

Predictors of Secukinumab Treatment Response and Continuation in Axial Spondyloarthritis: Results From the EuroSpA Research Collaboration Network

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ABSTRACT. *Objective.* In patients with axial spondyloarthritis (axSpA) initiating secukinumab (SEC), we aimed to identify baseline (treatment start) predictors of achieving low disease activity (LDA) after 6 months, as measured by the Axial Spondyloarthritis Disease Activity Score using C-reactive protein (ASDAS-CRP) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), as well as treatment continuation after 12 months.

Methods. From 11 European registries, patients with axSpA who initiated SEC treatment in routine care, with available data on 6-month ASDAS-CRP and BASDAI assessments were included. Logistic regression analyses on multiply imputed baseline data were performed; potential baseline predictors included demographic, diagnosis, lifestyle, clinical, and patient-reported variables.

Results. In a pooled cohort of 1174 patients with axSpA, 5 of 19 potential assessed variables were mutually predictive for achieving LDA by ASDAS-CRP and BASDAI: higher physician global assessment score, noncurrent smoking, lack of prior exposure to biologic/targeted synthetic disease-modifying antirheumatic drugs, and lower Health Assessment Questionnaire scores and BASDAI scores. Moreover, radiographic axSpA and CRP ≤ 10 mg/L were associated with achieving ASDAS-CRP LDA, and HLA-B27 positivity and history of psoriasis with achieving BASDAI LDA, whereas earlier time of secukinumab initiation (2015-2017) was associated with treatment continuation.

Conclusion. In this European real-world study of patients with axSpA initiating SEC, predictors of achieving LDA by ASDAS-CRP and BASDAI at 6 months and remaining on treatment at 12 months included both clinical, patient-reported, and lifestyle factors, underscoring the complex mechanisms of real-world drug effectiveness.

Key Indexing Terms: biologic therapy, epidemiology, spondyloarthritis

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Axial spondyloarthritis (axSpA) is a chronic rheumatic disease characterized by axial pain because of inflammation of the spine and sacroiliac joints. In patients with an insufficient response to physiotherapy and nonsteroidal antiinflammatory drugs, biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) are recommended.¹ In such a situation, secukinumab (SEC), a fully human IgG1 monoclonal antibody targeting interleukin (IL)-17A, is one of the first-line treatment options currently indicated.¹

Many factors, such as age, sex, disease duration, C-reactive protein (CRP), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), smoking status, and HLAB*2701–2759 (HLA-B27) positivity have been reported to be associated with treatment response to tumor necrosis factor inhibitors (TNFi) in axSpA in both randomized clinical trials (RCTs)^{2,3} and observational studies.^{4–7} However, only a few studies have described factors associated with treatment response to SEC in axSpA, showing inconsistent results.^{8–11}

To identify predictors of a good treatment outcome, the desired treatment target needs to be identified. In axSpA, the Axial Spondyloarthritis Disease Activity Score (ASDAS)¹² or the BASDAI¹³ are often used to measure disease activity. The ASDAS score using CRP (ASDAS-CRP) is internationally recommended by the Assessment of SpondyloArthritis international Society (ASAS),¹⁴ and the latest ASAS-European Alliance of Associations for Rheumatology recommendations for the management of axSpA suggest an evaluation of the disease activity with ASDAS at least 12 weeks after b/tsDMARD start. However, when serum inflammatory markers like CRP or erythrocyte sedimentation rate (ESR) are not available, the BASDAI may be an alternative to ASDAS for measuring the disease activity, although BASDAI only reflects the patient's perspective.

Validated cutoffs for the ASDAS score have been endorsed by both the ASAS and the Outcome Measures in Rheumatology groups and a value < 2.1 defines low disease activity (LDA).^{14,15} The BASDAI score does not have validated cutoff values for LDA or remission, but in addition to other criteria (eg, the clinician's opinion and failure of

conventional therapy), a value of BASDAI ≥ 4 (0–10 scale) is often required for inclusion into clinical trials, or to start treatment with a bDMARD,^{1,16,17} whereas a value < 4 is often considered to define LDA.¹⁸

Clinical registries are a key resource to increase knowledge about real-world treatment effectiveness. Large cohorts of patients are needed to identify predictive factors for treatment outcomes. The European Spondyloarthritis (EuroSpA) Research Collaboration Network (RCN) has been created to strengthen research by secondary use of prospectively collected data on patients with spondyloarthritis (SpA) in routine care from 17 European registries. Such data allow analyses in high numbers of patients, and provide a unique opportunity to identify predictors of a treatment's effectiveness across variables that are readily available in routine care (e.g. demographics, diagnosis, lifestyle, and clinical and patient-reported outcomes [PROs]).¹⁹

Based on this, the primary objective of the present study was to identify baseline predictors of achieving ASDAS-CRP LDA after 6 months in a European population of patients with axSpA initiating SEC treatment. The secondary aims were to identify baseline predictors of BASDAI LDA after 6 months and treatment continuation after 12 months.

METHODS

Patients. Eleven registries from the EuroSpA RCN with available data on ASDAS-CRP and BASDAI contributed to this study: AmSpA (tNetherlands), ATTRA (Czech Republic), biorx.si (Slovenia), DANBIO (Denmark), ICEBIO (Iceland), NOR-DMARD (Norway), Reuma.pt (Portugal), ROBFIN (Finland), RRRB (Romania), SCQM (Switzerland), and SRQ (Sweden). Based on a predefined study protocol, pseudonymized data were securely uploaded by the individual registries onto a central server. Subsequently, data were harmonized, and quality checked. Datasets from registries were pooled before statistical analyses were conducted.

Patients were included in the present study if they were registered with a diagnosis of axSpA and aged ≥ 18 years at the time of diagnosis. They should have been followed within the respective

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registry from the start of SEC treatment (with a SEC start year between 2015 and 2021 and at least 12 months of follow-up), and have available data on 6-month ASDAS-CRP and BASDAI assessments.

Visits and data collection. ASDAS-CRP and BASDAI values were collected at a baseline visit and after 6 months of follow-up in patients who were still treated with SEC. Baseline patient characteristics included demographics, clinical measures, lifestyle, treatment, and PROs (Table 1).

The visits were defined according to the following time windows: from 30 days prior to 30 days after SEC initiation (baseline), 90 days to 270 days (6 months), and 271 days to 450 days (12 months). For baseline, priority was given to the last visit before (or at) treatment start. Visit data collected outside of the predefined windows were not included in the dataset.

Statistical analyses. Statistical analyses were performed according to a predefined statistical analysis plan. Descriptive statistics were assessed by median (IQR) for continuous variables and percentages for categorical variables. All analyses were done in the pooled cohort.

Logistic regression analyses. To determine baseline predictors of ASDAS-CRP LDA (< 2.1) and BASDAI LDA (< 4), logistic regression analyses were performed to estimate odds ratios and their 95% CIs.

In order to use the same statistical methodology to determine and compare baseline predictors for patients who remained on SEC after 12 months, we created a binary variable called "treatment continuation" (defined as being on SEC 12 months after treatment start; yes/no). The reasons for assignment as no treatment continuation are presented in Supplementary Table S1 (available with the online version of this article). Logistic regressions were used to determine baseline predictors of treatment continuation (yes/no), as described above. The main cohort was restricted to patients with available data on the 3 outcomes.

Additional analyses. To determine if baseline predictors varied across different registries, analyses stratified by gross domestic product (GDP) were performed on subcohorts from countries with low and high GDP (USD; $< \$40,000$ vs $> \$40,000$). Data on GDP per capita per year for each country (USD) were obtained from the United Nations website.²⁰

To determine baseline predictors of achieving an ASDAS-CRP clinically important improvement (CII) and a BASDAI 50% response, analyses were performed in the subcohort of patients with available ASDAS-CRP and BASDAI at baseline and 6 months.

Covariates at baseline. Sex, smoking status (current/noncurrent), fulfillment of classification criteria (modified New York [mNY] criteria²¹ and/or the ASAS criteria²²), radiographic status (nonradiographic/radiographic, according to the mNY criteria for ankylosing spondylitis²¹), HLA-B27 status (positive/negative), presence of comorbidities during the disease course (cardiovascular disease, diabetes, kidney disease [ever/never]), presence of nonmusculoskeletal manifestations during the disease course [uveitis, inflammatory bowel disease, psoriasis (PsO) ever/never], enthesitis (ever/never), dactylitis (ever/

never), peripheral arthritis (defined by the presence of at least 1 swollen joint in a 28 or 66 swollen joint count at baseline or the presence of arthritis in ASAS criteria), calendar year of SEC start (2015-2017/2018-2021), concomitant conventional synthetic DMARDs (csDMARDs) at SEC start (yes/no), and CRP (≤ 10 / > 10 mg/L) were included as categorical independent variables. The CRP cutoff was determined based on the various detection limits used across registries. Age at treatment start, time since diagnosis (years), BMI (calculated as weight in kilograms divided by height in meters squared), number of previous b/tsDMARDs, patient pain assessment (0-10 integer scale), patient fatigue assessment (0-10 integer scale), Health Assessment Questionnaire (HAQ; score 0-3),²³ physician global assessment (PGA; 0-10 integer scale), BASDAI (0-10), and Bath Ankylosing Spondylitis Functional Index (BASFI; 0-10)²⁴ were included as continuous variables.

Missing values. Multiple imputation by chained equations (MICE) was used to impute all missing baseline covariates regardless of the extent of missingness (which varied from 3% to 56%). The number of imputed datasets was decided based on the missingness of values in the original data, considering all baseline covariates (30 imputed datasets).

Variable selection. For each endpoint, variable selection was performed separately in each of the 30 imputed datasets.²⁵ Initially, univariable logistic regression analyses were performed for all independent variables. Variables with $P < 0.20$ in univariable analyses were included in an initial multivariable model, where a backward stepwise selection was applied.²⁶ GDP per capita was a priori forced into the multivariable prediction models to adjust for socioeconomic differences between registries. Next, independent variables excluded in univariable analyses were introduced one at a time in the multivariable model and their significance tested. The first multivariable model in all imputed datasets included the predictors that appeared in at least half of the 30 separate models (Supplementary Table S2 and S3, available with the online version of this article). As this multivariable model may contain nonsignificant predictors, backward selection was applied to multiply imputed data to remove any nonrelevant variables from the final multivariable model. Multivariable models were fitted to all imputed datasets and the model estimates were pooled according to Rubin rules.²⁷ Likelihood ratio tests were used to assess all models and a significance level of 0.05 was applied, unless otherwise stated. Potential multicollinearity among the selected baseline predictors in the final regression model was tested separately in each of the imputed datasets.

Performance. The area under the receiver-operating curve (AUROC) of the final multivariable models was assessed using internal validation on multiply imputed data.²⁸ The applied internal validation strategy combined multiple imputation and bootstrapping by drawing (100) bootstrap samples from the 30 imputed datasets.

Statistical analyses were performed with R version 4.2.2 (R Foundation for Statistical Computing).

RESULTS

A total of 1940 patients with axSpA initiated SEC between

January 1, 2015, and December 1, 2021. At 6 months, ASDAS-CRP and BASDAI LDA assessments were available in 1033 patients. Of the 907 patients without an available 6-month assessment, 141 patients had stopped SEC within 6 months because of lack of effectiveness and were classified as not achieving ASDAS-CRP LDA and BASDAI LDA at 6 months. Thus, a total of 1174 patients were included in the analyses of all 3 outcomes, and 766 patients without either ASDAS-CRP or BASDAI assessments available at 6 months were excluded (Figure).

Baseline characteristics. Among patients included in the analyses, there were higher proportions of male individuals (53% vs 48%), HLA-B27 positivity (80% vs 67%), positive radiographic axSpA (r-axSpA) status (83% vs 71%), and a lower proportion with a history of enthesitis (24% vs 66%), than in patients excluded from analyses (ie, those without available 6-month follow-up assessment on ASDAS-CRP and/or BASDAI; Table 1).

No clinically relevant differences in age, BMI, smoking status, comorbidities, and peripheral arthritis were found between the groups. Baseline PROs (ie, pain, fatigue, PGA, HAQ, BASDAI, and BASFI) and ASDAS-CRP were similar between the groups, whereas a higher proportion of included patients had elevated CRP (49% vs 32%; Table 1).

Among the patients included in the analyses, 26% received concomitant csDMARDs at SEC start, and in 28% SEC was the first b/tsDMARD prescribed, whereas in 20% and 52% of patients, SEC was initiated as the second or later b/tsDMARD, respectively.

Variations in baseline characteristics and proportion of patients with available data were observed across registries (Supplementary Table S4 and S5, respectively, available with the online version of this article).

When comparing patients registered with r-axSpA vs nonra-

diographic axSpA (nr-axSpA), higher proportions of male individuals (64% vs 38%) and HLA-B27 positivity (87% vs 64%) were observed, whereas baseline PROs and PGA were comparable (Supplementary Table S6, available with the online version of this article).

Treatment outcomes. Of the 1174 patients included in the analyses of all 3 outcomes, 345 (29%) achieved ASDAS-CRP LDA at 6 months, 545 (46%) achieved BASDAI LDA at 6 months, and 618 (53%) were registered as still receiving SEC at 12 months.

Predictors for ASDAS-CRP LDA at 6 months. A total of 7 baseline predictors for ASDAS-CRP LDA at 6 months were identified in multivariable logistic regressions: higher baseline PGA score was associated with achieving ASDAS-CRP LDA, whereas current smoking, nr-axSpA, more previous b/tsDMARDs, CRP > 10 mg/L, higher HAQ scores, and higher BASDAI scores were associated with not achieving ASDAS-CRP LDA (Table 2).

Predictors for BASDAI LDA at 6 months and treatment continuation at 12 months. A total of 7 baseline predictors for BASDAI LDA at 6 months were identified by multivariable logistic regression, of which 5 were also baseline predictors of 6-month ASDAS-CRP LDA. HLA-B27 positivity, a history of PsO, and higher PGA scores were associated with achieving BASDAI LDA, whereas current smoking, more previous b/tsDMARDs, and higher HAQ and BASDAI scores were associated with not achieving BASDAI LDA (Table 2).

Earlier SEC start year (ie, 2015-2018) was the only baseline predictor associated with SEC continuation at 12 months (Table 2).

The performance of the final models, as assessed by the AUROC, was 0.73 (ASDAS-CRP LDA), 0.78 (BASDAI LDA), and 0.65 (12-month treatment continuation; Table 2).

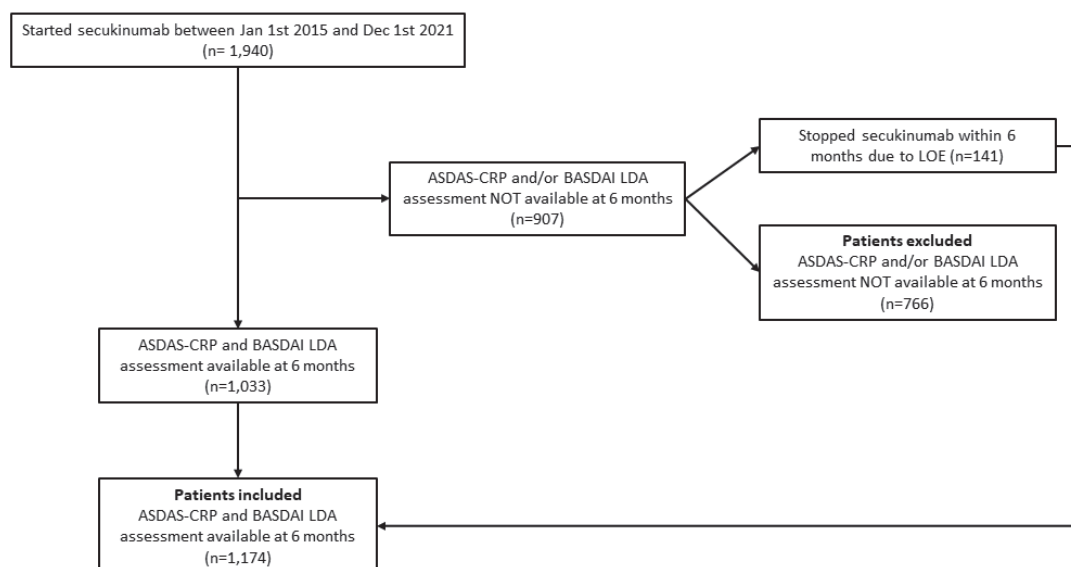


Figure. Participant flow chart and patient eligibility. ASDAS-CRP: Axial Spondyloarthritis Disease Activity Score using C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; LDA: low disease activity; LOE: lack of efficacy.

Table 1. Baseline characteristics of included and excluded patients with axSpA initiating SEC.

	Included, n = 1174		Excluded, n = 766	
	Value	n (%)	Value	n (%)
Demographics, diagnosis, and lifestyle				
Age at SEC initiation, yrs	47 (38-56)	1174 (100)	47 (38-56)	766 (100)
Age at diagnosis, yrs	36 (28-45)	991 (84)	37 (29-46)	572 (75)
Time since diagnosis, yrs	6 (2-13)	991 (84)	5 (2-13)	572 (75)
Sex, male	626 (53)	1174 (100)	368 (48)	766 (100)
BMI, kg/m ²	27.0 (24.2-31.1)	734 (54)	26.9 (23.1-30.7)	298 (39)
< 18.5	17 (3)	–	6 (2)	–
18.5-24.9	190 (30)	–	102 (34)	–
25.0-29.9	237 (37)	–	107 (36)	–
≥ 30	190 (30)	–	83 (28)	–
Current smoker	265 (23)	1233 (97)	168 (27)	627 (82)
Fulfillment of classification criteria				
ASAS	481 (84)	582 (50)	242 (90)	268 (35)
mNY	335 (76)	442 (38)	164 (67)	244 (32)
Radiographic status				
r-axSpA	502 (83)	604 (51)	184 (71)	259 (34)
nr-axSpA	102 (17)	–	75 (29)	–
Clinical measures				
HLA-B27 positive	571 (80)	717 (61)	237 (67)	352 (46)
Comorbidities^a				
CVD	185 (25)	676 (58)	85 (26)	321 (42)
Diabetes	47 (10)	468 (40)	17 (6)	295 (39)
Kidney disease	24 (4)	670 (57)	11 (3)	318 (42)
Nonmusculoskeletal manifestations^a				
Uveitis	91 (16)	579 (49)	30 (11)	277 (36)
IBD	22 (3)	650 (55)	10 (3)	300 (39)
Psoriasis	57 (9)	648 (55)	28 (9)	301 (39)
History of enthesitis ^a	133 (24)	553 (47)	117 (66)	176 (23)
History of dactylitis ^a	37 (11)	351 (30)	31 (19)	162 (21)
Peripheral arthritis ^b	308 (41)	748 (64)	208 (41)	508 (66)
CRP, mg/L	9.7 (2.9-25.0)	885 (75)	5.6 (2.0-14.0)	454 (59)
CRP (> 10 mg/L)	432 (49)	885 (75)	145 (32)	454 (59)
ASDAS-CRP	3.8 (3.0-4.5)	804 (68)	3.6 (2.9-4.2)	268 (35)
ID (< 1.3)	17 (2)	–	2 (1)	–
LDA (≥ 1.3 and < 2.1)	46 (6)	–	15 (6)	–
HDA (≥ 2.1 and ≤ 3.5)	257 (32)	–	111 (41)	–
VHDA (> 3.5)	484 (60)	–	140 (52)	–
ESR, mm/h	25 (10-42)	711 (61)	15 (7-32)	354 (46)
PGA (0-10)	5 (3-7)	511 (44)	4 (2-5)	258 (34)
SJC28	0 (0-1)	530 (45)	0 (0-1)	319 (42)
TJC28	0 (0-3)	501 (43)	0 (0-3)	268 (35)
Treatment				
SEC start year	–	1174 (100)	–	766 (100)
2015-2017	403 (34)	–	339 (44)	–
2018-2021	771 (66)	–	427 (56)	–
Previous b/ts DMARDs	2 (0-3)	1174 (100)	2 (1-3)	766 (100)
b/tsDMARD naïve	323 (28)	–	135 (18)	–
1 previous b/tsDMARD	237 (20)	–	211 (28)	–
≥ 2 previous b/tsDMARDs	614 (52)	–	420 (55)	–
Concomitant csDMARDs				
≥ 1 csDMARDs	309 (26)	1174 (100)	123 (16)	766 (100)
Methotrexate	136 (13)	1025 (87)	68 (10)	682 (89)
Sulfasalazine	171 (17)	1019 (87)	39 (6)	685 (89)
Leflunomide	9 (1)	1002 (85)	8 (1)	679 (89)
Others	23 (2)	985 (84)	21 (3)	617 (81)

Table 1. Continued.

	Included, n = 1174		Excluded, n = 766	
	Value	n (%)	Value	n (%)
PROs				
Pain (0-10)	7 (5-8)	665 (57)	7 (5-8)	380 (50)
Fatigue (0-10)	7 (5-8)	601 (51)	8 (6-9)	264 (34)
PtGA (0-10)	5 (3-7)	881 (75)	7 (6-8)	365 (48)
HAQ (0-3)	1.1 (0.8-1.6)	581 (59)	1.0 (0.6-1.4)	290 (38)
BASDAI (0-10)	6.5 (4.9-7.7)	856 (73)	6.4 (4.7-7.4)	369 (48)
< 2	23 (3)	–	12 (3)	–
≥ 2 and < 4	21 (2)	–	5 (1)	–
≥ 4 and ≤ 6	67 (8)	–	35 (9)	–
> 6	745 (87)	–	317 (86)	–
BASFI (0-10)	5.7 (3.5-7.5)	646 (55)	5.2 (3.0-7.2)	319 (42)

Values are presented as median (IQR) and n (%) for continuous and categorical variables, respectively. Pain, fatigue, PtGA, and PGA are scored on a 0-10 integer scale. ^a Defined as ever or never present. ^b Peripheral arthritis was based on the presence of at least 1 swollen joint (either in 28- or 66-joint count) at baseline or the presence of arthritis in ASAS criteria (ever/never). ASAS: Assessment of SpondyloArthritis international Society; ASDAS: Axial Spondyloarthritis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CVD: cardiovascular disease; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HDA: high disease activity; IBD: inflammatory bowel disease; ID: inactive disease; LDA: low disease activity; mNY: modified New York; nr-axSpA: nonradiographic axial spondyloarthritis; PGA: physician global assessment; PRO: patient-reported outcome; PtGA: patient global assessment; r-axSpA: radiographic axial spondyloarthritis; SEC: secukinumab; SJC28: swollen joint count in 28 joints; TJC28: tender joint count in 28 joints; tsDMARD: targeted synthetic disease-modifying antirheumatic drug; VHDA: very high disease activity.

Multicollinearity was not detected in any of the final regression models.

Additional analyses with stratification by GDP. A cutoff of \$40,000 was chosen in the present study to separate countries with low vs high GDP per capita, as this cutoff provided a clear differentiation between high and low GDP countries (Supplementary Table S4, available with the online version of this article).

More previous b/tsDMARDs was the only baseline predictor identified in the low GDP group, and was associated with not achieving all 3 outcomes. No mutual baseline predictor was found for ASDAS LDA, BASDAI LDA, and treatment continuation in the high GDP group. Higher BASDAI score was associated with not achieving 6-month LDA by ASDAS-CRP and BASDAI in both the low GDP and high GDP groups (Table 3).

The frequencies of appearances of predictors in the 30 separate imputed datasets for 6-month ASDAS-CRP and BASDAI LDA, and 12-month treatment continuation are shown in Supplementary Table S2 (total cohort) and Supplementary Table S3 (stratified cohorts by GDP; supplementary information is available with the online version of this article).

Additional analyses of predictors for ASDAS-CRP CII and BASDAI 50% response. In the subgroup of 802 patients with available ASDAS-CRP and BASDAI at the baseline and 6-month visit, 4 variables were identified as baseline predictors for ASDAS CII. CRP > 10 mg/L, higher PGA score, and higher BASDAI score were associated with achieving an ASDAS CII, whereas more previous b/tsDMARDs was associated with not achieving ASDAS CII. For BASDAI 50% response, male sex and higher baseline PGA were associated with achieving a

BASDAI 50% response, whereas more previous b/tsDMARDs was associated with not achieving a BASDAI 50% response (Supplementary Table S7, available with the online version of this article).

DISCUSSION

In this real-world study across 11 European countries, based on data from > 1000 patients with axSpA receiving SEC, 5 baseline predictors were identified for achieving LDA after 6 months of therapy according to both ASDAS-CRP and BASDAI: higher PGA scores, noncurrent smoking, lack of prior exposure to b/tsDMARDs, and lower HAQ and BASDAI scores.

Data regarding predictors of treatment response in patients with axSpA treated with SEC are very limited, as it has only been investigated in 3 previous studies.^{8,10,29} In line with our findings, lack of prior exposure to b/tsDMARDs has been reported to be associated with a better SEC response (for both drug retention and ASDAS LDA at 6 months) in those 3 studies. However, the above-mentioned studies included baseline variables that were only partly overlapping with those assessed in our study, making comparisons difficult. In a previous French retrospective study of 906 patients with nr-axSpA and r-axSpA, Dougados et al found that the absence of objective signs of inflammation (ie, CRP ≥ 5 mg/L or ESR ≥ 28 mm/h or inflammation on magnetic resonance imaging of the sacroiliac joints or spine) and absence of inflammatory bowel disease were associated with a better SEC retention at 1 year.¹⁰ Ramonda et al, in a study including 249 patients, showed that male sex was associated with BASDAI LDA at 6 months as well as better SEC retention and, contrary to our results, that high baseline CRP was associated

Table 2. Summary of predictors for ASDAS-CRP LDA and BASDAI LDA at 6 months and treatment continuation at 12 months on SEC (total cohort).

Baseline Characteristics	ASDAS-CRP LDA at 6 Months 345/1174 (29%) ^a		BASDAI LDA at 6 Months 545/1174 (46%) ^a		Treatment Continuation at 12 Months 618/1174 (53%) ^a	
	Univariable Analysis OR (95% CI)	Multivariable Analysis ^b OR (95% CI)	Univariable Analysis OR (95% CI)	Multivariable Analysis ^b OR (95% CI)	Univariable Analysis OR (95% CI)	Multivariable Analysis ^b OR (95% CI)
Age at SEC initiation, yrs	0.99 (0.98-1.00)	–	1.00 (0.99-1.01)	–	1.00 (0.99-1.01)	–
Sex, male	1.57 (1.22-2.03)	–	1.63 (1.30-2.06)	–	1.24 (0.98-1.56)	–
Time since diagnosis, yrs	0.99 (0.98-1.01)	–	1.01 (0.99-1.02)	–	1.01 (0.99-1.02)	–
BMI, kg/m ²	0.98 (0.95-1.01)	–	1.00 (0.97-1.05)	–	1.00 (0.97-1.03)	–
Current smoking	0.75 (0.55-1.02)	0.64 (0.45-0.89)	0.82 (0.62-1.08)	0.69 (0.49-0.95)	1.03 (0.78-1.36)	–
HLA-B27 positive	2.08 (1.52-2.88)	–	2.68 (1.95-3.70)	1.90 (1.25-2.89)	1.81 (1.35-2.43)	–
Peripheral arthritis ^c	0.89 (0.67-1.19)	–	1.02 (0.77-1.34)	–	1.04 (0.79-1.38)	–
nr-axSpA	0.42 (0.30-0.60)	0.56 (0.36-0.88)	0.37 (0.27-0.51)	–	0.52 (0.37-0.72)	–
History of uveitis	0.76 (0.47-1.21)	–	1.16 (0.73-1.83)	–	0.84 (0.56-1.25)	–
History of psoriasis	0.71 (0.46-1.10)	–	0.60 (0.40-0.91)	1.62 (1.02-2.59)	0.66 (0.47-0.91)	–
SEC start year (2018-2021)	1.36 (1.04-1.79)	–	1.42 (1.12 – 1.82)	–	0.80 (0.63-1.02)	0.62 (0.48-0.80)
No. of previous						
b/tsDMARDs	0.73 (0.67-0.80)	0.82 (0.74-0.92)	0.71 (0.65-0.76)	0.82 (0.74-0.91)	0.90 (0.84-0.97)	–
CRP (> 10 mg/L)	0.91 (0.70-1.20)	0.52 (0.35-0.77)	2.18 (1.69-2.82)	–	1.65 (1.26-2.16)	–
Pain (0-10)	0.87 (0.81-0.93)	–	0.88 (0.82-0.94)	–	1.05 (0.99-1.11)	–
Fatigue (0-10)	0.83 (0.78-0.89)	–	0.80 (0.74-0.86)	–	0.97 (0.91-1.04)	–
HAQ (0-3)	0.76 (0.60-0.97)	0.56 (0.39-0.81)	0.97 (0.77-1.22)	0.61 (0.44-0.84)	1.45 (1.19-1.78)	–
PGA (0-10)	1.08 (1.00-1.16)	1.11 (1.01-1.24)	1.18 (1.10-1.27)	1.19 (1.08-1.32)	1.12 (1.05-1.20)	–
BASDAI (0-10)	0.83 (0.77-0.88)	0.83 (0.75-0.91)	0.82 (0.77-0.87)	0.76 (0.69-0.84)	1.03 (0.97-1.09)	–
BASFI (0-10)	0.88 (0.83-0.94)	–	0.91 (0.85-0.96)	–	1.03 (0.98-1.09)	–
AUROC (95% CI) ^d	–	0.73 (0.69-0.76)	–	0.78 (0.75-0.81)	–	0.65 (0.62-0.69)

^a n (%) patients achieving the outcome. ^b GDP per capita was a priori forced into the multivariable prediction models to adjust for socioeconomic differences between countries/registries. ^c Peripheral arthritis was based on the presence of at least 1 swollen joint (either in 28- or 66-joint count) at baseline or the presence of arthritis in ASAS criteria (ever/never). ^d AUROC was estimated by calculating the 0.632+ bootstrap estimate. ASAS: Assessment of SpondyloArthritis international Society; ASDAS: Axial Spondyloarthritis Disease Activity Score; AUROC: area under the receiver-operating curve; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; GDP: gross domestic product; HAQ: Health Assessment Questionnaire; LDA: low disease activity; nr-axSpA: nonradiographic axial spondyloarthritis; OR: odds ratio; PGA: physician global assessment; SEC: secukinumab; tsDMARD: targeted synthetic disease-modifying antirheumatic drug.

with achieving ASDAS-CRP LDA at 6 months.⁸ A recent retrospective study showed that in patients with r-axSpA, obesity was associated with a lower risk of SEC discontinuation.²⁹

Compared to this previous literature, we found additional predictors of SEC effectiveness. These included lower baseline HAQ level and higher baseline PGA level associated with achieving both ASDAS-CRP and BASDAI LDA at 6 months. Earlier year of SEC initiation (2015-2018) was associated with treatment continuation at 12 months. This may partially be explained by the fact that prior to 2017, fewer treatment options were available (eg, ixekizumab [IXE] became available in many countries for the treatment of axSpA in approximately 2017), which possibly resulted in patients remaining on SEC for longer periods of time, despite the fact that LDA or remission were not achieved. Not surprisingly, as IL-17A inhibitors can be initiated in patients with moderate to severe plaque PsO and are known to be particularly efficacious for PsO,³⁰ we found a history of PsO to be associated with achieving BASDAI LDA at 6 months.

Some predictors of SEC effectiveness that we identified are similar to those reported for TNFi in the literature: pres-

ence of HLA-B27, lower baseline BASDAI scores, noncurrent smoking, and r-axSpA.^{2,3,7,31} In our study, we found that noncurrent smoking was associated with achieving LDA at 6 months, which is important because of the potentially modifiable nature of smoking behavior. We also report that nr-axSpA was associated with not achieving ASDAS LDA at 6 months. Previously, nr-axSpA has been associated with an increased risk for drug discontinuation in TNFi studies.^{32,33} Although TNFi and SEC have different modes of action, these similar results suggest that the identified predictors may be more generic for the disease itself, rather than related to the specific type of therapy. It should be noted as a potential bias that data included in this study have been collected prior to 2020, when SEC was not yet approved for nr-axSpA in Europe. However, the patients with nr-axSpA were a minority in our cohort, and compared to the patients with r-axSpA, were more often female (62% vs 36%), although they had similar values of PROs and disease activity measures. This is in line with previous studies comparing nr-axSpA with r-axSpA.³⁴ A total of 64% of the nr-axSpA group (compared with 87% of the r-axSpA group) were HLA B27 positive, and

Table 3. Summary of predictors in multivariable analyses for ASDAS-CRP LDA and BASDAI LDA at 6 months and treatment continuation at 12 months for SEC, stratified by GDP.

Baseline Characteristics	Low GDP (< \$40 ^a), n = 538			High GDP (> \$40 ^a), n = 636		
	ASDAS-CRP LDA at 6 Months	BASDAI LDA at 6 Months	Treatment Continuation LDA at 12 Months	ASDAS-CRP at 6 Months	BASDAI LDA at 6 Months	Treatment Continuation at 12 Months
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age at SEC initiation, yrs	-	-	-	-	-	-
Sex (male)	2.04 (1.35-3.12)	1.72 (1.14-2.60)	-	-	-	-
Time since diagnosis, yrs	-	-	-	-	-	-
BMI, kg/m ²	-	-	-	-	-	-
Current smoking	-	-	-	-	-	-
HLA-B27 positive	-	-	-	-	1.75 (1.00-3.05)	-
Peripheral arthritis ^b	-	-	0.66 (0.41-1.05)	-	-	-
nr-axSpA	-	-	-	-	-	-
History of uveitis	-	-	-	-	-	-
History of psoriasis	-	-	-	-	2.00 (1.14-3.54)	-
SEC start year (2018-2021)	-	-	0.48 (0.29-0.78)	-	-	0.61 (0.44-0.84)
No. of previous						
b/tsDMARDs	0.56 (0.45-0.70)	0.78 (0.66-0.93)	0.84 (0.72-0.98)	-	-	-
CRP (> 10 mg/L)	0.48 (0.30-0.76)	-	-	-	-	-
Pain (0-10)	-	-	-	-	-	-
Fatigue (0-10)	-	-	-	-	-	-
HAQ (0-3)	0.61 (0.39-0.95)	0.55 (0.35-0.87)	-	0.47 (0.25-0.85)	-	-
PGA (0-10)	-	1.20 (1.05-1.37)	-	-	1.14 (1.01-1.29)	-
BASDAI (0-10)	0.86 (0.76-0.97)	0.80 (0.69-0.92)	-	0.80 (0.70-0.90)	0.65 (0.58-0.74)	-
BASFI (0-10)	-	-	-	-	-	-
AUROC (95% CI) ^c	0.74 (0.69-0.78)	0.75 (0.70-0.79)	0.60 (0.54-0.64)	0.73 (0.66-0.79)	0.73 (0.68-0.78)	0.56 (0.51-0.60)

^a GDP per capita, in thousands (USD). ^b Peripheral arthritis was based on the presence of at least 1 swollen joint (either in 28- or 66-joint count) at baseline or the presence of arthritis in ASAS criteria (ever/never). ^c AUROC was estimated by calculating the 0.632+ bootstrap estimate. ASAS: Assessment of Spondyloarthritis international Society; ASDAS: Axial Spondyloarthritis Disease Activity Score; AUROC: area under the receiver-operating curve; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; GDP: gross domestic product; HAQ: Health Assessment Questionnaire; LDA: low disease activity; nr-axSpA: nonradiographic axial spondyloarthritis; OR: odds ratio; PGA: physician global assessment; SEC: secukinumab; tsDMARD: targeted synthetic disease-modifying antirheumatic drug.

31% and 17% of patients received SEC as their first or second bDMARD, respectively. These characteristics support our clinical experience that SEC was used off-label for nr-axSpA prior to approval by authorities.

We found that CRP > 10 mg/L was associated with not achieving ASDAS-CRP LDA at 6 months in both univariable and multivariable analyses, whereas increased CRP was associated with achievement of BASDAI LDA and 12-month treatment continuation in univariable analyses. Increased CRP was also strongly associated with achievement of ASDAS CII. To achieve a response (ie, change of a certain magnitude) the initial value will, by definition, need to be increased, and even though the ASDAS-CRP is a composite measure, the CRP values will heavily affect the calculation of change in ASDAS-CRP. Thus, increased CRP has been identified as a predictor of ASDAS CII in numerous studies, often from RCT data since these patients are included based on high disease activity levels. In contrast, a systematic literature review of predictors for remission (ASAS partial remission or ASDAS inactive disease) in axSpA showed inconsistent results, with increased CRP acting as both a positive and negative predictor.³¹ Fewer studies have investigated predic-

tors of LDA in an observational setting. In an observational cohort, Ramonda et al did report that high baseline CRP levels were associated with a higher chance to achieve ASDAS LDA at 6 months.⁸ Patient characteristics as well as methodology varied between our present study and the latter,⁸ which may explain the different results. Patients in our study were younger (median age 47 vs 51 yrs), more often male (53% vs 48%), HLA-B27 positive (80% vs 41%), with radiographic disease (83% vs 54%), and had higher baseline CRP levels (median 9.7 mg/L vs 4.5 mg/L). In the study by Ramonda et al, CRP was included as a continuous variable, whereas we categorized CRP as normal vs elevated. In line with our results, a recent study bringing together the latest data from literature concluded that baseline CRP level does not seem to influence the response to IL-17 inhibitors (ie, IXE and SEC) when looking across various outcomes.³⁵

The EuroSpA RCN has previously reported heterogeneity in baseline characteristics and treatment outcomes across countries,^{36,37} possibly reflecting differences in patient selection, prescription practices, and access to therapy.^{36,38} It has been reported that a country's wealth (measured by GDP and GDP per capita) is one of the factors explaining health dispar-

ities across countries,³⁹ and that in the field of SpA, patients in less socioeconomically developed countries have higher disease activity than in more socioeconomically developed countries.⁴⁰ In our study, the number of previous b/tsDMARDs was the only baseline predictor identified in the low GDP group and was associated with not achieving the 3 outcomes, in contrast to in countries with high GDP where we did not find any mutual predictor across the outcomes.

In our study, we chose to apply the same statistical analyses for the 3 outcomes. Thus, we assessed the potential predictors for treatment continuation (logistic regression) rather than drug retention (Cox regression). We found that 53% of patients were still registered as receiving SEC after 12 months. This proportion is lower than the previously published 12-month SEC retention of approximately 70%^{41,42} from our group, which is explained by the fact that in our present study, the constructed binary variable “treatment continuation” did not take into account censoring events, like withdrawal because of remission, pregnancy wish, or end of registry follow-up, in contrast to traditional survival analysis (Cox regression analyses).

An important strength of this study is that it represents the first-ever description, to our knowledge, of baseline predictors of SEC effectiveness (ie, LDA at 6 months and treatment continuation at 12 months) in a large prospective observational cohort of patients with axSpA. The generalizability of the results is high, as a result of the inclusion of multiple European registries and a large number of patients. Nevertheless, our study also has some limitations. Missing data, inherent in all registry studies, is the main limitation of our study. As a result of missing data, we had to exclude almost 800 patients in our analyses, as they did not have available data on ASDAS-CRP and/or BASDAI LDA assessment at 6 months. It would have been advantageous for the statistical power of our analyses if these patients could have been included in the study. Among included patients, we imputed data using MICE to overcome missing baseline covariates in the best possible way.

The performance of the final statistical models was found to be acceptable (between 0.70 and 0.80) for ASDAS LDA and BASDAI LDA at 6 months, whereas it was poorer (between 0.60 and 0.70) for treatment continuation at 12 months. This suggests that additional factors (eg, socioeconomic variables, comorbidities, and biomarkers [imaging and serological]), should preferably be included in future studies, to provide a better understanding of what determines the treatment outcomes, particularly long-term treatment continuation.

In conclusion, we identified baseline predictors of ASDAS-CRP LDA, BASDAI LDA, and treatment continuation in a large real-world European population of patients with axSpA initiating SEC. Ten baseline factors, including clinical, patient-reported, and lifestyle factors, were identified as predictors for either achievement of clinical LDA at 6 months or treatment continuation at 12 months, underscoring the complex mechanisms of real-world drug effectiveness.

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ETHICS AND PATIENT CONSENT

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 and performed in accordance with the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.⁴³

SUPPLEMENTARY DATA

Supplementary material accompanies the online version of this article.

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