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Characteristics associated with the presence and development of extra-articular manifestations in ankylosing spondylitis: 12-year results from OASIS

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Abstract

Objective. The aim of this study was to identify characteristics associated with the presence and development of extra-articular manifestations (EAMs) in a prevalence cohort of patients with AS.

Methods. Twelve-year follow-up data from the Outcome in Ankylosing Spondylitis International Study (OASIS) were used. In addition, medical charts were checked for the presence of acute anterior uveitis (AAU), IBD and psoriasis. Demographic, clinical and radiographic characteristics associated with the presence of (any) EAM at baseline or new development during follow-up were identified.

Results. Two hundred and sixteen patients were included [mean age 43.6 years (S.D. 12.7), 154 (71%) men, mean symptom duration 20.5 years (S.D. 11.7), mean follow-up 8.3 years (S.D. 4.3)]. At baseline, 39 (18%) patients had AAU, 15 (7%) had IBD and 9 (4%) had psoriasis. The history of AAU was univariably associated with increased age [odds ratio (OR) 1.04 (95% CI 1.01, 1.07)], longer symptom duration [OR 1.05 (95% CI 1.02, 1.08)] and more radiographic damage [OR 1.02 (95% CI 1.00, 1.04)]. The history of psoriasis was associated with greater age [OR 1.05 (95% CI 1.00, 1.11)] and lower CRP [OR 0.77 (95% CI 0.59, 1.00)]. At follow-up, 27 patients developed a new EAM. Newly developed IBD was associated with a higher time-varying AS Disease Activity Score [hazard ratio (HR) 2.80 (95% CI 1.43, 5.52)], worse physical function [HR 1.40 (95% CI 1.09, 1.80)] and worse patient global well-being [HR 1.46 (95% CI 1.10, 1.93)]. Newly developed AAU was associated with an elevated time-varying CRP [HR 1.02 (95% CI 1.01, 1.04)].

Conclusion. Development of EAMs was infrequent in this cohort, despite relatively long follow-up. In particular, markers of disease activity were associated with the development of IBD.

Key words: ankylosing spondylitis, anterior uveitis, inflammatory bowel disease, psoriasis.

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Introduction

AS is a chronic inflammatory disease of the SI joints and spine. AS is the most frequent subtype of SpA, a group of disorders that have several clinical features in common, show familial clustering and are associated with HLA-B27. Other diseases belonging to SpA are PsA, reactive arthritis and enteropathic-related spondylitis and arthritis [1]. In patients with AS, extra-articular manifestations (EAMs) frequently occur, comprising acute anterior uveitis (AAU), IBD and psoriasis [2, 3]. These EAMs also contribute to the burden of disease and may influence the choice of treatment [4].

AAU is the most frequently occurring EAM in AS, with a prevalence of up to 33%, and is associated with longer

disease duration [3, 5, 6]. Overt IBD is found in ~5–10% of patients with AS [3]. However, it has been suggested that up to 60% of patients with AS have subclinical gut inflammation [7]. Younger age, progressive disease, male sex and higher disease activity were found to be associated with microscopic gut inflammation in axial SpA (axSpA) [8]. Psoriasis is present in 10–25% of patients with AS [3, 5, 9]. Conflicting results exist with respect to effect of the presence of psoriasis on disease manifestations and disease severity in patients with AS. Three studies showed that the disease course was more severe in patients with concomitant psoriasis than in patients with primary AS, AS associated with IBD or recently diagnosed inflammatory back pain [5, 10, 11]. However, another study in patients with AS could not demonstrate differences in demographic and disease characteristics between patients with or without concomitant psoriasis [12]. Treatment might play an important role in the development of EAMs. New-onset IBD is infrequently seen in patients treated with a biologic [13], but differences might exist between different types of biologic agent [13, 14].

Knowledge of the characteristics associated with the presence and development of EAMs in patients with axSpA, including AS, is limited. Because EAMs are considered contributory to a diagnosis of axSpA [15], are part of the classification criteria for axSpA [16, 17] and are highly prevalent in axSpA, it is important to gain more insight into the characteristics that contribute to their development. The aims of the present study were to identify the characteristics associated with both a history of and development of EAMs in AS. This was investigated in a prevalence cohort of patients with AS with up to 12 years of follow-up.

Methods

Patients

The study was conducted within the framework of the Outcome in Ankylosing Spondylitis International Study (OASIS) cohort. OASIS started in October 1996 and included 217 patients from the Netherlands, Belgium and France. These patients were followed at regular intervals for 12 years. The modified New York criteria for AS were used as inclusion criteria [18]. There were no other eligibility criteria. Patients were treated according to standard care. Non-pharmacological treatment consisted of physiotherapy and (home) exercises. According to the judgment of the treating physician, patients were prescribed NSAIDs, analgesics and/or DMARDs. Biologics were prescribed from 2002 onwards. Patients were regularly assessed by questionnaire, clinical investigation, laboratory assessment and radiographic assessment of the pelvis and both the cervical and lumbar spine. Every patient signed an informed consent form. Approval was obtained from the medical ethics committee of every participating hospital.

Extra-articular manifestations

Information on the presence of an EAM was retrospectively collected with a standardized method from the medical charts by two independent extractors. EAMs were only recorded when a description on the diagnosis of psoriasis, IBD and/or AAU by a dermatologist, gastroenterologist or ophthalmologist, respectively, was present in the medical chart or when this information was provided in the medical history of the patient in a letter by these medical specialists or the general practitioner. Each of the extractors dealt with about half of the sample. If information about the presence of AAU, IBD or psoriasis in the medical charts was found, a patient was considered as having this specific EAM from this point in time.

Demographic, clinical and radiographic characteristics

Information about demographic, clinical and radiographic characteristics was retrieved from the OASIS database. The following characteristics were collected at baseline: age, sex, symptom duration, disease duration, HLA-B27 and hip involvement. Disease activity was measured with the BASDAI [9], laboratory tests (CRP and ESR) and the AS Disease Activity Score (ASDAS) [19]. Physical function was measured with the BASFI [20]. Spinal mobility was measured with the linear BASMI [21]. Spinal pain was measured using a 10 cm visual analogue scale. BAS-G was used as a global measure reflecting the impact of AS on a patient's well-being (mean last week and last 6 months) [22]. Radiographic damage of the spine was scored with the modified Stoke AS Spine Score (mSASSS), a reliable and recommended scoring system for quantifying radiographic damage in AS [23]. The radiographs were read by two independent experts [24]. Information about treatment was collected from the medical charts combined with data from OASIS.

Statistical analysis

Descriptive statistics were used to calculate mean (S.D.) for continuous data and frequencies for dichotomous data. Interrater and intrarater reliability for the data collection on EAMs from the medical charts were checked for a random 10 patients using Cohen's κ, both at all time points taken together and for every single time point at follow-up. A κ value >0.4 was considered as moderate reliability, >0.6 as substantial and >0.8 as almost perfect [25].

Baseline characteristics associated with the presence of any EAM and of AAU, IBD or psoriasis separately at baseline were identified with univariable followed by multivariable logistic regression analysis. Where data on EAMs could not be retrieved, the patient was excluded from this logistic analysis. Only characteristics in the univariable analysis with a *P*-value <0.20 were entered in the (backward) multivariable analysis. Furthermore, the assumption that a variable could only be included in the model if there was a minimum of 10 patients with the EAM of interest at baseline was taken into account. Colinearity and interactions were checked.

Survival analysis was used to calculate annual incidence rates for the development of an EAM during follow-up. Cox regression analysis was used to identify demographic, clinical and radiographic characteristics associated with the development of an EAM. Where data on EAMs could not be retrieved, the patient was excluded from this Cox regression analysis. First, baseline characteristics were investigated, then time-varying characteristics, i.e. values from the characteristics at the time of diagnosis of the EAM, were used. For those patients who did not develop an EAM, all the available values of the characteristic were used. One characteristic per analysis was included in the Cox regression analysis. Statistical analyses were performed with SPSS 20.0 (IBM, Armonk, NY, USA) and STATA 12.0 (StataCorp, College Station, TX, USA).

Results

At baseline, the total population consisted of 216 patients. One patient from the original 217 patients was excluded from further analysis because of inconsistencies in baseline and follow-up data that could not be retrieved from the relevant hospital. At baseline, the mean age was 43.6 years (S.D. 12.7) and 154 (71.3%) patients were male. The mean symptom duration was 20.5 years (S.D. 11.7) and 174 (84.5%) patients were HLA-B27 positive. The total number of patients with a history of any EAM was 59 (27.3%), with AAU 39 (18.1%), with IBD 15 (6.9%) and with psoriasis 9 (4.2%), among which were 4 patients with a history of more than one EAM at baseline: 2 patients had a history of AAU and IBD, 1 patient of IBD and psoriasis and 1 patient of AAU and psoriasis. At baseline, 146 (67.6%) patients were treated with NSAIDs, 18 (8.3%) patients with DMARDs and no patients with biologics. In the total follow-up period, 204 patients (94.4%) were ever treated with an NSAID, 43 (19.9%) with DMARDs and 43 (19.9%) with a biologic.

Interrater- and intrarater reliability of data extraction

The interrater reliability for data extraction from the medical charts on the presence of EAM was checked. For all time points together, this was almost perfect for AAU (0.85), IBD (0.99) and psoriasis (0.93). For the separate time points, the interrater reliability ranged from 0.64 to 1.00 for AAU, from 0.77 to 1.00 for IBD and from 0.77 to 1.00 for psoriasis. Also, the intrarater reliability calculated for all time points was almost perfect for AAU (0.91), IBD (0.98) and psoriasis (0.88). For the separate time points, the intrarater reliability ranged from 0.64 to 1.00 for AAU, from 0.77 to 1.00 for IBD and from 0.64 to 1.00 for psoriasis.

Characteristics of patients with and without an EAM at baseline

In order to identify characteristics associated with a history of any EAM at baseline, a logistic regression analysis was performed. Patients with any EAM compared with patients without any EAM were older [48.3 years (S.D. 11.6) *vs* 41.9 years (S.D. 12.5)] and had longer symptom duration [24.3 years (S.D. 11.8) *vs* 19.1 years (S.D. 11.5)]. The presence of any EAM at baseline was univariably associated with greater age [odds ratio (OR) 1.04 (95% CI 1.02, 1.07)] and longer symptom duration [OR 1.04 (95% CI 1.01, 1.07)].

Table 1 presents the comparisons between patients with and without a history of AAU, IBD and psoriasis, respectively, at baseline. A history of AAU at baseline was associated with greater age [OR 1.04 (95% CI 1.01, 1.07)], longer symptom duration [OR 1.05 (95% CI 1.02, 1.08)] and a higher mSASSS [OR 1.02 (95% CI 1.00, 1.04)]. In the multivariable analysis, a history of AAU was only associated with greater age [OR 1.05 (95% CI 1.02, 1.08)]. None of the baseline demographic, clinical and radiographic variables contributed to a history of IBD. The history of psoriasis was univariably associated with greater age [OR 1.05 (95% CI 1.00, 1.11)], lower CRP [OR 0.77 (95% CI 0.59, 1.00)] and negative HLA-B27 [OR 0.13 (95% CI 0.03, 0.51)]. No multivariable analysis was performed as too few patients had psoriasis at baseline ($n = 9$).

Development of new EAMs

The mean follow-up period was 8.3 years (S.D. 4.3), of which 98 patients completed 12 years of follow-up. During follow-up, 27 patients developed any new EAM for the first time, of which 19 patients developed AAU, 9 patients developed IBD and 5 patients developed psoriasis (2 patients developed both IBD and psoriasis). Of these 27 patients, 4 patients already had another EAM at baseline (2 patients with a history of AAU developed IBD and 2 patients with a history of IBD developed AAU). The incidence rate for any new EAM was 2.4% per year, for AAU 1.4% per year, for IBD 0.6% per year and for psoriasis 0.3% per year. Disease activity remained more or less stable over time and the proportional development of new-onset EAM did not decrease despite the introduction of biologics (Table 2).

Characteristics associated with the development of EAMs during follow-up

In order to identify characteristics associated with the development of EAMs during follow-up, first a Cox regression analysis with baseline characteristics was performed. The development of any EAM was weakly associated with shorter symptom duration [hazard ratio (HR) 0.96 (95% CI 0.93, 1.00)]. The development of IBD was associated with a higher baseline BASDAI [HR 1.35 (95% CI 1.01, 1.82)] and more baseline spinal pain [HR 1.34 (95% CI 1.02, 1.77)] (Table 3). None of the baseline characteristics contributed to the development of AAU or psoriasis. The association between hip involvement and the development of IBD and between HLA-B27 and the development of AAU, IBD or psoriasis could not be calculated, because of a lack of variation, i.e. none of the patients with new IBD had hip involvement at baseline and only one patient was HLA-B27 negative in those who newly developed AAU, IBD and psoriasis (Table 3).

Table 1 Comparison of baseline characteristics between patients with and without uveitis, IBD and psoriasis

Baseline characteristic	Acute anterior uveitis			IBD			Psoriasis		
	Present ($n = 39$)	Absent ($n = 177$)	OR (95% CI)	Present ($n = 15$)	Absent ($n = 201$)	OR (95% CI)	Present ($n = 9$)	Absent ($n = 207$)	OR (95% CI)
Male, *n* (%)	28 (71.7)	126 (71.6)	1.01 (0.47, 2.18)	12 (80.0)	142 (71.0)	1.63 (0.45, 6.00)	6 (71.8)	138 (66.7)	0.78 (0.19, 3.24)
Age, years	49.1 (11.7)	42.4 (12.6)	**1.04 (1.01, 1.07)**	45.2 (13.6)	43.5 (12.6)	1.01 (0.97, 1.05)	51.3 (10.0)	43.3 (12.7)	**1.05 (1.00, 1.11)**
Symptom duration, years	25.9 (11.1)	19.3 (11.6)	**1.05 (1.02, 1.08)**	23.4 (13.2)	20.3 (11.6)	1.02 (0.98, 1.07)	19.7 (14.3)	20.6 (11.7)	0.99 (0.93, 1.06)
HLA-B27 positive, *n* (%)	35 (89.7)	138 (83.1)	1.78 (0.58, 5.39)	11 (73.3)	162 (85.3)	0.48 (0.14, 1.60)	4 (44.4)	169 (86.2)	**0.13 (0.03, 0.51)**
Hip involvement present, *n* (%)	12 (31.6)	33 (19.1)	1.96 (0.90, 4.28)	5 (33.3)	40 (20.4)	1.95 (0.63, 6.03)	1 (11.1)	44 (21.8)	0.45 (0.06, 3.69)
ASDAS-CRP	2.7 (0.8)	2.7 (1.1)	0.94 (0.67, 1.31)	2.8 (1.2)	2.7 (1.1)	1.10 (0.65, 1.88)	1.8 (0.7)	2.7 (1.1)	0.27 (0.10, 0.76)
BASDAI (0–10)	3.4 (2.0)	3.5 (2.2)	0.96 (0.75, 1.23)	3.3 (2.5)	3.5 (2.1)	0.96 (0.75, 1.23)	2.6 (1.9)	3.5 (2.2)	0.81 (0.57, 1.15)
CRP, mg/l	15.4 (15.1)	18.6 (26.2)	0.99 (0.98, 1.01)	26.6 (30.0)	17.5 (24.1)	1.01 (0.99, 1.03)	5.0 (3.2)	18.6 (24.9)	**0.77 (0.59, 1.00)**
ESR, mm/h	11.7 (7.9)	15.3 (17.0)	0.98 (0.95, 1.01)	17.0 (9.3)	14.5 (16.1)	1.01 (0.99, 1.03)	8.0 (6.1)	14.9 (16.0)	0.93 (0.84, 1.04)
BASFI (0–10)	3.3 (2.3)	3.4 (2.7)	0.98 (0.86, 1.13)	4.1 (2.5)	3.3 (2.6)	1.12 (0.92, 1.35)	2.6 (2.6)	3.4 (2.6)	0.87 (0.63, 1.21)
BASMI (0–10)	4.1 (1.7)	3.8 (1.6)	1.12 (0.90, 1.39)	4.3 (1.8)	3.8 (1.6)	1.19 (0.88, 1.62)	3.1 (1.1)	3.9 (1.7)	0.72 (0.44, 1.18)
BAS-G (0–10)	3.9 (2.7)	3.9 (2.6)	1.01 (0.88, 1.16)	3.7 (2.4)	3.9 (2.6)	0.97 (0.78, 1.19)	3.3 (2.5)	3.9 (2.6)	0.91 (0.69, 1.20)
mSASSS (0–72)	16.9 (18.1)	10.6 (15.6)	**1.02 (1.00, 1.04)**	14.1 (13.0)	11.5 (16.4)	1.01 (0.98, 1.04)	3.8 (3.8)	12.1 (16.5)	0.93 (0.83, 1.04)
Spinal pain (0–10)	3.4 (2.6)	3.6 (2.4)	0.98 (0.84, 1.13)	3.2 (2.8)	3.6 (2.4)	0.93 (0.75, 1.17)	3.4 (2.7)	3.5 (2.4)	0.97 (0.74, 1.29)

Data represented as mean (S.D.) unless stated otherwise. Univariate logistic regression analysis was performed to identify baseline characteristics associated with the presence of uveitis, IBD or psoriasis. Bold: significant ($P < 0.05$). ASDAS: Ankylosing Spondylitis Disease Activity Score; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; OR: odds ratio.

TABLE 2 Characteristics of patients at each of the follow-up visits

Variable	Baseline	Follow-up visit					
		2 years	4 years	6 years	8 years	10 years	12 years
Patients, *n*	216	201	157	134	100	107	98
Male, *n* (%)	154 (71.3)	141 (70.1)	109 (69.4)	93 (69.4)	71 (71.0	71 (66.4)	67 (68.4)
Age, years	43.6 (12.7)	45.4 (12.6)	48.3 (11.9)	50.9 (11.5)	52.8 (11.6)	55.3 (11.3)	57.3 (11.1)
Symptom duration, years	20.5 (11.7)	22.4 (12.0)	25.4 (11.6)	27.8 (11.6)	29.8 (11.4)	32.1 (11.3)	34.5 (11.3)
HLA-B27 positive, *n* (%)	174 (80.6)	163 (81.1)	126 (80.3)	102 (76.1)	84 (84.0)	89 (83.1)	84 (85.7)
Hip involvement present, *n* (%)	45 (20.8)	41 (20.4)	33 (21.0)	25 (18.7)	19 (19.0)	22 (20.6)	22 (22.4)
ASDAS-CRP	2.7 (1.1)	2.7 (1.2)	2.5 (1.1)	2.4 (1.0)	2.5 (1.0)	2.2 (0.9)	2.2 (0.09)
BASDAI (0–10)	3.4 (2.1)	3.5 (2.5)	3.3 (2.3)	3.3 (2.2)	3.8 (2.2)	3.3 (1.9)	3.4 (1.9)
CRP, mg/l	18.0 (24.4)	16.0 (17.1)	11.9 (16.5)	8.9 (9.5)	8.0 (8.3)	7.2 (8.4)	7.3 (11.9)
ESR, mm/h	14.6 (15.7)	15.3 (15.2)	15.1 (14.7)	14.1 (13.1)	17.8 (16.4)	15.2 (15.8)	15.1 (16.0)
BASFI (0–10)	3.4 (2.6)	3.5 (2.7)	3.5 (2.7)	3.6 (2.4)	4.2 (2.5)	3.7 (92.6)	4.1 (2.7)
BASMI (0–10)	3.8 (1.6)	4.1 (1.6)	3.8 (1.7)	3.9 (1.7)	4.1 (1.6)	4.2 (1.6)	4.0 (1.6)
BAS-G (0–10)	3.9 (2.6)	4.0 (2.7)	3.7 (2.6)	3.5 (2.3)	4.1 (2.4)	3.4 (2.2)	3.8 (2.2)
mSASSS (0–72)	11.6 (16.2)	12.9 (16.6)	15.1 (16.7)	16.9 (17.9)	20.4 (19.8)	21.0 (21.0)	24.5 (21.7)
Spinal pain (0–10)	3.5 (2.4)	3.8 (2.8)	3.5 (2.4)	3.5 (2.1)	3.7 (2.3)	3.3 (2.2)	3.4 (2.1)
Any EAM, *n* (%)	59 (27.3)	66 (32.8)	64 (40.8)	51 (38.1)	58 (58.0)	54 (50.5)	49 (50.0)
New case[a], *n*	—	9	2	2	6	3	5
AAU, *n* (%)	39 (18.1)	42 (20.9)	43 (27.4)	40 (29.9)	41 (41.0)	36 (33.6)	32 (32.7)
New case[a], *n*	—	5	3	1	5	1	4
IBD, *n* (%)	15 (23.6)	19 (9.5)	18 (11.5)	16 (11.9)	16 (16.0)	16 (15.0)	16 (16.3)
New case[a], *n*	—	4	1	0	1	2	1
Psoriasis, *n* (%)	9 (4.2)	11 (5.5)	11 (7.0)	10 (7.5)	9 (9.0)	10 (.3)	8 (8.2)
New case[a], *n*	—	2	0	1	1	1	0
DMARDs, *n* (%)	18 (46.2)	24 (11.9)	20 (12.7)	13 (9.7)	8 (8.0)	10 (9.3)	10 (10.2)
Biologics, *n* (%)	0 (0)	0 (0)	1 (0.6)	9 (6.7)	23 (23.0)	35 (32.7)	30 (30.6)

Data are presented as mean (S.D.) unless stated otherwise. [a]Number of cases with a new-onset EAM between two time points of 2 years. AAU: acute anterior uveitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; EAM: extra-articular manifestation; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score.

Second, a Cox analysis with time-varying characteristics was performed (Table 4). In this analysis the values of the variables at the time of diagnosis of an EAM were used. The development of any EAM was weakly but significantly associated with elevated CRP [HR 1.02 (95% CI 1.01, 1.04)] and elevated ESR [HR 1.02 (95% CI 1.00, 1.05)] at the time of diagnosis of an EAM. Development of a new AAU was associated with elevated CRP [HR 1.02 (95% CI 1.01, 1.04)] at the time of diagnosis of AAU. Development of IBD was significantly associated with markers of increased disease activity in AS, but also to some extent with worse physical function and worse patient global well-being at the time of diagnosis of IBD. No association could be found between the use of biologics and the development of IBD. The association between DMARD or NSAID use and IBD could not be calculated, because of a lack of variation, i.e. none of the patients with new IBD used a DMARD or NSAID at the time of development of IBD (Table 4). None of the characteristics contributed to the development of psoriasis.

Discussion

The present study showed that in this prevalence cohort of patients with relatively long symptom duration, a substantial number of patients already had an EAM at baseline and that the development of new EAMs was infrequently observed, despite relatively long follow-up. Cross-sectionally at baseline, a history of AAU was associated with longer symptom duration and greater age. Longitudinally, the development of IBD was particularly associated with increased markers of disease activity of AS, but also with worse physical function and worse patient global well-being. Also, the development of AAU was associated with elevated CRP. For psoriasis, no such association could be found.

It is known that the prevalence of EAMs is higher in patients with AS compared with the general population. In a recent meta-analysis that combined results from 156 studies including in total >40 000 patients with AS, the pooled prevalence of AAU was 25.8%, of IBD 6.8% and of psoriasis 9.3% [3]. The lifetime cumulative incidence of AAU in the general population is reported to be 0.2% in HLA-B27-negative patients and 1% in HLA-B27-positive patients [26]. General population estimates vary for IBD from 0.01 to 0.5%, and for psoriasis from 0.3 to 2.5% [27, 28]. In our study, AAU, IBD and psoriasis were present in 18.0%, 6.9% and 4.1% of the patients, respectively, at baseline, which is in line with the findings from the meta-analysis [3]. An interesting observation from both the meta-analysis and the current study is that AAU is associated with longer disease duration, however, this

Table 3 Baseline characteristics associated with the development of EAM during 12 years of follow-up

Baseline characteristic	Any EAM		Acute anterior uveitis		IBD		Psoriasis	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Male	1.01	0.45, 2.26	0.99	0.38, 2.62	1.71	0.35, 8.26	0.29	0.05, 1.75
Age	0.99	0.95, 1.02	0.99	0.95, 1.03	0.96	0.90, 1.02	0.95	0.87, 1.03
Symptom duration	**0.96**	**0.93, 1.00**	0.99	0.45, 1.03	0.94	0.88, 1.02	0.89	0.79, 1.04
HLA-B27 positive[a]	1.91	0.45, 8.11	—	—	1.39	0.17, 11.08	—	—
Hip involvement[b]	1.37	0.55, .3.40	1.63	0.59, 4.53	—	—	0.89	0.10, 7.92
ASDAS-CRP	1.24	0.86, 1.79	1.25	0.82, 1.92	1.72	0.95, 3.11	1.19	0.47, 3.03
CRP	1.00	0.98, 1.01	1.00	0.99, 1.02	1.00	0.96, 1.03	0.97	0.90, 1.05
ESR	1.00	0.98, 1.02	1.00	0.96, 1.03	1.00	0.97, 1.05	1.02	0.98, 1.05
BASDAI (0–10)	1.13	0.94, 1.36	1.05	0.85, 1.31	**1.35**	**1.01, 1.82**	1.31	0.84, 2.06
mSASSS (0–72)	0.97	0.92, 1.01	0.96	0.91, 1.02	0.94	0.85, 1.05	0.99	0.92, 1.06
BASFI (0–10)	1.03	0.90, 1.19	1.00	0.84, 1.19	1.21	0.95, 1.55	1.14	0.83, 1.58
BASMI (0–10)	1.06	0.83, 1.37	1.10	0.82, 1.48	1.08	0.66, 1.76	0.73	0.35, 1.51
BAS-G (0–10)	1.15	0.99, 1.33	1.13	0.95, 1.36	1.11	0.86, 1.43	1.32	0.93, 1.88
Spinal pain (0–10)	1.11	0.93, 1.32	0.96	0.78, 1.18	**1.34**	**1.02, 1.77**	1.22	0.85, 1.77
NSAIDs	0.73	0.32, 1.69	0.49	0.19, 1.26	1.29	0.25, 6.67	1.14	0.10, 12.52
DMARDS	—	—	0.70	0.09, 5.24	—	—	—	—

Analysis performed with Cox regression, one predictor per analysis. Analyses were performed for any extra-articular manifestation (uveitis, IBD and/or psoriasis) or for uveitis, IBD or psoriasis separately. Bold: significant ($P < 0.05$). [a]Because of the lack of variation in HLA-B27 status, no Cox regression analysis could be performed with this variable for the outcome development of uveitis, IBD and psoriasis. [b]Because of the lack of variation in hip involvement, no Cox regression analysis could be performed with this variable for the outcome development of IBD. ASDAS: Ankylosing Spondylitis Disease Activity Score; EAM: extra-articular manifestation; HR: hazard ratio; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score.

Table 4 Characteristics at the time of diagnosis of an EAM associated with the development of EAM during 12 years of follow-up

Characteristic	Any EAM		Acute anterior uveitis		IBD		Psoriasis	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
ASDAS-CRP	1.42	0.91, 2.21	1.07	0.65, 1.74	**2.80**	**1.43**, **5.52**	2.53	0.60, 10.86
CRP	**1.02**	**1.01**, **1.04**	**1.02**	**1.01**, **1.04**	**1.02**	**1.00**, **1.05**	0.88	0.62, 1.25
ESR	**1.02**	**1.00**, **1.05**	1.01	0.98, 1.04	1.02	1.00, 1.06	1.00	0.94, 1.08
BASDAI (0–10)	1.02	0.84, 1.23	0.93	0.74, 1.17	**1.46**	**1.09**, **1.97**	1.25	0.77, 2.04
mSASSS (0–72)	0.98	0.94, 1.03	0.96	0.91, 1.02	0.99	0.94, 1.03	0.92	0.70, 1.21
BASFI (0–10)	1.04	0.89, 1.20	0.96	0.80, 1.15	**1.40**	**1.09**, **1.80**	1.12	0.74, 1.68
BASMI (0–10)	1.03	0.77, 1.39	1.08	0.78, 1.50	1.00	0.64, 1.56	0.51	0.17, 1.57
BAS-G (0–10)	1.02	0.86, 1.20	0.96	0.78, 1.18	**1.46**	**1.10**, **1.93**	1.10	0.70, 1.71
Spinal pain (0–10)	0.94	0.79, 1.12	0.89	0.72, 1.10	1.23	0.93, 1.62	1.12	0.58, 1.73
NSAIDs	2.51	0.58, 10.84	0.69	0.22, 2.16	—	—	—	—
DMARDS	0.68	0.09, 5.07	1.20	0.27, 5.23	—	—	—	—
Biologics	0.48	0.10, 2.20	0.35	0.04, 2.82	1.00	0.10, 9.79	—	—

Time-varying analysis performed with Cox regression, one predictor per analysis. Analyses were performed for any EAM (uveitis, IBD and/or psoriasis) or for uveitis, IBD or psoriasis separately. Bold: significant ($P < 0.05$). ASDAS: Ankylosing Spondylitis Disease Activity Score; EAM: extra-articular manifestation; HR: hazard ratio; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score.

association could not be demonstrated for either IBD or psoriasis. This suggests that psoriasis and IBD may already be present before the onset or before the diagnosis of AS or perhaps may even have contributed to its diagnosis.

Knowledge of the characteristics of patients who develop any new EAM over time is limited. In the present study we were able to use longitudinal data of patients who were followed up for up to 12 years. We applied two approaches to identify possible demographic, clinical

and radiographic characteristics associated with the development of an EAM. First, baseline characteristics were used in our regression analyses. These baseline characteristics can be considered predictors of outcome or could give us an impression of the profile of patients who are prone to developing EAMs. Only a limited number of weak associations were found. Second, time-varying characteristics were used. For time-varying analysis we used values from characteristics at the time of diagnosis of the EAM, which enabled us to better investigate this relationship at the time of an event. In the present study we found that in particular the development of IBD was associated with markers of higher AS disease activity. Not only was an association with ASDAS found, including CRP, which could be increased because of active IBD, but also clear associations with BASDAI and patient's global well-being. It may also be possible that the high BASDAI is due to the patients' avoidance of NSAIDs, because of IBD, but we were not able to explore this association because of a lack of or variation in NSAID use. Furthermore, it was expected that the development of new-onset IBD would decrease during follow-up, because of the initiation of treatment with biologics in many patients. However, we failed to demonstrate this. Furthermore, the development of IBD was associated with the BASFI. Although the BASFI is in fact a measure of physical function, it is also influenced by active disease [29]. These findings are in line with results from a recent cross-sectional study showing an association between disease activity and the presence of microscopic gut inflammation in patients with axSpA [8].

Some limitations of the present study need to be addressed. First, medical charts were not available for all patients. In the Netherlands, which represents most of the population, information on the presence of the EAMs was collected from rheumatology, internal medicine, dermatology and ophthalmology charts, but unfortunately, for some patients no medical charts could be retrieved. In Belgium and France, only rheumatology charts were available. This may have resulted in an underestimation of the prevalence of EAMs and highlights the importance of systematically checking the occurrence of EAMs in daily practice. This could be achieved by a few simple questions, allowing the identification of patients who should be referred to other medical specialists for diagnostic workup. Second, because the mean symptom duration was long at baseline, many patients already had an EAM and we were therefore unable to include these in the survival analyses. In early SpA cohort studies, a high prevalence of EAMs has been demonstrated early in the disease course [30, 31]. In a German inception cohort including 236 patients with axSpA (mean symptom duration 5.2 years) the prevalence of AAU, psoriasis and IBD was 20.9%, 10.2% and 2.6%, respectively, in the subgroup of patients with AS [31]. In an inflammatory back pain cohort from France, prevalence of 11.1% (AAU), 14.4% (psoriasis) and 7.2% (IBD) were found in the subgroup of 181 newly diagnosed patients with AS (mean symptom duration 1.6 years) [30]. In these early cohorts it would be interesting to investigate which came first, the EAM or axSpA, and the relationship between the onset of axSpA and the onset of EAMs.

In conclusion, at baseline a substantial number of patients already had an EAM in this prevalence cohort with relatively long symptom duration. Development of new EAMs was infrequently observed. In particular, the development of IBD was associated with markers of increased disease activity in AS. The findings from our study may have implications for clinical practice. Especially, it can be important to closely monitor those patients with active AS, as these patients may be prone to developing EAMs.

Rheumatology key messages

- At baseline, 27.3% of this long-standing AS cohort had any extra-articular manifestation.
- Development of any new extra-articular manifestation was infrequently observed (incidence rate 2.4% per year) in this AS cohort.
- Markers of AS disease activity were associated with the development of IBD.

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