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ORIGINAL ARTICLE

Predicting extra-musculoskeletal and peripheral manifestations and their role on biologic treatment in patients with axial spondyloarthritis: TReasure experience

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ABSTRACT

Objectives: This study aimed to examine the frequency and associated factors of extra-musculoskeletal manifestations (EMMs) and peripheral manifestations in an axial spondyloarthritis (axSpA) cohort and their impact on the choice of first biologic treatment.

Patients and methods: A total of 1,687 patients with axSpA (978 males, 709 females; mean age: 38.5±11 years) who started their first biologic disease modifying antirheumatic drug (bDMARD) were included from a national prospective database of TReasure between its inception and 2018-2021. Demographic and clinical characteristics, disease-related features, and treatment patterns were compared between patients with and without EMMs or peripheral involvement.

Results: Of the patients, 1,283 had radiographic axSpA (r-axSpA), while 404 had nonradiographic axSpA (nr-axSpA). Acute anterior uveitis (AAU) was the most common (11.4%) EMM, and older age, female sex, human leukocyte antigen B27 (HLA-B27) positivity, and a lower Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score were associated with AAU. Female sex, methotrexate use, dactylitis, and higher Ankylosing Spondylitis Disease Activity Score (ASDAS)-serum C-reactive protein (CRP) scores were related to psoriasis (PsO). Inflammatory bowel disease (IBD) and PsO were negatively associated with HLA-B27 positivity. Enthesitis was the most frequent (28.2%) peripheral manifestations, and peripheral arthritis, dactylitis, and enthesitis were independent predictor of each other. In addition, dactylitis and peripheral arthritis were related to more frequent use of conventional disease modifying antirheumatic drugs. In addition, IBD history was associated with less frequent use of etanercept. Older age, less use of sulfasalazine, the absence of enthesitis, and lower Bath Ankylosing Spondylitis Functional Disease Index (BASFI) scores were associated with secukinumab use.

Conclusion: Acute anterior uveitis was associated with HLA-B27 positivity, while PsO or IBD were negatively associated with HLA-B27 in patients with axSpA. Peripheral manifestations appeared to be related to each other. Among EMMs, we found that only IBD had an effect on the bDMARD preference.

Keywords: Adult rheumatic disease, axial spondyloarthritis, extra-muskuloskeletal manifestations, peripheral manifestations.

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease that mainly affects sacroiliac joints and spine. It is subdivided into two forms: radiographic axSpA (r-axSpA), formerly known as ankylosing spondylitis (AS), and nonradiographic axSpA (nr-axSpA).[1] Despite spinal inflammation and structural damage are major features of axSpA, extra-musculoskeletal manifestations (EMMs; acute anterior uveitis [AAU], psoriasis [PsO], inflammatory bowel disease [IBD]) and peripheral involvement (peripheral arthritis, dactylitis, and enthesitis) may accompany. Although EMMs and peripheral manifestations are not rare in patients with axSpA, there is limited data regarding their predictors and their impact on treatment preference.

Results from a recent meta-analysis showed the pooled prevalence of AAU as 25.8%, PsO as 9.3%, and IBD as 6.8% in patients with AS.[2] In another meta-analysis evaluating the prevalence of EMMs and peripheral manifestations in patients with both AS and nr-axSpA showed that the pooled cumulative prevalence of peripheral arthritis was 29.7%, enthesis was 28.8%, and dactylitis was 6.0% in patients with AS, and the cumulative prevalence of each peripheral involvement was similar in patients in nr-axSpA.[3] It is well known that some of these involvements might have an impact on the treatment decision.

There are several studies about related factors with EMMs and the impact of EMMs on treatment choice in patients with axSpA.[4,5] A recent observational cohort study reported higher occurrence of AAU and lower occurrences of PsO and IBD in HLA-B27-positive patients with axSpA.[4] In another population-based study, a history of IBD was associated with higher disease activity, and a history of PsO was associated with both higher disease activity and functional impairment.[5] However, a history of AAU was not related with either disease activity or functional status. Additionally, the presence of EMMs had an impact on the treatment preference of axSpA; patients with current IBD or PsO more frequently received biologic disease modifying antirheumatic drugs (bDMARDs) and conventional synthetic disease modifying antirheumatic drugs (csDMARDs) in addition to systemic steroids. However, current AAU was found to be only associated with a higher use of csDMARDs in the same study.

In 2019, the American College of Rheumatology, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network published recommendations for the treatment of patients with axSpA, and they suggested to use of monoclonal tumor necrosis factor inhibitors (TNFi) for axSpA patients with a history of IBD or recurrent AAU.[6]

Therefore, the presence of EMMs, in particular IBD and AAU has influence on the choice of bDMARDs; however, little is known regarding the role of peripheral manifestations, along with the presence of PsO, on the prescribing patterns in patients with axSpA. Hence, this study aimed to examine the cumulative prevalence and associated factors of EMMs and peripheral involvement in patients with axSpA prescribed their first bDMARD and determine the factors related with bDMARD preferences in a real-life setting.

PATIENTS AND METHODS

TReasure is a national, multicenter, and observational database, in which RA and SpA patients receiving bDMARDs therapy are registered. Entry of patient data started in December 2017.[7] At the time of data collection, there were a total of 5,661 patients with spondyloarthritis (axial and peripheral spondyloarthritis) in the database, and 3,974 patients had bDMARD use history. Of these, 1,687 patients (978 males, 709 females; mean age: 38.5±11 years) with axSpA who started their first bDMARD were included in the study. All patients registered to the database fulfilled the Assessment of Spondyloarthritis International Society (ASAS) classification criteria[1] and were aged 18 years and over. Ethics committee approval for use of the TReasure database was obtained from the Hacettepe University Ethics Committee (KA-17/058) in May 2017 and from the Ministry of Health of Türkiye (93189304-14.03.01) in October 2017. Written informed consent was obtained from all participants.

Baseline information regarding sociodemographic (e.g., age, sex, education level, smoking status, and body mass index

[BMI]) and axSpA-related features (e.g., disease duration, the presence of peripheral [arthritis, enthesitis, and dactylitis], EMMs [AAU, PsO, and IBD], csDMARD usage, comorbidities and family history of SpA-related diseases, serum C-reactive protein [CRP] levels, erythrocyte sedimentation rate [ESR], disease activity, and functional assessment) were collected. We defined AAU, IBD, and PsO as diagnosed by a physician and reported by patients. The diagnosis of hip involvement was made through radiography by rheumatologists. Family history of SpA-related diseases in first- or second-degree relatives, in addition to SpA, IBD, and PsO, were also screened in the relatives.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[8] Bath Ankylosing Spondylitis Functional Disease Index (BASFI),[9] and Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP[10] were recorded as disease activity and function measurements. The bDMARDs prescribed for axSpA patients were etanercept (ETA), secukinumab (SEC) or monoclonal antibodies (MAb; infliximab, adalimumab [ADA], golimumab, and certolizumab).

Statistical analysis

All statistical analyses were conducted using PASW version 18.0 software (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov). Most of the continuous variables were nonnormally distributed; therefore, values were presented as medians and interquartile range for continuous and as percentages for categorical variables. The Mann-Whitney U test was used to compare nonnormally distributed variables between the groups. The chi-square test or Fisher exact test was used for the comparison of categorical data. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the backward stepwise logistic regression analysis to determine independent predictors. The clinical significance of the findings was examined, and relevant variables were included in the model to ensure that the clinical significance of the findings did not deteriorate. A p-value <0.05 was considered statistically significant.

RESULTS

Of the patients, 1,283 had r-axSpA, while 404 had nr-axSpA. Fifty-four percent of the patients were HLA-B27 positive. The median time from diagnosis to the initiation of bDMARD treatment was 80 (36-149) months. Of the patients, 397 (23.7%) had one or more EMMs, and 697 (41.5%) had one or more peripheral manifestations. The baseline demographic and disease-related characteristics of all patients and patients in each bDMARD group are summarized in Table 1.

Extra-musculoskeletal manifestations of axSpA

Acute anterior uveitis was the most common EMM in the entire cohort, and 193 (11.4%) patients had AAU. Patients with AAU were older, and the proportion of female patients and HLA-B27 positivity were higher in this group. The duration from symptom onset to initiation of bDMARD treatment was longer in patients with AAU compared to patients without AAU. In addition, we found lower BASDAI scores at baseline and higher percentage of SpA-related family history in patients with AAU. However, there was no relation between AAU and csDMARD use or smoking status (Table 2). In multivariate analysis, older age (odds ratio [OR]=1.024, 95% confidence interval [CI]: 1.006-1.043, p=0.01), female sex (OR=2.023, 95% CI: 1.358-3.013, p=0.001), HLA-B27 positivity (OR=3.704, 95% CI: 2.360-5.815, p<0.001), and lower BASDAI score at baseline (OR=0.875, 95% CI: 0.809-0.947, p=0.001) were associated with AAU in patients with axSpA (Supplementary Table 2).

Psoriasis was reported in 152 (9.0%) patients. Patients with PsO were older at diagnosis and had less common HLA-B27 positivity and higher BMI, and the percentage of female patients and those who never smoked were higher in this group. In addition, patients with PsO had shorter duration from symptom onset to bDMARD treatment initiation, higher percentage of csDMARD use, more common peripheral arthritis, and dactylitis. Moreover, BASDAI, ASDAS-CRP scores, and ESR values at baseline were higher and SpA-related family history was less frequent in patients with PsO (Table 2). In the multivariate analysis, we

Table 1. Characteristics of all patients and treatment groups

	All patients (n=1,687)	SEC treatment group (n=80)	TNFi treatment group (n=1607)	*p*	ETA treatment group (n=330)	MAb treatment group (n=1,277)	*p*
Age (year), (Mean±SD)	38.5±10.9	43±11	38±11	**0.001**	39±13	38±10	0.20
Sex (male), n (%)	974 (57.7)	49 (61.3)	925 (57.6)	0.51	206 (62.4)	719 (56.3)	**0.045**
Time from diagnosis to treatment (months), median (IQR 25-75%)	80 (36-149)	108 (54-189)	28 (60-80)	**0.028**	36 (11-92)	26 (5-75)	**0.003**
Education (>12 years), n (%)	542 (34)	24 (33)	518 (34)	0.98	115 (36)	403 (33)	0.30
Ever-smoker, n (%)	1002 (61)	37 (51)	965 (61)	0.06	210 (64)	755 (61)	0.21
BMI, median (IQR 25-75%)	26.8 (23.8-30.0)	28.4 (25.4-31.2)	26.7 (23.7-30.0)	**0.012**	26.6 (23.5-29.6)	26.7 (23.8-30.1)	0.31
AAU (ever), n (%)	193 (11.4)	6 (7.5)	187 (11.6)	0.26	35 (10.6)	152 (11.9)	0.51
Psoriasis (ever), n (%)	152 (9.0)	6 (7.5)	146 (9.1)	0.63	27 (8.2)	119 (9.3)	0.52
IBD (ever), n (%)	78 (4.6)	1 (1.3)	77 (4.8)	0.18	6 (1.8)	71 (5.6)	**0.005**
Peripheral arthritis (ever), n (%)	445 (26.4)	16 (20)	429 (26.7)	0.19	95 (28.8)	334 (26.2)	0.34
Enthesitis (ever), n (%)	476 (28.2)	11 (13.8)	79 (4.9)	**0.003**	18 (5.5)	61 (4.8)	0.61
Dactylitis (ever), n (%)	81 (4.8)	2 (2.5)	465 (28.9)	0.43	91 (27.6)	374 (29.3)	0.54
Hip involvement (ever), n (%)	412 (24.4)	17 (21.3)	395 (24.6)	0.50	106 (32.1)	289 (22.6)	**<0.001**
BASDAI, median (IQR 25-75%)	5.8 (3.8-6.8)	5.8 (4.6-7.2)	5.8 (3.7-6.7)	0.21	5.7 (2.8-6.4)	5.8 (3.8-6.8)	**0.001**
BASFI, median (IQR 25-75%)	4.0(2-5.7)	5.0 (2.7-6.1)	4.0 (2.0-5.7)	**0.017**	4.0 (1.7-5.0)	4.0 (2.0-5.8)	**0.002**
Current MTX use, n (%)	151 (9)	1 (1.3)	150 (9.3)	**0.013**	34 (10.3)	116 (9.1)	0.50
Current SLZ use, n (%)	298 (17.7)	24 (30)	274 (17.1)	**0.003**	68 (20.6)	206 (16.1)	0.05

SEC: Secukinumab; TNFi: Tumor necrosis factor inhibitors; ETA: Etanercept; MAb: Monoclonal antibodies; SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index; AAU: Acute anterior uveitis; IBD: Inflammatory bowel disease; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Disease Index; MTX: Methotrexate; SLZ: Sulfasalazine.

Table 2. Characteristics of patients with and without EMMs

	AAU			PsO			IBD		
	Yes (n=193)	No (n=1494)	*p*	Yes (n=152)	No (n=1535)	*p*	Yes (n=78)	No (n=1609)	*p*
Age (year), (mean±SD)	41±11	38±11	**<0.001**	40±11	38±11	0.096	42±12	38±11	**0.018**
Sex (male), (%)	50	59	**0.017**	36	60	**<0.001**	55	58	0.63
Time from diagnosis to treatment (month), median (IQR 25-75%)	43 (10-122)	27 (6-77)	**0.001**	20 (4-68)	29 (7-83)	0.06	21 (3-61)	29 (6-83)	0.17
HLA-B27 positivity, (%)	77	51	**<0.001**	36	55	**<0.001**	27	55	**<0.001**
Education (>12 years), (%)	37	33	0.35	30	34	0.40	30	34	0.54
BMI, median (IQR 25-75%)	26.6 (23.8-29.9)	26.8 (23.8-30.0)	0.99	28.0 (25.0-31.6)	26.6 (23.7-29.8)	**<0.001**	24.6 (22.0-28.8)	26.8 (23.9-30.1)	**<0.001**
Ever-smoker, (%)	63	61	0.20	50	62	**0.007**	60	61	0.50
AAU (ever), (%)				7.2	11.9	0.11	11.5	11.4	0.98
Psoriasis (ever), (%)	5.7	9.4	0.09				7.7	9.1	0.68
IBD (ever), (%)	4.7	4.6	0.98	3.9	4.7	0.68			
Peripheral arthritis (ever), (%)	23.8	26.7	0.39	40.1	25.0	**<0.001**	29.5	26.2	0.52
Enthesitis (ever), (%)	27.5	28.3	0.80	29.6	28.1	0.69	24.4	28.4	0.44
Dactylitis (ever), (%)	3.1	5.0	0.24	16.4	3.6	**<0.001**	2.6	4.9	0.58
Hip involvement (ever), (%)	28.5	23.9	0.16	30.9	23.8	0.05	30.8	24.1	0.18
BASDAI, median (IQR 25-75%)	5.5 (2.8-6.4)	5.8 (3.8-6.8)	**0.012**	5.9 (4.65-7)	5.8 (3.6-6.7)	**0.042**	5.5 (3.6-6.2)	5.8 (3.8-6.8)	0.08
BASFI, median (IQR 25-75%)	4 (1.1-5.5)	4 (2.1-5.7)	0.06	4 (2.6-5.5)	4 (2-5.7)	0.50	3.9 (1.9-5.3)	4 (2-5.7)	0.36
ASDAS-CRP, median (IQR 25-75%)	3.2 (1.85-4.1)	3.4 (2.5-4.2)	0.16	3.62 (2.76-4.39)	3.4 (2.34-4.135)	**0.017**	3.2 (2.4-4.3)	3.4 (2.4-4.2)	0.95
ESR, median (IQR 25-75%)	25 (9-39)	19 (7-36)	0.070	24.5 (11-40)	19 (7-36)	**0.029**	28.5 (13-43)	19 (7-36)	**0.003**
Current csDMARD use, (%)	27.5	24.6	0.38	38.2	23.6	**<0.001**	30.8	24.6	0.22
Current MTX use, (%)	8.3	9.0	0.73	26.3	7.2	**<0.001**	10.3	8.9	0.68
Current SLZ use, (%)	21.8	17.1	0.11	11.8	18.2	**0.048**	24.4	17.3	0.11
SpA-related family history, (%)	40.4	32.1	**0.02**	20.4	34.3	**0.001**	24.4	33.4	0.10

EMMs: Extra-musculoskeletal manifestations; AAU: Acute anterior uveitis; PsO: Psoriasis; IBD: Inflammatory bowel disease; SD: Standard deviation; IQR: Interquartile range; HLA-B27: Human leukocyte antigen (HLA) B27; BMI: Body mass index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Disease Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; csDMARD: Conventional synthetic disease modifying anti-rheumatic drugs; SLZ: Sulfasalazine; SpA: Spondyloarthritis.

discovered that PsO was associated with female sex (OR=2.101, 95% CI: 1.276-3.458, p=0.004), a higher percentage of methotrexate (MTX) use (OR=3.834, 95% CI: 1.982-7.416, p<0.001), dactylitis (OR=5.276, 95% CI: 2.475-11.248, p<0.001), and higher ASDAS-CRP scores (OR=1.409, 95% CI: 1.155-1.719, p=0.001) in patients with axSpA (Supplementary Table 3). In addition, PsO was related to HLA-B27 negativity (OR=0.537, 95% CI: 0.324-0.888, p=0.015) in multivariate analysis.

Inflammatory bowel disease was reported in 78 (4.6%) patients. Patients with IBD were older and had lower BMI, lower percentage of HLA-B27 positivity, and higher ESR values (Table 2). In multivariate analysis, only the HLA-B27 negativity (OR=0.297, 95% CI: 0.162-0.543, p<0.001) and higher ESR values (OR=1.015, 95% CI: 1.005-1.026, p=0.004) were associated with IBD (Supplementary Table 4).

Peripheral manifestations of axSpA

Enthesitis was the most common peripheral manifestation in our cohort, and 476 patients reported to have enthesitis (28.2%). When we compared patients with and without enthesitis, we found that the percentages of females were higher in patients with enthesitis. The percentages of peripheral arthritis, dactylitis, and SpA-related family history were higher; however, the frequency of hip involvement was lower in patients with enthesitis. In addition, duration from symptom onset or diagnosis to bDMARD treatment initiation was shorter than patients without enthesitis. Moreover, higher BASDAI scores but lower ASDAS-CRP scores were reported in patients with enthesitis (Table 3). In multivariate analysis, shorter time from diagnosis to bDMARD treatment initiation (OR=0.998, 95% CI: 0.996-1.000, p=0.02), peripheral arthritis (OR=4.045, 95% CI: 3.056-5.354, p<0.001), dactylitis (OR=2.037, 95% CI: 1.157-3.586, p=0.014), and lower percentage of hip involvement (OR=0.412, 95% CI: 0.285-0.596, p<0.001) were found to be associated with the presence of enthesitis in axSpA patients (Supplementary Table 5).

Peripheral arthritis was reported in 445 (26.4%) patients. When we compared patients with and without peripheral arthritis, we found that females, HLA-B27-negative patients, those who never smoked, and those who had higher BMI were more common in the peripheral arthritis group. In addition, shorter duration from diagnosis to bDMARD treatment initiation and more common dactylitis, enthesitis, and PsO were reported in patients with peripheral arthritis (Table 3). Additionally, we found that patients with peripheral arthritis had higher percentage of csDMARD, MTX, and sulfasalazine (SLZ) use, lower BASFI and ASDAS-CRP scores, and higher percentage of SpA-related family history, diagnosis of diabetes mellitus, and hypertension. In multivariate analysis, we found that the female sex (OR=1.888, 95% CI: 1.355-2.632, p<0.001), more frequent csDMARD use (OR=2.599, 95% CI: 1.780-3.795, p<0.001), enthesitis (OR=3.143, 95% CI: 2.240-4.410, p<0.001), dactylitis (OR=9.496, 95% CI: 3.979-22.660, p<0.001), and higher ASDAS-CRP scores (OR=0.882, 95% CI: 0.788-0.988, p=0.03) were associated with the presence of peripheral arthritis (Supplementary Table 6).

Dactylitis was reported in 81 (4.8%) patients. Dactylitis was more common in female patients. In addition, the percentages of peripheral arthritis, enthesitis, and PsO were higher in the dactylitis-positive group; however, the presence of hip involvement and ASDAS-CRP scores were lower. They had shorter duration from symptom onset or diagnosis to treatment start. In addition, higher percentage of MTX or SLZ use was reported in the dactylitis-positive group (Table 3). In multivariate analysis, peripheral arthritis (OR=11.211, 95% CI: 5.479-22.938, p<0.001), enthesitis (OR=2.758, 95% CI: 1.550-4.908, p=0.001), PsO (OR=4.087, 95% CI: 2.190-7.627, p<0.001), and csDMARD use (OR=2.051, 95% CI: 1.189-3.539, p=0.010) were associated with presence of dactylitis in patients with axSpA (Supplementary Table 7).

We also compared patients with and without any peripheral musculoskeletal manifestations. Peripheral manifestations were more frequent in HLA-B27-negative patients, those who never smoked, and female patients. Higher BASDAI, lower ASDAS-CRP scores, and higher percentage of csDMARD use were reported in patients with peripheral manifestations, and they had shorter duration from diagnosis to treatment start. In addition, patients with peripheral manifestations had more common SpA-related family history

Table 3. Characteristics of patients with and without peripheral manifestations

	Peripheral arthritis			Enthesitis			Dactylitis		
	Yes (n=445)	No (n=1242)	*p*	Yes (n=476)	No (n=1211)	*p*	Yes (n=81)	No (n=1606)	*p*
Age (year), (Mean±SD)	38.3±11.6	38.5±10.7	0.76	37.8±11	38.6±11	0.29	37.0±11	38.5±11	0.42
Sex Male, n (%)	41.3	63.6	**<0.001**	50	60.8	**<0.001**	42	58.5	**0.003**
Time from diagnosis to treatment (years), median (IQR 25-75%)	21 (5-70)	32 (7-86)	**0.003**	21 (6-68)	33 (6-87)	**0.008**	14 (5-55.5)	29 (6-84)	**0.020**
HLA-B27 positivity, (%)	46	56	**0.002**	49	56	0.05	52	54	0.79
Education (>12 years), (%)	34	33	0.64	34	33	0.95	41	33	0.15
BMI, median (IQR 25-75%)	27.6 (23.6-30.8)	26.5 (23.9-29.7)	**0.042**	27.1 (23.6-31.0)	26.7 (23.9-29.7)	0.19	27.2(23.6-29.4)	26.7 (23.8-30.1)	0.92
Ever-smoker, (%)	54	64	**<0.001**	60	61	0.78	53	61	0.30
AAU (ever), (%)	10.3	11.8	0.39	11.1	11.6	0.80	7.4	11.6	0.24
Psoriasis (ever), (%)	13.7	7.3	**<0.001**	9.5	8.8	0.69	30.9	7.9	**<0.001**
IBD (ever), (%)	5.2	4.4	0.52	4.0	4.9	0.44	2.5	4.7	0.58
Peripheral arthritis (ever), (%)				47.9	17.9	**<0.001**	85.2	23.4	**<0.001**
Enthesitis (ever), (%)	51.2	20.0	**<0.001**				52 (64.2)	424 (26.4)	**<0.001**
Dactylitis (ever), (%)	15.5	1.0	**<0.001**	10.9	2.4	**<0.001**			
Hip involvement (ever), (%)	38.2	20.1	**<0.001**	13.9	28.6	**<0.001**	14.8	24.9	**0.039**
BASDAI, median (IQR 25-75%)	5.9 (3.4-7.4)	5.8 (3.8-6.5)	0.18	6.0 (3.7-7.4)	5.8 (3.8-6.5)	**0.007**	6 (3.8-7.8)	5,8 (3.8-6.7)	0.13
BASFI, median (IQR 25-75%)	3.8 (0-6.0)	4 (2.3-5.6)	**0.001**	4.0 (1.4-6.1)	4.0 (2.2-5.5)	0.66	3.8 (0.1-6.4)	4.0 (2.1-5.7)	0.15
ASDAS-CRP, median (IQR 25-75%)	3.1 (0-4.1)	3.5 (2.6-4.2)	**<0.001**	3.2 (1.9-4.0)	3.5 (2.5-4.2)	**<0.001**	3.0 (0-3.9)	3.5 (2.4-4.2)	**0.009**
ESR, median (IQR 25-75%)	21 (8-41)	19 (7-35)	0.08	17.5 (6-37)	20 (8-36)	0,11	18 (5-44)	20 (8-36)	0.57
Current csDMARD use, (%)	38.2	20.1	**<0.001**	27.9	23.7	0.07	48.1	23.7	**<0.001**
Current MTX use, (%)	18.9	5.4	**<0.001**	10.9	8.2	0.08	22.2	8.3	**<0.001**
Current SLZ use, (%)	23.4	15.6	**<0.001**	93 (19.5)	205 (16.9)	0.21	29.6	17.1	**0.004**
SpA-related family history, (%)	38.0	31.2	**0.01**	37.4	31.3	0.017	30.9	33.1	0.67

SD: Standard deviation; IQR: Interquartile range; HLA-B27: Human leukocyte antigen (HLA) B27; BMI: Body mass index; AAU: Acute anterior uveitis; IBD: Inflammatory bowel disease; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Disease Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; csDMARD: Conventional synthetic disease modifying anti-rheumatic drugs; MTX: Methotrexate; SLZ: Sulfasalazine; SpA: Spondyloarthritis.

as well as hypertension (Supplementary Table 1). In multivariate analysis, female sex (OR=1.630, 95% CI: 1.226-2.168, p=0.001), shorter duration from diagnosis to bDMARD treatment initiation (OR=0.996, 95% CI: 0.994-0.998, p=0.001), more common csDMARD use (OR=1.995, 95% CI: 1.418-2.808, p<0.001), lower ASDAS-CRP scores (OR=0.829, 95% CI: 0.751-0.916, p<0.001), and SpA-related family history (OR=1.430, 95% CI: 1.063-1.925, p=0.018) were associated with the presence of peripheral manifestations.

Table 4. Multivariate analysis of ETA *vs.* MAb

	OR	%95 CI	*p*
Model 1			
Male sex	1.09	0.82-1.43	0.56
Duration from diagnosis till treatment start	1.00	0.100-1.00	0.18
Hip involvement (ever)	1.64	1.22-2.200	**0.001**
IBD (ever)	0.29	0.11-0.73	**0.009**
BASDAI	0.94	0.87-1.01	0.10
BASFI	0.95	0.88-1.03	0.21
Model 2			
Hip involvement (ever)	1.68	1.26-2.23	**<0.001**
IBD (ever)	0.29	0.11-0.72	**0.008**
BASDAI	0.91	0.86-0.95	**<0.001**

ETA: Etanercept; MAb: Monoclonal antibodies; OR: Odds ratio; CI: Confidence interval; IBD: Inflammatory bowel disease; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Disease Index.

Table 5. Multivariate analysis of SEC *vs.* TNFi

	OR	%95 CI	*p*
Model 1			
Age	1.03	0.99-1.07	0.10
BMI	1.03	0.98-1.07	0.28
Age at diagnosis	0.99	0.95-1.03	0.56
Sulfasalasine use	2.18	1.24-3.83	**0.007**
Enthesitis	0.41	0.20-0.81	**0.01**
BASFI	1.13	1.02-1.26	**0.02**
Delaying diagnosis	1.00	0.10-1.00	0.78
Model 2			
Age	1.03	1.01-1.05	**0.017**
Sulfasalasine use	2.21	1.26-3.87	**0.006**
Enthesitis	0.41	0.20-0.81	**0.010**
BASFI	1.14	1.02-1.26	**0.017**

SEC: Secukinumab; TNFi: Tumor necrosis factor inhibitors; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; BASFI: Bath Ankylosing Spondylitis Functional Disease Index.

Determinants of the preferences in bDMARDs prescription

The bDMARDs prescribed in our cohort were ADA originator and biosimilar (n=572, 33.9%), ETA (n=330, 19.6%), infliximab originator and biosimilar (n=298, 17.7%), certolizumab (n=205, 12.2%), golimumab (n=202, 12.0%), and SEC (n=80, 4.7%). To identify characteristics associated with the choice of the first bDMARD treatment in axSpA patients, we analyzed patients prescribed ETA and compared them with MAb. Furthermore, patients who used SEC were compared with those who used TNFi.

ETA *vs.* MAb prescription

When we compared patients prescribed ETA to MAb, we found that patients in the ETA treatment group had longer symptom duration to bDMARD prescription, and male patients were more common in this group. In addition, the absence of IBD history, the presence of hip involvement, and lower BASDAI or BASFI scores were significantly associated with ETA use over MAb. However, other peripheral manifestations or EMMs were found not to be associated with the ETA prescription in patients with axSpA. In multivariate analysis, we found that hip involvement (OR=1.678, 95% CI: 1.260-2.234, p<0.001), the absence of IBD (OR=0.287, 95% CI: 0.114-0.724, p=0.008), and lower BASDAI scores (OR=0.905, 95% CI: 0.859-0.954, p<0.001) were associated with choice of ETA treatment (Table 4). ADA was the most commonly used monoclonal TNFi in our cohort; therefore, we repeated the analysis for the preference of ETA *vs.* ADA and found that lower BASDAI scores and the presence of hip involvement were associated with the choice of ETA over ADA (data not shown).

SEC vs TNFi prescription

Although a limited number of axSpA patients were prescribed SEC as a first bDMARD, we compared patients who were initiated on SEC with those started on TNFi to evaluate whether there were determinants associated with the choice of SEC treatment. Patients in the SEC treatment group were older and had longer duration from symptom onset to treatment start, as well as less common enthesitis. Higher baseline BASFI scores were significantly associated with the use of SEC over TNFi. The lower percentage of MTX and the higher percentage of SLZ use were reported in patients treated with SEC. In multivariate analysis, older age (OR=1.027, 95% CI: 1.005-1.049, p=0.017), the absence of enthesitis (OR=0.406, 95% CI: 0.204-0.807, p=0.010), more common SLZ use (OR=2.207, 95% CI: 1.258-3.874, p=0.006), and higher baseline BASFI scores (OR=1.135, 95% CI: 1.023-1.260, p=0.017) were associated with the preference of SEC treatment (Table 5). We repeated the analysis for SEC *vs.* MAb, and the results were similar to SEC *vs.* TNFi (data not shown).

In multivariate analysis, older age (OR=1.027, 95% CI: 1.005-1.049, p=0.017), the absence of enthesitis (OR=0.406, 95% CI: 0.204-0.807, p=0.010), more common SLZ use (OR=2.207, 95% CI: 1.258-3.874, p=0.006), and higher baseline BASFI scores

DISCUSSION

The results of this observational study showed that AAU could be more frequent in older and female axSpA patients. PsO was more common in women, and patients with PsO had higher disease activity and were more frequently treated with MTX. As expected, AAU was found to be significantly related to HLA-B27 positivity. However, PsO or IBD was negatively associated with HLA-B27. The presence of each peripheral manifestation, namely arthritis, dactylitis, or enthesitis, was an independent predictor for the others, and they were more common in female patients. In addition, the presence of peripheral involvement might cause earlier bDMARD initiation, as disease duration was shorter in axSpA patients with peripheral involvement. When we evaluated the impact of the presence of EMMs or peripheral involvement on bDMARD prescription, IBD, enthesitis, and hip involvement appeared to have importance in decision-making.

In our study, 11.4% of patients had a history of AAU. The prevalence of AAU in patients with axSpA was reported to be 25.8% in a recent meta-analysis.[2] The lower proportion of AAU in the present study might be related to our patient population with low HLA-B27 positivity, including patients with nr-axSpA and AS. However, some recent cross-sectional studies reported lower prevalence of AAU, similar to our cohort.[11,12]

In previous studies, uveitis was reported to be more common in axSpA patients who had a longer disease duration.[13,14] In accordance with the previous findings in the present study, patients with AAU had longer duration from symptoms onset or diagnosis to treatment start. Older age might be the other factor associated with the presence of AAU in axSpA patients, as it was shown in both the present study and the OASIS cohort.[15] Previous studies report conflicting results regarding the association with AAU and sex in axSpA patient.[16-18] We found that AAU was more common in female patients, similar to a meta-analysis.[13] However, we did not show any impact of the presence of AAU on the treatment preferences.

It is well known that cumulative prevalence of AAU was higher in HLA-B27-positive patients with AS.[13,19] Similar to previous studies, AAU was associated with HLA-B27 positivity in the present study. However, PsO or IBD were negatively associated with HLA-B27 in our study. In a previous study, the authors reported that patients without PsO had more frequent HLA-B27 positivity than the patients with PsO (87.7% *vs.* 74.5%, $p<0.0001$).[4] In another study, patients with axSpA and PsO or IBD had significantly lower HLA-B27 positivity.[5]

The peripheral arthritis, enthesis, and dactylitis were independent determinants for each other. PsO was related to dactylitis. In addition, we found that female sex was related to PsO or peripheral arthritis. Furthermore, patients who had any EMMs or peripheral involvements had higher disease activity measurements (assessed by disease-related composite scores or laboratory analyses). Similar to our findings, in a recent study in patients with axSpA, females more frequently had peripheral arthritis and enthesitis than males.[20] A recent cluster analysis of patients with axSpA showed that patients were clustered in two groups as the axial group and the extra-axial group, and the extra-axial group included patients who had higher disease activity measurements and higher proportion of peripheral arthritis, enthesitis, and PsO.[21] Moreover, in the extra-axial group, there was a higher proportion of female than the axial group. In a recent study that compared patients with axial involvement owing to psoriatic arthritis and axSpA with PsO, the group with axSpA and PsO was older and had a lower HLA-B27 positivity, similar to our study.[22] In light of these findings, axSpA may have different subgroups, and one of them may be characterized by peripheral symptoms and a female predominant group.

Although csDMARD was not effective in axial involvement,[23] the results of the present study supported that cDMARDs might have a role in peripheral manifestations and PsO in axSpA patients since we found significantly more frequent use of csDMARDs, particularly SLZ or MTX, in those patients.

The results of the present study provide additional evidence regarding the impact of EMMs or peripheral manifestations on the choice of bDMARD. We found that, in axSpA patients, the presence of IBD was related to less frequent use of ETA, although the presence of PsO, AAU, or peripheral arthritis had no impact on the preference of bDMARD. TNFi is efficacious for the treatment of EMMs in addition to axial symptoms in patients with axSpA. It is well known that ETA has no effect on IBD observed in axSpA patients and that it might be less effective for the prevention of AAU attacks compared to MAb.[24-27] However, the presence of EMMs other than IBD had no impact on the bDMARD preferences in the current study, which might be due to the relatively easier management of AAU with topical agents.

In the current study, we could not find any relationship between EMMs and the choice of SEC. There are several possible explanations. First, there were only 80 (4.7%) patients who were prescribed SEC as the first bDMARD in our study. The limited presence of PsO or AAU among patients treated with SEC might also contribute to the findings, although it was an effective treatment option in psoriatic skin lesion and nail changes. It should be kept in mind that the present study was the first study to evaluate physicians' bDMARD preference for patients who had EMMs or peripheral involvement in a real-life setting. The results suggest that further investigations investigating the impact of enthesitis or other peripheral manifestations on bDMARD preference are needed.

This study had some limitations. First, it was a multicenter, real-life study, and treatment choices were at the discretion of physicians.

Second, we did not include conventionally treated patients as a control group. There were only 80 patients in the SEC treatment group. Additionally, as the present study was a cross-sectional study, we could not evaluate the consequences of treatment preferences on EMMs and peripheral manifestations. Finally, we did not evaluate the impact of the presence of EMMs and peripheral manifestations on bDMARD survival. The strengths of the study were its nation-wide design and sample size. AxSpA patients treated with MAb, ETA, and SEC could be evaluated in addition to EMMs. Additionally, peripheral involvement was analyzed in the present study.

In conclusion, this is the first study to evaluate the impact of peripheral manifestations, in addition to EMMs, on the choice of bDMARDs. Our results showed that AAU was significantly associated with HLA-B27 positivity, whereas patients with PsO or IBD were negatively associated with HLA-B27. Peripheral arthritis, enthesis, and dactylitis were independent predictors of each other. Although the history of IBD was associated with less frequent use of ETA, there was no relationship between the presence of EMMs and the use of SEC.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary Table 1. Characteristics of patients with and without peripheral involvement

	Peripheral involvement*										
	Yes					No					
	n	%	Mean±SD	Median	IQR 25-75%	n	%	Mean±SD	Median	IQR 25-75%	*p*
Age (year)			38±11					39±11			0.60
Sex Male	332	47.6				642	64.8				<0.001
Time from diagnosis to treatment (year)				21	6-72				35	7-90	0.001
HLA-B27 positivity	244	49				377	58				0.003
Education (>12 years)	230	34				312	33.1				0.70
Ever-smoker	391	57				611	63.8				0.001
BASDAI				5.8	3.5-7.3				5.8	3.8-6.5	0.03
BASFI				4	1.2-6.0				4	2.4-5.5	0.06
ASDAS-CRP				3.2	1.7-4.1				3.5	2.6-4.21	<0.001
ESR				20	7-38				19	8-35	0.75
Current csDMARD use	225	32.3				195	19.7				<0.001
Current MTX use	101	14.5				50	5.1				<0.001
Current SLZ use	147	21.1				151	15.3				0.002
SpA-related family history	254	36.4				303	30.6				0.012

SD: Standard deviation; IQR: Interquartile range; HLA-B27: Human leukocyte antigen (HLA) B27; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Disease Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; csDMARD: Conventional synthetic disease modifying anti-rheumatic drugs; MTX: Methotrexate; SLZ: Sulfasalazine; SpA: Spondyloarthritis; * At least one of peripheral (peripheral arthritis, enthesitis, dactylitis) involvements.

Supplementary Table 2. Multivariate analysis of AAU

	OR	95% CI	
Model 1			
Age	1.02	1.01-1.04	0.010
Sex Female	2.02	1.36-3.01	0.001
HLA-B27 positivty	3.70	2.35-5.82	<0.001
Duration from diagnosis till treatment start	1.00	1.00-1.01	0.06
BASDAI score	0.88	0.81-0.95	0.001
SpA-related family history	1.01	0.68-1.52	0.95
Model 2			
Age	1.02	1.01-1.04	0.010
Sex Female	2.02	1.36-3.01	0.001
HLA-B27 positivty	3.70	2.36-5.82	<0.001
Duration from diagnosis till treatment start	1.00	1.00-1.01	0.06
BASDAI score	0.88	0.81-0.95	0.001

AAU: Acute anterior uveitis; OR: Odds ratio; CI: Confidence interval; HLA-B27: Human leukocyte antigen (HLA) B27; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; SpA: Spondyloarthritis.

Supplementary Table 3. Multivariate analysis of PsO

	OR	95% CI	
Model 1			
Sex Female	1.96	1.16-3.33	0.013
HLA-B27 positivity	0.54	0.32-0.89	0.015
Delay in diagnosis	0.998	0.994-1.002	0.42
MTX use	3.71	1.87-7.34	<0.001
SLZ use	0.51	0.22- 1.15	0.11
Dactylitis	5.41	2.37-12.36	<0.001
Enthesis	1.00	0.58-1.713	1.0
Peripheral arthritis	0.96	0.54-1.71	0.9
SpA-related family history	0.60	0.32-1.11	0.10
ASDAS-CRP	1.41	1.15-1.72	0.001
Smoking (ever)	0.76	0.46-1.25	0.28
Model 2			
Sex Female	2.10	1.28-3.46	0.004
HLA-B27 positivity	0.54	0.32-0.89	0.015
MTX use	3.83	1.98-7.42	<0.001
SLZ use	0.50	0.22-1.14	0.10
Dactylitis	5.28	2.48-11.25	<0.001
SpA-related family history	0.57	0.31-1.03	0.06
ASDAS-CRP scores	1.41	1.16-1.72	0.001

PsO: Psoriasis; OR: Odds ratio; CI: Confidence interval; HLA-B27: Human leukocyte antigen (HLA) B27; MTX: Methotrexate; SLZ: Sulfasalazine; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein.

Supplementary Table 4. Multivariate analysis of IBD

	OR	95% CI	
Model 1			
Age	1.01	0.99-1.04	0.25
HLA-B27 positivty	0.30	0.16-0.54	<0.001
ESR	1.01	1.00-1.03	0.007
Model 2			
HLA-B27 positivity	0.29	0.16-0.52	<0.001
ESR	1.02	1.01-1.03	0.004

IBD: Inflammatory bowel disease; OR: Odds ratio; CI: Confidence interval; HLA-B27: Human leukocyte antigen (HLA) B27; ESR: Erythrocyte sedimentation rate.

Supplementary Table 5. Multivariate analysis of enthesitis

	OR	95% CI	
Model 1			
Sex Female	1.08	0.83-1.41	0.56
Duration from diagnosis till treatment start	0.998	0.995-1.000	0.017
Peripheral arthritis	3.94	2.96-5.24	<0.001
Dactylitis	2.10	1.19-3.70	0.010
Hip involvement	0.42	0.29-0.61	<0.001
ASDAS-CRP score	0.93	0.85-1.01	0.09
SpA-related family history	1.26	0.96-1.65	0.10
Model 2			
Duration from diagnosis till treatment start	0.998	0.996-1.000	0.020
Peripheral arthritis	4.05	3.06-5.35	<0.001
Dactylitis	2.04	1.16-3.59	0.014
Hip involvement	0.41	0.29-0.60	<0.001
ASDAS-CRP score	0.92	0.85-1.00	0.06

OR: Odds ratio; CI: Confidence interval; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein.

Supplementary Table 6. Multivariate analysis of peripheral arthritis

	OR	95% CI	
Model 1			
Sex Female	1.69	1.18-2.42	0.004
BMI	1.02	0.989-1.052	0.20
HLA-B27 positivity	0.91	0.63-1.30	0.59
Duration from diagnosis till treatment start	0.999	0.996-1.001	0.35
csDMARD use	2.59	1.77-3.81	<0.001
Enthesitis	2.97	2.11-4.18	<0.001
Dactylitis	9.63	3.97-23.35	<0.001
Psoriasis	1.19	0.68-2.11	0.54
ASDAS-CRP scores	0.89	0.80-1.00	0.06
SpA-related family history	1.40	0.98-2.00	0.06
Smoking (ever)	0.88	0.62-1.25	0.46
Model 2			
Sex Female	1.89	1.36-2.63	<0.001
csDMARD use	2.60	1.78-3.80	<0.001
Enthesitis	3.14	2.24-4.41	<0.001
Dactylitis	9.50	3.98-22.66	<0.001
ASDAS-CRP scores	0.88	0.79-1.00	0.030

OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; HLA-B27: Human leukocyte antigen (HLA) B27; csDMARD: Conventional synthetic disease modifying anti-rheumatic drugs; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein.

Supplementary Table 7. Multivariate analysis of dactylitis

	OR	95% CI	
Model 1			
Sex Female	0.79	0.45-1.38	0.40
Duration from diagnosis till treatment start	0.997	0.993-1.002	0.25
csDMARD use	1.97	1.12-3.45	0.018
Peripheral arthritis	11.31	5.45-23.46	<0.001
Enthesitis	2.55	1.42-4.60	0.002
Hip involvement	0.69	0.30-1.57	0.38
Psoriasis	4.98	2.56-9.66	<0.001
ASDAS-CRP socres	0.92	0.79-1.08	0.31
Model 2			
csDMARD use	2.05	1.19-3.54	0.010
Peripheral arthritis	11.21	5.48-22.94	<0.001
Enthesitis	2.76	1.55-4.91	0.001
Psoriasis	4.09	2.19-7.63	<0.001

OR: Odds ratio; CI: Confidence interval; csDMARD: Conventional synthetic disease modifying anti-rheumatic drugs; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein.