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Extraskeletal Manifestations in Axial Spondyloarthritis Are Associated With Worse Clinical Outcomes Despite the Use of Tumor Necrosis Factor Inhibitor Therapy

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ABSTRACT. ***Objective.*** To investigate the prevalence and 4-year incidence of acute anterior uveitis (AAU), inflammatory bowel disease (IBD) and psoriasis (PsO), and to explore associations of newly developed extraskeletal manifestations (ESMs) with clinical disease outcome in a large cohort of patients with axial spondyloarthritis (axSpA).

Methods. All consecutive patients included in the Groningen Leeuwarden Axial Spondyloarthritis (GLAS) cohort between 2004 and 2011 were analyzed. History of ESMs at baseline and newly developed ESMs during 4-year follow-up were only recorded when diagnosis by an ophthalmologist, gastroenterologist, or dermatologist was present.

Results. Of the 414 included patients with axSpA, 31.4% had a positive history of ≥ 1 ESMs: 24.9% AAU, 9.4% IBD, and 4.3% PsO. History of PsO was significantly associated with more radiographic damage, especially of the cervical spine. Of the 362 patients with 4-year follow-up data, 15.7% patients developed an ESM: 13.3% patients had AAU (of which 3.6% had a first episode and 9.7% had recurrent AAU), 1.9% developed IBD, and 0.8% developed PsO. Patients with newly developed ESMs (without history of ESMs) had worse Ankylosing Spondylitis Quality of Life scores (mean 10.0 vs. 5.8, $P = 0.001$), larger occiput-wall distance (median 6.3 vs. 2.0, $P = 0.02$) and more limited modified Schober test (mean 12.6 vs. 13.6, $P = 0.01$) after 4 years of follow-up. The majority of patients developing an ESM used anti–tumor necrosis factor therapy.

Conclusion. History of ESMs was present at baseline in one-third of patients with axSpA. The 4-year incidence of ESMs was relatively low, but patients who developed a new ESM reported worse quality of life.

Key Indexing Terms: ankylosing spondylitis, outcomes, quality of life, spondyloarthropathy

Spondyloarthritis (SpA) refers to a group of interrelated chronic autoinflammatory rheumatic disorders including ankylosing spondylitis (AS), nonradiographic axial SpA (nr-axSpA), psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease (IBD), reactive arthritis, and undifferentiated SpA.[1,2] Overlapping features are often observed such as involvement of the axial skeleton, predominantly as sacroiliitis and spondylitis, and the involvement of the peripheral skeleton such as peripheral arthritis, enthesitis, and dactylitis. Further, extraskeletal manifestations (ESMs)—previously, only extraarticular manifestations were identified—can be present in patients with SpA. The 3 most well-known ESMs are acute anterior uveitis (AAU), IBD, in particular Crohn disease and ulcerative colitis, and psoriasis (PsO).

Previously published pooled data showed prevalence rates of 26% for uveitis, 7% for IBD, and 9% for PsO in axSpA.[3] The presence of these ESMs in patients with chronic inflammatory back pain or peripheral arthritis increased the likelihood of having SpA.[4,5,6,7] Therefore, these ESMs are included in the Assessment of Spondyloarthritis international Society (ASAS) classification criteria.[8] Further, the presence of ≥ 1 ESMs may influence treatment decisions.[9,10]

Although data on prevalence rates of ESMs are abundant, knowledge of incidence rates in axSpA are scarce. A Dutch observational cohort study reported an overall incidence rate for any new ESM of 2.4% per year during a mean follow-up time of 8 years: 1.4% for AAU, 0.6% for IBD, and 0.3% for

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PsO. This study started in 1996; therefore, none of the patients were treated with biologics at baseline and approximately 20% started tumor necrosis factor-α inhibitor (TNFi) therapy during follow-up after registration of these drugs.[11]

Until now, conflicting results with respect to the influence of ESMs on axSpA disease outcome have been published. It has been suggested that having an ESM contributes to disease burden and may worsen clinical outcome measures.[12,13,14,15] To our knowledge, there are no data available on incidence rates and the relationship with disease outcome and treatment strategies.

Therefore, the aim of the present study was to investigate the prevalence and 4-year incidence of AAU, IBD, and PsO in a large Dutch cohort of patients with axSpA and most importantly, to explore associations of the history of ESMs and newly developed ESMs with axSpA disease outcome and treatment.

METHODS

Patients. All consecutive patients from the prospective observational Groningen Leeuwarden Axial Spondyloarthritis (GLAS) cohort who had a baseline visit between November 2004 and December 2011 and 4 years of follow-up were included in the analyses. GLAS is an ongoing prospective, longitudinal, observational cohort study in the northern part of the Netherlands. Since November 2004, this cohort included consecutive AS outpatients who started TNFi therapy at the University Medical Centre Groningen (UMCG) or the Medical Centre Leeuwarden (MCL) because of active disease.[16] All patients were aged > 18 years, fulfilled the modified New York criteria for AS,[17] and the ASAS criteria to start TNFi therapy (active disease defined as Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥ 4 and/or based on expert opinion).[18] Since 2009, the inclusion of the GLAS cohort was extended to all consecutive patients with axSpA regardless of treatment regimes. Patients were clinically evaluated at baseline, after 3 months, and then every 6 months according to a fixed protocol.

The GLAS cohort was approved by the local ethics committees of the MCL and the UMCG (approval number RTPO364/604). All patients provided written informed consent according to the Declaration of Helsinki.

Data collection. At baseline, age, sex, symptom duration, HLA-B27 status, BMI, smoking status (ever/never), smoking duration, swollen joint involvement (yes/no), and tender enthesis (yes/no) were collected. The use of pharmacological therapies was also recorded, including use of nonsteroidal antiinflammatory drugs (NSAIDs), conventional disease-modifying antirheumatic drugs (cDMARDs), and TNFis. Clinical assessment of disease activity was performed at baseline and each follow-up visit using the BASDAI[19] and Ankylosing Spondylitis Disease Activity Score (ASDAS).[20] Health-related quality of life (QOL) of the patients was assessed at each visit using the Ankylosing Spondylitis QOL (ASQoL) questionnaire,[21] physical function using the Bath Ankylosing Spondylitis Functional Activity Index (BASFI),[22] and spinal mobility using occiput-wall distance, chest expansion, lateral spinal flexion, modified Schober test, and cervical rotation (from 2009 and later).[23] Radiographic damage of the spine was scored only at baseline using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).[24]

ESMs. At baseline and each follow-up visit, standardized questions were used to gather information on AAU, IBD, and PsO. Data of ESMs were verified in the medical records. ESMs were only recorded and used for analyses when a description of the diagnosis by an ophthalmologist, dermatologist, or gastroenterologist was present.

Statistical analysis. History of ESMs at baseline and the development of new ESMs during 4-year follow-up were analyzed. Descriptive statistics were used to calculate the mean ± SD or median (IQR) for normally or nonnormally distributed continuous data, respectively. Frequencies were calculated for dichotomous data. Independent *t* test, Mann-Whitney *U* test, chi-square test, or Fisher exact test were used when appropriate to compare differences in characteristics, clinical assessments, and medication use of patients with and without a history of ESM. Multivariable logistic regression analysis was performed to correct the association of history of ESM with the disease outcome measures ASQoL and mSASSS at baseline for potential confounders (patient characteristics, medication use, and disease activity). Regression assumptions including linearity of relationship, normal distribution of residuals, homoscedasticity, and absence of multicollinearity were tested. Independent *t* test, Mann-Whitney *U* test, chi-square test, or Fisher exact test were also performed when applicable to compare differences in characteristics, clinical assessments, and medication use of patients with and without newly developed ESM at 4 years. Finally, multivariable analyses to correct the association between newly developed ESM and the disease outcome measures ASQoL and mSASSS at 4 years for potential confounding could not be performed because of low incidence numbers of ESMs. All statistical analyses were performed using SPSS 25.0 (IBM Corp.). *P* values ≤ 0.05 were considered statistically significant.

RESULTS

Four hundred and fourteen patients with axSpA were included, with 360 (87%) classified as AS and 54 (13%) as nr-axSpA. The inclusion strategy is depicted in Supplementary Figure 1 (available with the online version of this article). At baseline, patients had mean age of 43.1 ± 12.5 years, 64% were male, mean symptom duration was 15 (8–24) years, 77% were HLA-B27 positive, mean ASDAS was 3.3 ± 1.1, and 67% started TNFi at baseline. All patient characteristics are presented in Table 1. Of the 414 included patients, 362 had 4-year follow-up data available and the mean follow-up period was 4.0 ± 0.3 years. The remaining 52 patients were not included in follow-up analysis (Supplementary Figure 1). These patients (mainly lost to follow-up) had a significantly shorter symptom duration, lower BMI, fewer swollen joints, less NSAID and anti-TNF use, and a lower ASDAS. There were no differences in the prevalence of ESMs at baseline (Table 1).

Prevalence of ESMs. At baseline, 130 (31.4%) of 414 patients had a positive history of ≥ 1 ESMs at baseline, of which 103 (24.9%) had a history of AAU, 39 (9.4%) a history of IBD, and 18 (4.3%) a history of PsO. Twenty-nine (7.0%) patients had a history of 2 ESMs, of which 21 (5.1%) had the combination of IBD and AAU, 4 (1.0%) AAU and PsO, and 3 (0.7%) PsO and IBD. Only 1 (0.2%) patient had a history of all 3 ESMs combined.

History of ESMs associated with axSpA characteristics and outcome. The 130 patients with axSpA with a history of any ESM were significantly older, had longer symptom duration, and used cDMARDs more often compared to patients without ESMs. According to the spinal mobility assessments, patients with axSpA with a history of any ESM had larger occiput-wall distance and less lateral spinal flexion. Patients with a history of any ESM also had significantly more spinal radiographic damage (mSASSS; Table 2).

Stratifying for the 3 different ESMs, patients with a history of AAU were also significant older, had longer symptom duration, were more often HLA-B27–positive and more often nonsmokers compared to patients without AAU. Patients with IBD used DMARDs significantly more often and experienced worse QOL

Table 1. Characteristics at baseline of 414 patients with axSpA.

	Baseline, n = 414	4-year Follow-up, n = 362	Lost to Follow-up, n = 52	*P**
Patient characteristics				
Age, yrs, mean (SD)	43.1 (12.5)	43.4 (12.2)	41.1 (14.2)	0.79
Male	265 (64)	238 (66)	27 (52)	**0.02**
Symptom duration, yrs, median (IQR)	15.0 (8.0–24.0)	17.0 (8.0–25.0)	11.0 (7.1–18.0)	**0.05**
HLA-B27+	313 (77)	278 (78)	35 (69)	0.35
BMI, kg/m², mean (SD)	26.2 (4.4)	26.6 (4.4)	24.0 (3.8)	**0.005**
Never smoker	113 (31)	98 (30)	15 (33)	0.95
Swollen joint involvement	53 (13)	51 (15)	2 (3.8)	**0.02**
Tender entheses	253 (62)	221 (62)	32 (62)	0.96
NSAID use	314 (80)	283 (82)	31 (65)	**0.02**
DMARD use	57 (14)	53 (15)	4 (7.7)	0.20
TNFi use	276 (67)	251 (69)	24 (47)	**< 0.001**
Disease activity, mean (SD)				
BASDAI	5.4 (2.1)	5.5 (2.1)	4.8 (2.1)	0.05
ASDAS	3.3 (1.0)	3.3 (1.0)	2.9 (1.0)	**0.02**
Disease outcome				
ASQoL, mean (SD)	8.8 (4.7)	8.9 (4.8)	8.4 (4.2)	0.54
BASFI, mean (SD)	4.9 (2.4)	4.9 (2.4)	4.6 (2.6)	0.91
Occiput-wall distance, median (IQR)	3.0 (0–9.9)	3.0 (0–10.0)	0.0 (0.0–8.0)	0.59
Cervical rotation, mean (SD)[a]	57.5 (24.5)	56.5 (25.1)	62.9 (20.8)	0.42
Chest expansion, mean (SD)	4.0 (2.2)	4.0 (2.2)	4.3 (2.4)	0.31
Lateral spinal flexion, mean (SD)	10.5 (5.6)	10.3 (5.4)	11.5 (5.6)	0.42
Modified Schober test	13.1 (1.7)	13.0 (1.7)	13.1 (1.8)	0.92
mSASSS at baseline, median (IQR)	4.5 (1.0–15.5)	4.8 (1.0–15.6)	3.2 (1.0–13.5)	0.18
Cervical mSASSS	3.0 (0.5–9.6)	3.5 (0.5–10.1)	2.0 (0.5–5.1)	0.08
Lumbar mSASSS	1.5 (0.0–7.5)	2.0 (0–8.0)	1.0 (0–5.5)	0.18

Values are n (%) unless otherwise indicated. Values in bold are statistically significant. * Patients lost to follow-up compared to patients in follow-up (362 vs. 52). [a] Available since 2009 (n = 216). ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; DMARD: disease-modifying antirheumatic drug; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; NSAID: nonsteroidal antiinflammatory drug; TNFi: tumor necrosis factor-α inhibitor.

(ASQoL) than patients without IBD. Patients with a history of PsO were more often HLA-B27–positive, experienced lower disease activity (BASDAI), and had more spinal radiographic damage, particularly with respect to cervical mSASSS (Table 2).

In multivariable regression analysis, we corrected the association with the disease outcome measures ASQoL and mSASSS for potential confounding patient characteristics and disease activity (Table 3). There was no significant association between history of ESMs and ASQoL in the multivariable model. In patients with a history of any ESM, more spinal radiological damage was found (mSASSS OR 2.26, $P = 0.05$). When analyzing individual ESMs, we found that patients with a history of PsO had significantly more spinal radiological damage (mSASSS OR 6.88), especially at the cervical spine (cervical mSASSS OR 23.27).

Four-year incidence of ESMs. During 4 years of follow-up, 57 (15.7%) of the 362 patients developed an ESM. In total, 18 (4.3%) patients developed an ESM without ever having a history of ESM. Of these, 13 (3.6%) patients developed a first episode of AAU, 7 patients (1.9%) developed IBD, and 3 patients (0.8%) developed PsO. The remaining 35 patients had recurrent AAU.

One patient developed 2 ESMs (IBD and AAU). Of the 48 patients with AAU, 17 (35.4%) developed > 1 episode of AAU during the 4-year follow-up period.

Development of ESMs associated with axSpA characteristics and outcome. Patients who developed an ESM without a history of any ESMs at baseline (n = 18) had worse QOL (ASQoL), larger occiput-wall distance, and more limited modified Schober. Patient characteristics were comparable between the patients with and without a newly developed ESM (Table 4). Patients who developed a first episode of AAU (n = 13) had significantly longer symptom duration and were more often HLA-B27–positive. They also had significantly less frequent swollen joint involvement, worse QOL (ASQoL), larger occiput-wall distance, and a more limited modified Schober. Since the number of patients who newly developed IBD and PsO was relatively small (n = 7 and n = 3, respectively), we did not perform subgroup analysis in these patients.

ESMs and anti-TNF treatment. In total, 15 of 212 (7%) patients treated with anti-TNF therapy developed a new ESM during the 4-year follow-up period compared to 3 of 150 (2%) patients on conventional treatment. During follow-up, 67 patients switched once or more to a different anti-TNF agent, of which 15 patients developed an ESM during follow-up compared to 52 patients without a new ESM. Of those 15 patients, 10 patients who had recurrent uveitis most frequently switched from etanercept to adalimumab (ADA).

Table 2. The prevalence of ESMs in relation to axSpA disease characteristics and outcomes.

	Any ESM		AAU		IBD		Psoriasis	
	Present, n = 130	Absent, n = 284	Present, n = 103	Absent, n = 311	Present, n = 39	Absent, n = 375	Present, n = 18	Absent, n = 396
Patient characteristics								
Age, yrs, mean (SD)	**45.6 (12.4)**	**42.1 (12.3)**	**45.5 (11.8)**	**42.4 (12.6)**	46.5 (12.3)	42.8 (12.4)	47.4 (13.4)	43.0 (12.4)
Male	81 (62.3)	184 (65.0)	68 (66.0)	197 (63.5)	24 (59.0)	242 (64.7)	10 (55.6)	255 (64.6)
Symptom duration, yrs, median (IQR)	**18.0 (11–27.0)**	**13.0 (7.0–23.0)**	**26.0 (11–28.0)**	**13.0 (7.0–23.0)**	19.0 (10.5–28.5)	15.0 (7.8–24.0)	11.0 (3.8–16.3)	16.0 (8.0–24.8)
HLA-B27+	102 (79.7)	211 (75.9)	**87 (86.1)**	**226 (74.1)**	30 (76.9)	283 (77.1)	**8 (44.4)**	**305 (78.6)**
BMI, kg/m^2, mean (SD)	25.9 (4.7)	26.4 (4.3)	26.2 (4.7)	26.2 (4.4)	25.9 (6.1)	26.3 (4.3)	25.9 (5.4)	26.2 (4.4)
Never smoker	43 (37.4)	70 (2.7)	**37 (40.7)**	**76 (27.4)**	10 (27.0)	103 (31.1)	7 (46.7)	106 (30.0)
Swollen joint involvement	18 (14.1)	35 (12.4)	14 (13.9)	39 (12.6)	5 (13.2)	48 (12.9)	3 (17.6)	50 (12.7)
Tender enthesis	84 (65.1)	169 (60.4)	65 (63.7)	188 (61.2)	26 (66.7)	227 (61.4)	14 (77.8)	239 (61.1)
NSAID use	97 (78.9)	217 (80.7)	79 (79.8)	235 (80.2)	28 (75.7)	286 (80.6)	14 (87.5)	306 (79.8)
DMARD use	**29 (22.3)**	**28 (9.9)**	20 (19.4)	37 (11.9)	**18 (46.2)**	**39 (10.4)**	2 (11.1)	55 (13.9)
Disease activity, mean (SD)								
ASDAS	3.3 (1.1)	3.3 (1.0)	3.3 (1.1)	3.3 (1.0)	3.6 (1.1)	3.3 (1.0)	3.1 (1.2)	3.3 (1.0)
BASDAI	5.3 (2.1)	5.4 (2.1)	5.3 (2.1)	5.4 (2.2)	5.5 (2.1)	5.4 (2.1)	**4.4 (2.1)**	**5.4 (2.1)**
Disease outcome								
ASQoL, mean (SD)	8.8 (4.6)	8.9 (4.7)	8.6 (4.4)	8.9 (4.8)	**10.4 (4.5)**	**8.7 (4.7)**	7.5 (4.4)	8.9 (4.7)
BASFI, mean (SD)	5.0 (2.5)	4.9 (2.4)	5.0 (2.3)	4.9 (2.5)	5.3 (2.3)	4.9 (2.9)	4.6 (2.9)	4.9 (2.4)
Occiput-wall distance, median (IQR)	**4.0 (0–12.4)**	**2.0 (0–8.3)**	3.5 (0.0–11.3)	2.0 (0.0–8.4)	3.8 (0.0–12.2)	2.5 (0.0–9.8)	5.5 (0.0–14.3)	2.5 (0.0–9.0)
Cervical rotation, mean (SD)	54.8 (27.2)	58.6 (23.7)	53.6 (28.4)	58.2 (24.4)	54.1 (29.1)	57.9 (24.1)	65.4 (30.1)	57.0 (24.2)
Chest expansion, mean (SD)	3.8 (2.3)	4.1 (2.2)	3.6 (2.0)	4.0 (2.2)	3.5 (2.0)	4.1 (2.3)	3.9 (2.2)	4.0 (2.6)
Lateral spinal flexion, mean (SD)	**9.4 (5.3)**	**10.8 (5.5)**	9.2 (4.8)	10.7 (5.5)	9.1 (4.9)	10.5 (5.5)	9.6 (5.5)	10.4 (5.5)
Modified Schober test	12.9 (1.7)	13.2 (1.7)	13.2 (1.6)	13.1 (1.7)	13.2 (1.7)	13.1 (1.7)	13.0 (2.0)	13.1 (1.7)
Total mSASSS median (IQR)	**7.0 (1.5–29.8)**	**3.8 (0.6–11.4)**	6.8 (1.0–31.2)	4.0 (1.0–13.0)	7.0 (3.0–24.8)	4.1 (1.0–14.0)	**10.3 (2.1–33.5)**	**4.1 (1.0–15.0)**
Cervical mSASSS	4.5 (1.0–21.0)	3.0 (0.5–8.3)	4.4 (0.5–21.0)	3.0 (0.5–9.2)	3.8 (1.2–10.8)	3.0 (0.5–9.6)	**7.0 (4.6–31.1)**	**3.0 (0.5–15.0)**
Lumbar mSASSS	2.5 (0.0–9.8)	1.0 (0.0–7.0)	3.0 (0.0–10.5)	1.0 (0.0–7.5)	1.8 (0.0–6.6)	1.8 (0.0–8.0)	7.0 (0.0–22.5)	1.5 (0.0–7.5)

Values are n (%) unless otherwise indicated. Values in bold are statistically significant. AAU: acute anterior uveitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life questionnaire; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; DMARD: disease-modifying antirheumatic drug; ESM: extraskeletal manifestation; IBD: inflammatory bowel disease; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; NSAID: nonsteroidal antiinflammatory.

DISCUSSION

In our prospective cohort, a history of any ESM was present in one-third of the patients with axSpA. The highest prevalence was found for AAU (24.9%), followed by IBD (9.4%), and PsO (4.3%).

Interestingly, history of ESMs at baseline was associated with significantly less spinal mobility and more spinal radiographic damage. Further, as expected, patients with a history of an ESM at baseline were significantly older and had a longer symptom duration since timespan is the main condition necessary for events to occur. Baseline disease activity was similar between patients with and without a history of ESMs, but it should be kept in mind that disease activity was not measured at exactly the same time as ESM occurrence. Finally, our multivariable analysis showed that history of ESMs, most prominently PsO, was associated with more radiographic damage, especially in the cervical spine.

Our prevalence rates of ESMs at baseline were comparable to other large cohort studies. In 216 patients from the OASIS cohort, 18% had uveitis, 7% had IBD, and 4% had PsO at baseline.[12] A systemic review and metaanalysis showed that prevalence rates of ESMs varied between studies as a result of clinical and methodological heterogeneity. The pooled prevalence rates were 25.8% (95% CI 24.1–27.6%) for uveitis, 6.8% (95% CI 6.1–7.7%) for IBD, and 9.3% (95% CI 8.1–10.6%) for PsO.[25] Thus far, conflicting results regarding the influence of ESMs on axSpA disease outcome are published. In the DESIR cohort of 692 patients with inflammatory back pain suggestive of SpA, patients with PsO had higher disease activity (BASDAI) and poorer functional status (BASFI).[26] In a cross-sectional cohort of 146 Chinese patients with AS, higher disease activity (BASDAI) and worse physical functioning (BASFI, spinal mobility) was found in the 23 patients with a history of

Table 3. The prevalence of ESMs in relation to axSpA disease outcome in multivariable models.

Disease	Any ESM[a]		AAU[a]		IBD[b]		Psoriasis[c]	
Outcome	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
ASQoL	1.00 (0.95–1.04)	0.95 (0.88–1.02)	0.98 (0.94–1.03)	0.93 (0.86–1.02)	**1.08 (1.01–1.16)**	1.08 (0.98–1.19)	0.94 (0.85–1.04)	0.93 (0.80–1.08)
Total mSASSS	**1.84 (1.21–2.77)**	2.26 (0.99–5.15)	**1.57 (1.11–2.44)**	0.98 (0.41–2.32)	1.72 (0.93–3.18)	2.03 (0.89–4.63)	**2.71 (1.08–6.81)**	**6.88 (1.62–29.16)**
Cervical mSASSS	1.77 (1.00–3.13)	3.08 (0.86–11.02)	1.45 (0.79–2.69)	1.17 (0.34–4.03)	1.31 (0.56–3.04)	2.20 (0.73–6.68)	**4.50 (1.19–17.10)**	**23.27 (1.81–299.49)**
Lumbar mSASSS	1.32 (0.79–2.21)	0.99 (0.33–3.01)	1.34 (0.77–2.33)	0.53 (0.15–1.88)	0.65 (0.22–1.91)	0.65 (0.22–1.91)	1.88 (0.65–5.40)	3.15 (0.67–14.86)

Data are presented as OR (95% CI). Values in bold are statistically significant. [a] Data for all ESMs and AAU corrected for sex, symptom duration, HLA-B27 status, BMI, smoking status, NSAID use, DMARD use, and ASDAS. [b] IBD data are corrected for symptom duration, DMARD use, and ASDAS. [c] Psoriasis data corrected for symptom duration, HLA-B27 status, and ASDAS. AAU: acute anterior uveitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life questionnaire; axSpA: axial spondyloarthritis; DMARD: disease-modifying antirheumatic drug; ESM: extraskeletal manifestation; IBD: inflammatory bowel disease; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; NSAID: nonsteroidal antiinflammatory drug.

AAU; unfortunately no treatment data were available for these patients.[13] Also, a cross-sectional study including 131 patients with AS, 110 with PsA, and 46 with SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome reported higher disease activity (ASDAS, BASDAI, and C-reactive protein [CRP]) in patients with AAU, higher CRP in patients with IBD, but lower BASDAI in patients with skin PsO.[14] However, they did not report a subanalysis for AS patients only.

On the other hand, a cross-sectional analysis of 20 patients with AS and PsO and 201 patients with AS with active disease without PsO (before starting TNFi therapy) did not show any significant differences in disease activity, physical function, spinal mobility, QOL, and radiographic damage between patient groups.[27] Also, a previous cross-sectional study of 352 patients with AS and 193 patients with nr-axSpA showed that the presence of ESMs did not result in major differences in disease activity, physical function, spinal mobility status, and QOL in both patient groups.[28] The patients in this cohort were mostly similar to ours, except for a relatively low number of HLA-B27–positive patients (66%), and there were no data on treatment strategy.

Our group of patients with AS starting anti-TNF therapy was relatively large, since the inclusion of the GLAS cohort, including this subgroup of patients, started in 2004. In 2009, inclusion was extended to all patients with axSpA regardless of treatment regimen. We found that the majority of patients who developed an ESM during follow-up used anti-TNF therapy. This may be related to more severe disease, but also confounding by indication may have played a role. For example, patients with uveitis have a higher probability of developing another episode of uveitis and of being treated with a TNFi. In our cohort, patients with recurrent uveitis mainly switched to ADA, based on previous findings about the positive effect of ADA on the number of attacks of AAU.[29] In addition, we found that patients with a history of ESM at baseline, especially IBD, more often used cDMARDs. Our hypothesis is that the ESM of these patients mainly required treatment with cDMARDs.

In our study, the association with more spinal radiographic damage was found particularly in patients with a history of PsO. When stratifying for cervical and lumbar mSASSS, we found that these patients had more radiographic damage in the cervical spine. This is in line with our previous study in 99 patients with AS with active disease in which radiographic damage of the cervical facet joints was associated with history of ESM.[15] In contrast, a previous cross-sectional study in 1,023 patients with AS did not demonstrate a significant association between PsO and radiographic damage. However, this study did not use the validated mSASSS scoring method, but classified patients into 3 groups (no damage, syndesmophytes, and ankylosis), which is less sensitive to show differences.[30]

With respect to the incidence of ESM, during 4 years of follow-up, 35 (9.7%) patients had recurrent AAU, 13 (3.6%) developed a first episode of AAU, 8 (1.9%) developed IBD, and 3 (0.8%) developed PsO. The incidence of ESMs was also associated with worse QOL. Research on incidence rates of ESMs is scarce. The incidence rates of the different ESMs we found in our cohort match the rates previously reported in a few other axSpA cohorts.[3,11] One study performed in the framework of the OASIS cohort included 216 patients with a mean follow-up period of 8.3 (SD 4.3) years and found an incidence rate of 2.4% per year for any ESM, 1.4% per year for new AAU, 0.6% per year for IBD, and 0.3% per year for PsO.[11] Another study with patients with AS from the UK Clinical Practice Research Datalink calculated the incidence rates over a follow-up period of 20 years. In this study, the cumulative incidence rates were 24.5%, 7.5%, and 10.1% for AAU, IBD, and PsO, respectively.[3]

To our knowledge, our study is the first to demonstrate that the development of a new ESM does influence spinal mobility outcomes and disease-QOL. Unfortunately, no mSASSS data were available at follow-up. When stratifying the analysis for specific ESM, the development of a new AAU during 4-year follow-up was also associated with less spinal mobility and worse QOL. Although we also observed a lower QOL in patients who developed IBD or PsO during follow-up (with similar differences as for uveitis; data not shown), this difference did not reach statistical significance, likely because of the small number of patients who developed IBD (n = 7) and PsO (n = 3). In the previously mentioned 216 patients with AS from the OASIS cohort, longitudinal associations between incidence of ESMs and disease outcome have also been investigated. In univariable

Table 4. Patient characteristics after 4 years of follow-up.

	Any Newly Developed ESM		New IBD		New Psoriasis		New AAU		Recurrent AAU	
	Present, n = 18	Absent, n = 233	Present, n = 7	Absent, n = 353	Present, n = 3	Absent, n = 357	Present, n = 13	Absent, n = 347	Present, n = 35	Absent, n = 325
Patient characteristics										
Age, yrs, mean (SD)	41.3 (11.7)	42.2 (12.0)	39.7 (10.3)	43.4 (12.1)	49.3 (8.0)	43.2 (12.1)	42.9 (12.7)	43.3 (12.1)	46.0 (10.9)	43.0 (12.2)
Male	14 (77.8)	152 (65.2)	3 (42.8)	233 (66.0)	2 (66.7)	234 (65.5)	11 (84.6)	225 (64.8)	24 (68.5)	212 (65.2)
Symptom duration, yrs, median (IQR)	21.0 (11–24)	13.5 (7–24)	17.0 (2–23)	16.0 (8–25)	19.0 (12–26)	16.5 (8–25)	**24.0 (19–26)**	**16.0 (8–25)**	**22.0 (12–26)**	**16.0 (8–25)**
HLA-B27+	16 (88.9)	174 (76.3)	4 (57.1)	272 (77.0)	3 (100)	273 (76.4)	**13 (100)**	**263 (75.7)**	29 (82.8)	247 (76.0)
BMI, kg/m^2, mean (SD)	25.9 (5.6)	26.5 (4.6)	28.1 (7.1)	27.1 (4.7)	24.1 (7.1)	27.1 (4.7)	24.8 (4.0)	27.2 (4.8)	26.7 (5.2)	27.2 (4.7)
Never smoker	3 (18.8)	60 (28.7)	1 (14.2)	97 (27.4)	0 (0)	98 (27.4)	2 (15.3)	96 (27.6)	9 (25.7)	89 (27.3)
Swollen joint involvement	0 (0)	6 (2.6)	0 (0)	13 (3.7)	0 (0)	13 (3.6)	0 (0)	13 (3.7)	2 (5.7)	11 (3.4)
Tender enthesis	5 (27.8)	83 (35.6)	1 (14.2)	129 (36.5)	2 (66.7)	128 (35.9)	4 (30.7)	126 (36.3)	14 (40.0)	116 (35.7)
NSAID use	8 (44.4)	122 (52.4)	4 (57.1)	175 (49.6)	2 (66.7)	177 (49.6)	4 (30.7)	175 (50.4)	13 (37.1)	166 (51.1)
DMARD use	1 (5.6)	12 (5.2)	2 (28.5)	27 (7.6)	1 (33.3)	28 (7.8)	1 (7.7)	28 (8.1)	3 (8.6)	26 (8.0)
Anti-TNF use	15 (83.3)	154 (66.1)	6 (85.7)	242 (68.5)	2 (66.7)	246 (68.9)	11 (84.7)	237 (68.3)	27 (77.1)	221 (68.0)
Disease activity, mean (SD)										
ASDAS	2.7 (1.2)	2.2 (1.0)	2.9 (1.0)	2.3 (1.0)	2.7 (1.2)	2.3 (1.0)	2.5 (1.2)	2.3 (0.9)	2.2 (0.8)	2.3 (1.0)
BASDAI	4.2 (2.0)	3.7 (2.2)	4.8 (1.4)	3.7 (2.2)	4.6 (2.6)	3.8 (2.2)	4.0 (2.2)	3.7 (2.2)	3.5 (2.0)	3.7 (2.2)
Disease outcome										
ASQoL, mean (SD)	**10.0 (5.3)**	**5.8 (4.8)**	8.3 (4.5)	6.0 (4.9)	11.3 (6.1)	6.0 (4.9)	**9.8 (5.5)**	**5.9 (4.8)**	5.2 (4.9)	6.1 (4.9)
BASFI, mean (SD)	4.4 (2.9)	3.4 (2.3)	4.2 (2.9)	3.6 (2.4)	5.4 (3.7)	3.6 (2.4)	4.4 (3.0)	3.6 (2.4)	3.6 (2.2)	3.7 (2.5)
Occiput-wall distance, median (IQR)	**6.3 (2–16)**	**2.0 (0–8)**	3.0 (0–7)	3.0 (0–10)	14.0 (2–16)	3.0 (0–10)	**8.0 (5–16)**	**2.5 (0–9)**	7.0 (0–14)	3.0 (0–9)
Cervical rotation, mean (SD)	68.8 (24.3)	69.1 (20.7)	79.6 (18.7)	65.7 (22.5)	64.3 (27.1)	65.9 (22.5)	58.8 (24.4)	66.1 (22.4)	**56.9 (20.9)**	**66.8 (22.5)**
Chest expansion, mean (SD)	4.9 (3.4)	5.0 (2.4)	4.4 (1.7)	5.0 (2.4)	3.2 (1.4)	5.0 (2.4)	5.0 (3.9)	5.0 (2.3)	5.4 (2.1)	5.0 (2.4)
Lateral spinal flexion, mean (SD)	11.2 (6.4)	12.2 (5.7)	12.6 (4.0)	11.6 (5.7)	9.1 (0.1)	11.6 (5.7)	10.6 (6.7)	11.6 (5.7)	10.9 (5.6)	11.7 (5.7)
Modified Schober test, mean (SD)	**12.6 (1.6)**	**13.6 (1.5)**	13.3 (1.1)	13.4 (1.7)	12.5 (1.8)	13.4 (1.6)	**12.3 (1.6)**	**13.5 (1.6)**	**12.8 (1.4)**	**13.5 (1.7)**

Values are n (%) unless otherwise indicated. Values in bold are statistically significant. AAU: acute anterior uveitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; DMARD: disease-modifying antirheumatic drug; ESM: extraskeletal manifestation; IBD: inflammatory bowel disease; NSAID: nonsteroidal antiinflammatory drug; TNF: tumor necrosis factor.

analysis, PsO was significantly associated with ASQoL and radiographic damage over time, and IBD was significantly associated with BASFI over time, but these associations disappeared in the multivariable model. AAU was not associated with any outcome over time. Their multivariable model showed a significant association between IBD and better EuroQol 5-dimension (EQ-5D) questionnaire scores over time and no association with ASQoL. The EQ-5D is a generic questionnaire, whereas the ASQoL is a disease-specific questionnaire.[31]

Strengths of our study are the prospective study design with standardized follow-up visits and the large heterogeneous population of patients with axSpA, reflecting the population in current daily clinical practice. Further, data of ESMs were verified in the medical records for diagnosis by an ophthalmologist, dermatologist, or gastroenterologist.

In conclusion, history of ESMs at baseline was present in one-third of the 414 patients with axSpA: 24.9% AAU, 9.4% IBD, and 4.3% PsO. The prevalence of ESMs was significantly associated with older age, longer symptom duration, more cDMARD use, less spinal mobility, and more spinal radiographic damage. There was an independent association between PsO and radiographic spinal damage, especially of the cervical spine. During 4 years of follow-up, 9.7% patients had recurrent AAU, 3.6% developed a first episode of AAU, 1.9% developed IBD, and 0.8% developed PsO. The majority of patients developing an ESM used anti-TNF therapy. Patients who developed a new ESMs demonstrated worse spinal mobility and worse QOL.

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