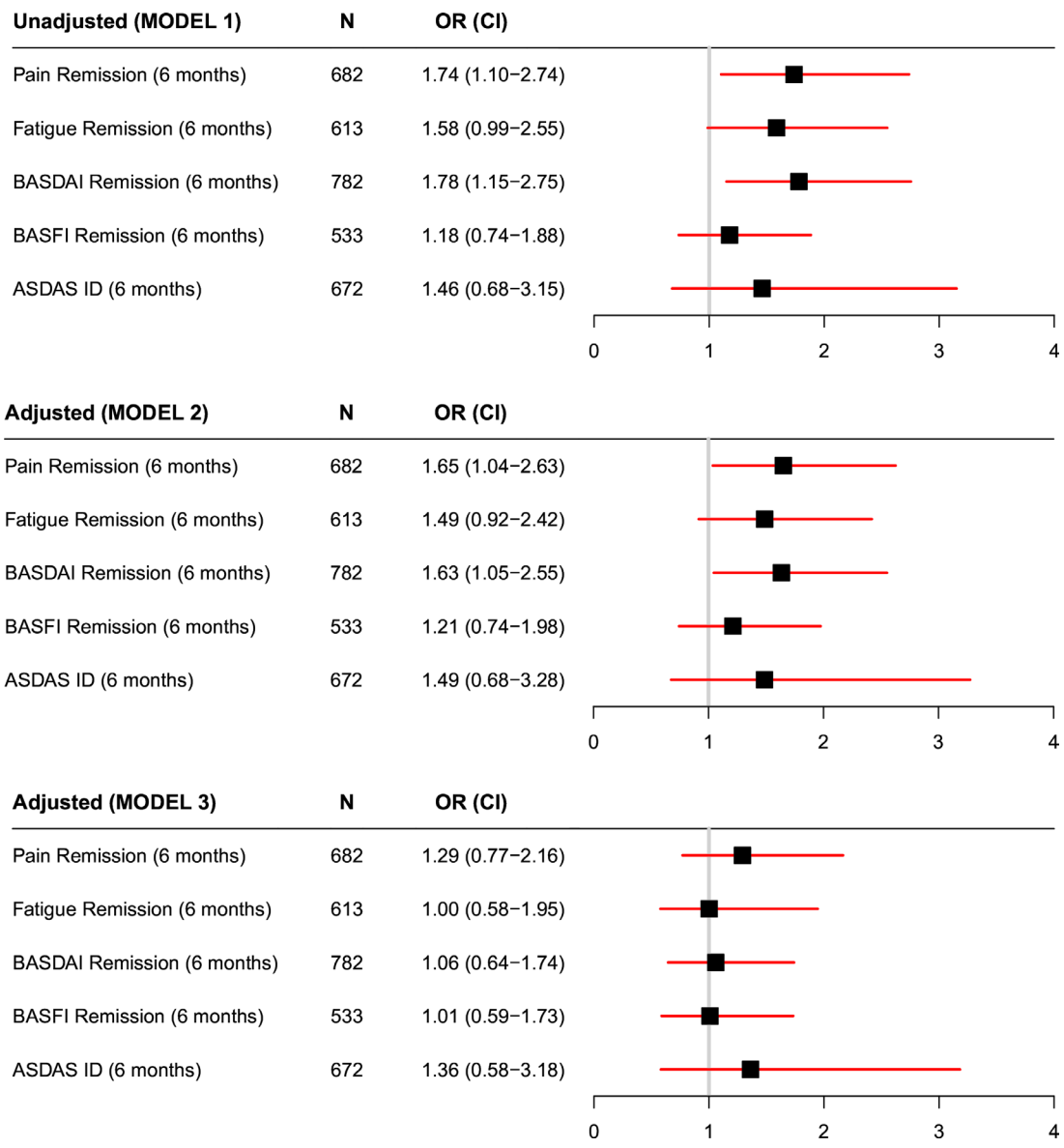
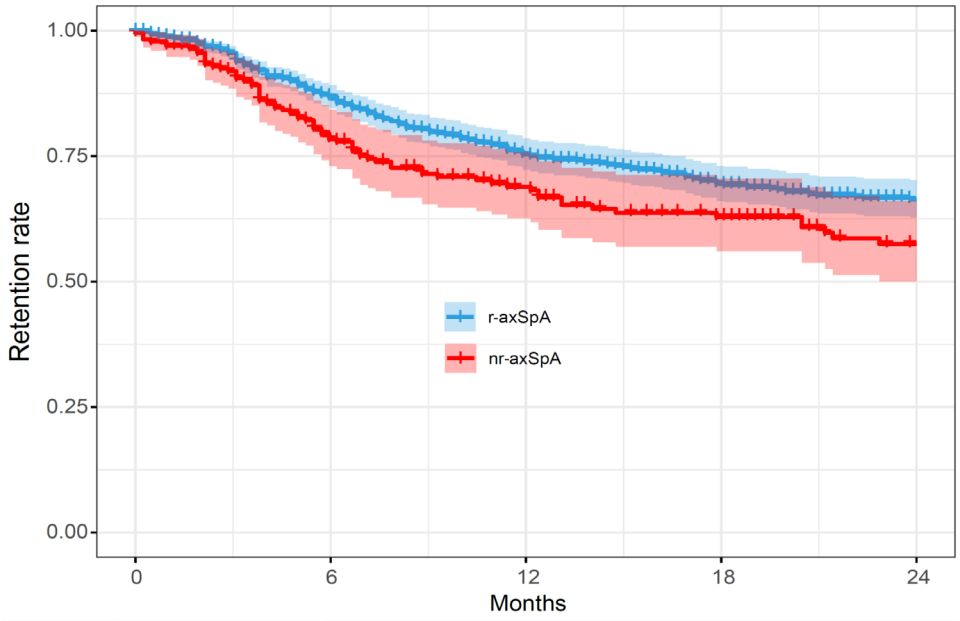


Figure 2 Comparison of 6 months patient-reported outcome remission rates and ASDAS inactive disease in European secukinumab-treated radiographic axSpA patients versus non-radiographic axSpA patients (reference group). Logistic regression analyses adjusted for model 2: age and sex; model 3: Age, sex, baseline CRP, registry, time from diagnosis to secukinumab initiation and numbers of previous b/tsDMARDs (0/1/≥2). ASDAS ID, Ankylosing Spondylitis Disease Activity Score-inactive disease<1.3; axSpA, axial spondyloarthritis; BASDAI remission, Bath Ankylosing Spondylitis Disease Activity Index ≤2 on a 0–10 integer scale; BASFI remission, Bath Ankylosing Spondylitis Functional Index ≤2 0–10 integer scale; b/tsDMARDs, biological or targeted synthetic disease-modifying antirheumatic drugs; CRP, C reactive protein.

responses in r-axSpA compared with nr-axSpA patients,[23] but no relevant differences in adjusted PROs,[26] ASDAS[21] and BASDAI response,[22] which is in line with our findings in secukinumab-treated patients. Although univariate analyses of TNFi treatment retention have also shown superior outcomes for r-axSpA compared with nr-axSpA patients,[25] no relevant differences in adjusted TNFi retention rates have been reported,[21 22 25 26] which again is in line with our secukinumab-treated patient cohort.

In the subgroup analyses investigating the effect of individual confounders, we found registry to be an important factor associated with treatment outcomes. Variation in treatment outcomes across registries has also been observed in previous studies from the EuroSpA Collaboration and other international collaboration of registries.[38–40] This may reflect different treatment guidelines and varying access to treatments across Europe. In the setting of the current study, an additional component may be variations in approval status for secukinumab in nr-axSpA, and the degree of off-label use of secukinumab in these patients.

Lindström *et al*[40] investigated the between-country heterogeneity in the EuroSpA collaboration using random-effect meta-analyses and found relatively uniform results for the response rates but pronounced intercountry differences regarding the drug (TNFi)



	Retention rates		24-months Hazard ratios (CI)		
	r-axSpA	nr-axSpA	Unadjusted MODEL1	**Adjusted:** Age + sex MODEL2	**Adjusted:** All* MODEL3
6 months	0.87	0.78	**0.73 (0.56–0.94)**	**0.77 (0.59–0.99)**	0.98 (0.69–1.38)
12 months	0.75	0.69			
24 months	0.66	0.58			

Figure 3 Secukinumab retention rates in r-axSpA and nr-axSpA patients (Kaplan-Meier plot), including adjusted and unadjusted HRs for drug survival in nr-axSpA patients versus r-axSpA patients (reference group). *Values adjusted for age, sex, registry, baseline CRP, time from diagnosis to secukinumab initiation and numbers of previous biological/targeted synthetic disease-modifying antirheumatic drugs (0/1/≥2). Significant values are indicated by bold type. axSpA, axial spondyloarthritis; CRP, C reactive protein; nr-axSpA, non-radiographic axSpA; r-axSpA, radiographic axSpA.

retention rate.[39] To assess the robustness of our findings, we did additional analyses. Thus, we performed all analyses both in a subcohort excluding the registry with the highest proportion of patients with nr-axSpA (SCQM) and additionally in the registries with >100 patients (ATTRA, DANBIO, reuma.pt, SCQM, RRBR). These analyses showed largely similar estimates. Due to lower patient numbers, some of the unadjusted analyses no longer showed statistically significant differences between nr-axSpA and r-axSpA while all adjusted comparisons were non-significant (data are not shown). This also underlines the need for pooling of data to get sufficient power.

The number of previous b/tsDMARDs was also an important factor associated with treatment outcomes in our study, which is in accordance with other studies generally showing the line of bDMARD treatment to vastly affect treatment outcomes for both TNFi and secukinumab.[17 38]

Adjustments for baseline CRP did not significantly alter treatment outcomes in our study. In contrast, other studies have shown baseline CRP to predict significantly higher improvements in pain and global scores,[26] superior BASDAI response rates[25] and to be significantly associated with better treatment retention.[25 26] In patients with nr-axSpA, the PREVENT study[41] demonstrated, that secukinumab overall improved signs and symptoms of the disease while the largest treatment effect was seen in patients with both elevated CRP and evidence of sacroiliitis on MRI while HLA-B27 status showed minimal effect on outcomes. We cannot rule out that —despite our attempt to compensate for missingness in baseline CRP by using MICE imputation—the amount of missing data on baseline CRP in our study (22% in r-axSpA and 34% in nr-axSpA) could potentially be a contributing factor to our non-significant findings.

Ciurea *et al* investigated 2080 patients with nr-axSpA and r-axSpA but with the latter stratified by level of severity (nr-axSpA (≤grade 2 unilateral sacroiliitis), bilateral grade 2 sacroiliitis and unilateral/bilateral grades 3–4 sacroiliitis).[27] They found that while no differences existed between patients with nr-axSpA and patients with bilateral grade 2 sacroiliitis in terms of CRP, ASDAS, BASFI and drug retention (TNFi), both these groups differed significantly from patients with unilateral/bilateral grades 3–4 sacroiliitis, where disease activity measures, response rates and drug retention were higher.[27] Since our data did not include information on levels of radiographic damage, we cannot confirm if such differences also apply to our population.

Finally, it cannot be ruled out that a calendar effect contributed to the observed unadjusted differences between r-axSpA and nr-axSpA patients both due to general changes in axSpA management over the recent

years (eg, focus on treat-to-target recommendations) and the fact that secukinumab was approved for r-axSpA in 2015 and for nr-axSpA in 2020.

Strengths of our study include it being the first to evaluate differences in baseline characteristics, long-term (2 years) remission and drug retention rates in r-axSpA versus nr-axSpA patients treated with secukinumab in routine care. Since we pooled data from nine European registries, we were able to collect data on more than 1100 secukinumab-treated patients with known radiographic status. In contrast to randomised controlled trials, this study was not limited by strict inclusion or exclusion criteria. Hence, our findings can be expected to more closely reflect routine clinical practice across countries.

A major limitation of this study is the missing data in both baseline and especially outcome assessments, which is a challenge for most observational registry studies. We chose to only assess clinical outcomes in patients with available data at the different assessment timepoints, hence no imputation of clinical data during follow-up was performed. The LUNDEX adjustment was added to integrate information on response and drug retention into one combined measurement, hence somewhat accounting for missing data due to drug discontinuation. Furthermore, the risk of selection bias based on data availability cannot be ruled out since subjects more likely to visit their physician regularly may be different from those who do not, resulting in more complete registry data potentially leading to either overestimation or underestimation of, for example, remission rates depending on circumstances. Moreover, it is well known that radiographic SIJ assessment performed in routine care may have limited reliability, and thus misclassification of nr-axSpA/r-axSpA cannot be ruled out. However, this study reflects real-life practice where clinicians must routinely consider this possibility. We observed that the nr-axSpA group was more likely to be HLA-B27 negative, and one could, therefore, assume that this group may potentially include patients with a diagnosis other than axSpA. Finally, the lack of data on MRI findings prevents us from stratifying, perhaps most importantly, the nr-axSpA group into patients with objective versus no objective signs of inflammation, which could have been a very relevant analysis.

In conclusion, we found that secukinumab-treated European patients with r-axSpA and nr-axSpA differed in several baseline characteristics while baseline PRO levels were similar. Crude remission and drug retention rates were higher in r-axSpA compared with nr-axSpA patients. These differences disappeared, however, after adjusting for multiple confounders. Altogether, our study shows similar secukinumab treatment effectiveness in r-axSpA and nr-axSpA patients in adjusted analyses, thereby indicating that observed differences between the two groups are explained by factors other than radiographic status per se.

Author affiliations
[1]Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre for Head and Orthopedics, Rigshospitalet Glostrup, Glostrup, Denmark
[2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[3]Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway
[4]Research Unit, Sørlandet Sykehus HF, Kristiansand, Norway
[5]Institute of Rheumatology and Department of Rheumatology, First Faculty of Medicine, Charles University, Praha, Czech Republic
[6]Center for Rheumatic Diseases, University of Medicine and Pharmacy Carol Davila Bucharest, Bucuresti, Romania
[7]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland
[8]Department of Rheumatology, Hospital Garcia de Orta EPE, Almada, Portugal
[9]Faculdade de Medicina da Universidade de Lisboa, Universidade de Lisboa Instituto de Medicina Molecular, Lisboa, Portugal
[10]Division of Rheumatology, Dokuz Eylul Universitesi Tip Fakultesi, Izmir, Turkey
[11]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia
[12]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[13]Centre for Rheumatology Research, Landspitali National University Hospital of Iceland, Reykjavik, Iceland
[14]Faculty of Medicine, University of Iceland, Reykjavik, Iceland
[15]Aberdeen Centre for Arthritis and Musculoskeletal Health (Epidemiology Group), University of Aberdeen, Aberdeen, UK
[16]Inflammation Center, Rheumatology, Helsinki University Central Hospital, Helsinki, Finland
[17]Rheumatology Unit, DiMePRe-J, University of Bari, Bari, Italy
[18]Department of Rheumatology, East Tallinn Central Hospital, Tallinn, Estonia
[19]Department of Clinical Sciences Lund, Lund University, Lund, Sweden
[20]Department of Rheumatology, Skåne University Hospital Lund, Lund, Sweden
[21]Amsterdam UMC, Department of Rheumatology & Clinical Immunology and Department of Experimental Immunology, Amsterdam Institute for Infection & Immunity, University of Amsterdam, Amsterdam, Netherlands
[22]Amsterdam Rheumatology and Immunology Center, Amsterdam, Netherlands
[23]Public Health Section, Inland Norway University of Applied Sciences, Elverum, Norway
[24]Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[25]Faculty of Medicine, Complutense University of Madrid, Madrid, Spain
[26]Department of Rheumatology, Geneva University Hospitals, Geneve, Switzerland
[27]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark
[28]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[29]Rheumatology Department, Centro Hospitalar do Baixo Vouga EPE, Aveiro, Portugal
[30]Comprehensive Health Research Centre, NOVA Medical School, Universidade NOVA de Lisboa, Lisboa, Portugal
[31]Department of Rheumatology, Bakircay Universitesi, Izmir, Turkey
[32]Department for Rheumatology, Landspitali National University Hospital of Iceland, Reykjavik, Iceland
[33]Department of Medicine, Helsinki University and Helsinki University Hospital, Helsinki, Finland
[34]Rheumatology, Allergology and Clinical Immunology, University of Rome Tor Vergata, Roma, Italy
[35]National Institute for Health Development, Tallinn, Estonia
[36]Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institute, Stockholm, Sweden
[37]Faculty of Medicine, University of Oslo, Oslo, Norway
[38]Research Unit, Spanish Society of Rheumatology, Madrid, Spain
[39]Rheumatology, Radboud University Medical Center, Nijmegen, Netherlands

X Gary J Macfarlane @UAberdeenEpi, Michael J Nissen @#michaelnissen, Gareth T Jones @hteraG_senoJ and Maria Sole Chimenti @MSoleChimenti

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ORCID iDs
Sara Nysom Christiansen http://orcid.org/0000-0002-5063-9932
Brigitte Michelsen http://orcid.org/0000-0003-0103-2840
Adrian Ciurea http://orcid.org/0000-0002-7870-7132
Bente Glintborg http://orcid.org/0000-0002-8931-8482
Maria Jose Santos http://orcid.org/0000-0002-7946-1365
Ziga Rotar http://orcid.org/0000-0002-9323-9189
Bjorn Gudbjornsson http://orcid.org/0000-0003-4631-6505
Gary J Macfarlane http://orcid.org/0000-0003-2322-3314
Florenzo Iannone http://orcid.org/0000-0003-0474-5344
Sella Aarrestad Provan http://orcid.org/0000-0001-5442-902X
Michael J Nissen http://orcid.org/0000-0002-6326-1764
Gareth T Jones http://orcid.org/0000-0003-0016-7591
Maria Sole Chimenti http://orcid.org/0000-0002-1343-1729
Tore K Kvien http://orcid.org/0000-0002-8441-3093
Irene van der Horst-Bruinsma http://orcid.org/0000-0002-8086-9915
Merete Lund Hetland http://orcid.org/0000-0003-4229-6818
Lykke Midtbøll Ørnbjerg http://orcid.org/0000-0002-7832-6831

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