Do extra-articular manifestations influence outcome in ankylosing spondylitis? 12-year results from OASIS

I. Essers[1], S. Ramiro[2], C. Stolwijk[1], M. Blaauw[1], R. Landewé[3], D. van der Heijde[2], F. Van den Bosch[4], M. Dougados[5], A. van Tubergen[1]

[1]Department of Medicine, Division of Rheumatology, Maastricht University Medical Center, and School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, the Netherlands; [2]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands; [3]Department of Clinical Immunology and Rheumatology, Academic Medical Center, Amsterdam, and Department of Rheumatology, Atrium Medical Center, Heerlen, the Netherlands; [4]Department of Rheumatology, Ghent University Hospital and Ghent University, Ghent, Belgium; [5]Department of Rheumatology, Paris-Descartes University, Hôpital Cochin, Assistance Publique, Hôpitaux de Paris, INSERM (U1153); Clinical Epidemiology Biostatistics, PRES Sorbonne Paris-Cité, Paris, France.

Abstract

Objective

To assess in patients with ankylosing spondylitis (AS) whether extra-articular manifestations (EAMs) are associated with worse functioning, worse quality of life (QoL), and more radiographic damage over time.

Methods

12-year follow-up data from the Outcome in Ankylosing Spondylitis International Study were used, complemented with data on EAMs extracted from medical charts. Functioning was assessed by the BASFI and physical component of the SF-36, QoL by ASQoL and EuroQoL, and radiographic damage by the mSASSS. Generalised estimating equations analyses were made to assess whether EAMs were associated with these outcomes over time.

Results

216 patients were included (154 (71%) men, mean age 43.6 years (SD 12.7), mean symptom duration 20.5 years (SD 11.7), and mean follow-up 8.3 years (SD 4.3). In total, 58 (26.9%) patients had acute anterior uveitis (AAU), 24 (11.1%) inflammatory bowel disease (IBD), and 14 (6.5%) psoriasis. Univariably, IBD was associated with worse BASFI over time (B=1.26, 95%-CI 0.13 to 2.39, p=0.03), but not in a multivariable model. Furthermore, in a multivariable model, IBD was associated with EuroQoL over time (B=2.93, 95%-CI 0.14 to 5.72, p=0.04). Univariably, psoriasis was associated with radiographic damage (B=-7.25, 95%-CI -14.38 to -0.12, p=0.05) and ASQoL (B= -1.94, 95%-CI -3.32 to -0.57, p<0.01) over time, but not in a multivariable model. AAU was not associated with any outcome over time.

Conclusion

In this longstanding AS cohort, the presence of EAMs was not associated with functional disability, QoL or radiographic damage over time, except for IBD, which was associated with a better EuroQoL.

Key words

ankylosing spondylitis, uveitis, psoriasis, inflammatory bowel disease, outcome measures

Ivette Essers, MD
Sofia Ramiro, MD
Carmen Stolwijk, MD
Marc Blaauw, MD
Robert Landewé, MD, PhD
Désirée van der Heijde, MD, PhD
Filip Van den Bosch, MD, PhD
Maxime Dougados, MD,
Astrid van Tubergen, MD, PhD

Please address correspondence to:
Ivette Essers, MD,
Department of Medicine,
Division of Rheumatology,
Maastricht University Medical Center;
School for Public Health and Primary Care (CAPHRI),
University of Maastricht,
P.O. Box 5800,
Maastricht 6202 AZ, The Netherlands.
E-mail:
ivette.essers@maastrichtuniversity.nl

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disorder, showing features of axial and peripheral involvement in various phenotypes and gradation (1). AS is associated with the presence of extra-articular manifestations (EAMs), comprising acute anterior uveitis (AAU), inflammatory bowel disease (IBD), and psoriasis (2, 3). These EAMs may contribute to the diagnosis of axial spondyloarthritis (axSpA) (4), are part of the classification criteria (5, 6), and may influence the choice of treatment (7).

Important clinical outcomes for patients with AS are functioning, quality of life (QoL), and radiographic damage. These outcomes are also part of a core set of outcomes recommended by the Assessment of SpondyloArthritis international Society (ASAS) (8-10), and are included in a model for health related QoL for patients with AS (11). It is thought that the presence EAMs contribute to the burden of disease, and that they might be predictors of a worse clinical outcome in patients with AS, although the literature reporting on this association is scarce. It has been suggested that patients with AS accompanied by psoriasis and/or IBD have worse functional outcome compared with patients with idiopathic AS in a cross-sectional study (12). Also, AAU might be a severity marker for functional disability in AS (13). Conflicting results have been reported for the influence of AAU on radiographic damage. One study found that AAU was independently associated with radiographic damage (14), whereas two other studies failed to demonstrate this association (15, 16). Most studies previously conducted were cross-sectional, and knowledge about the influence of EAMs on the outcomes functioning, QoL, and radiographic damage over time is limited. It may, however, be important to gain more insight into the contribution of these EAMs to the burden of the disease, and to know whether these EAMs are indeed a worse prognostic factor for clinical outcome over time. The aim of the present study was to assess in a longitudinal cohort study of patients with AS whether the presence of EAMs is associated with more functional disability, worse QoL, and more radiographic damage on the long term.

Patients and methods

Patients

This study was conducted within the framework of the Outcome in Ankylosing Spondylitis International Study cohort (OASIS) (17). In total, 217 patients from the Netherlands, Belgium, and France were included, and were followed at regular intervals from 1996 and onwards. Patients were included when the modified New York Criteria for AS were fulfilled (18) without any other in- or exclusion criteria. Patients were treated according to standard care. Non-pharmacological treatment consisted of (home-) exercises and physiotherapy. According to the judgment of the treating physician, patients were prescribed non-steroidal anti-inflammatory drugs (NSAIDs), analgesics and/or disease-modifying anti-rheumatic drugs (DMARDs). Biologicals were prescribed from 2002 onwards and only on indication, which comprised a small subgroup of patients. Patients were regularly assessed by questionnaires, clinical investigations, laboratory assessments, and radiographic assessments 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 (17).

Extra-articular manifestations

A standardised method was used to retrospectively collect information on the presence of an EAM from the medical charts by two independent extractors. EAMs were only recorded when a description in the medical chart on the diagnosis of psoriasis, IBD and/or AAU by a dermatologist, gastroenterologist, or ophthalmologist respectively was present, or when this information was provided in the medical history of the patient in a letter by these medical specialists or by the general practitioner (19). Because both extractors dealt with about the half of the sample, beforehand the intra- and inter reliability

was calculated to make sure that agreement between the two extractors was high. The inter- and intra-reliability of this data extraction from the medical charts was almost perfect (Cohen's kappa 0.86–0.99 and 0.88–098, respectively) (19). For the current study, the presence of an EAM was binary recoded (yes/no) and could occur at any time in the past or during follow-up of OASIS. The degree or severity of a flare occurring of an EAM was not taken into account.

Demographic, clinical and radiographic assessments

At baseline sex, age, symptom duration (*i.e.* time since onset symptoms), HLA-B27, and hip involvement were recorded. Information on clinical outcomes and spinal radiographic damage was collected at baseline and every 2 years thereafter. The Bath AS Patient Global Score (BAS-G) was used to reflect the impact of AS on a patients' well-being (20). Disease activity was measured with the Bath AS Disease Activity Index (BASDAI) (21), acute phase reactants (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), and the AS Disease Activity Score with CRP (ASDAS-CRP) (22). Functioning was measured with the Bath AS Functional Activity Index (BASFI) (23) and the physical component of the Short Form-36 (SF-36PCS) (24), QoL with the disease-specific ASQoL (25) and the generic EuroQoL (26), spinal pain with a 10 cm visual analogue scale (VAS), and spinal mobility with the Bath AS Metrology Index (BASMI) (27). The total number of swollen joints was counted (0–44). Radiographic damage of the spine was scored with the modified Stoke AS Spine Score (mSASSS), which is a reliable and recommended scoring system for quantifying radiographic damage in AS (28). The radiographs were read by two independent experts (29). Information about treatment with NSAIDs, DMARDs, and biologicals was collected at baseline and at each visit during follow-up. Furthermore, the NSAID-index was calculated as recommended by ASAS (30). All variables were available from baseline onwards, except for the SF-36PCS and ASQoL, which were included as of month 36 in OASIS.

Statistical analysis

For the present study, all available data at baseline and during 12 years of follow up were used. Descriptive statistics were used to calculate the mean with standard deviation for continuous data, and frequencies were calculated for dichotomous data.

All analyses were done with the individual EAMs separately and with the combined variable 'any EAM', defined as the presence of at least one EAM (AAU, IBD and/or psoriasis). At baseline, patients with and without an EAM were compared using ANOVA or Mann-Whitney U-test for continuous data, and Chi-Square tests or Fisher's exact test for binary outcomes. The association between EAMs and functional disability, QoL, and radiographic damage, respectively, over time was investigated using a Generalized Estimating Equation (GEE) technique with exchangeable correlation structure. This is a suitable analytical technique for longitudinal data, making use of all collected data and adjusting for within-patient correlation. Missing data were considered as completely at random. Factors considered to be potentially associated with functional disability, QoL, and radiographic damage were age, gender, symptom duration, HLA-B27 status, hip involvement at baseline, smoking (current *vs.* past/never smoker), disease activity and medication use. Radiographic damage was also considered as potentially associated with functioning and QoL. First, univariable analyses were performed to investigate associations between each EAM (or other variables) and functional disability, QoL or radiographic damage over time. Second, age, gender, and variables with a p-value <0.20 in the univariable analysis were analysed in a multivariable GEE model using a forward selection method. A change in the beta of the main variable (*i.e.* an individual EAM or 'any EAM') of more than 10% after including a new variable was considered as a confounder, and therefore kept in the model. Collinearity was checked, and interactions between the variables were explored.

A significance level of 0.05 was used, except when stated otherwise, and all statistics were performed with SPSS v.19.0.

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 (SD 12.7 years) and 154 (71.3%) patients were male. The mean symptom duration was 20.5 years (SD 11.7 years) and 174 (84.5%) patients were HLA-B27 positive. At baseline, the total number of patients with any EAM was 60 (27.8%), of which 40 (18.5%) with AAU, 15 (6.9%) with IBD, and 9 (4.2%) with psoriasis. Four patients had 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.

The mean follow-up duration was 8.3 years (SD 4.3). In this period, 27 patients newly developed any EAM, of which 19 AAU, 9 IBD, and 5 psoriasis. Two patients developed both IBD and psoriasis.

Association between extra-articular manifestations and clinical outcomes at baseline

Baseline differences between patients with and without EAMs are shown in Table I. Patients with a history of any EAM compared with patients without a history of any EAM had a significantly higher age (47.9 (SD 12.2) *vs.* 41.9 years (SD 12.5), $p<0.01$) and longer symptom duration (24.0 (SD 11.9) *vs.* 19.1 years (SD 11.5), $p<0.01$). In particular, patients with a history of AAU compared with patients without a history of AAU had a significantly higher age (48.5 (SD 12.1) *vs.* 42.4 years (SD 12.6), $p<0.01$)), longer symptom duration (25.4 (SD 11.4) vs 19.3 years (SD 11.6), $p<0.01$), more swollen joints (1.9 (SD 5.2) *vs.* 0.6 (SD 1.5), $p<0.01$), and more radiographic damage (mSASSS

Table I. Comparison of baseline characteristics between patients with and without a history of an extra-articular manifestation.

Baseline characteristic	Any extra-articular manifestation			Acute anterior uveitis			Inflammatory bowel disease			Psoriasis		
	Present (n=60)	Absent (n=156)	*p*-value	Present (n=40)	Absent (n=176)	*p*-value	Present (n=15)	Absent (n=201)	*p*-value	Present (n=9)	Absent (n=207)	*p*-value
Male gender (%)	43 (71.7%)	111 (71.2%)	0.94	28 (70.0%)	126 (71.6%)	0.84	12 (80.0%)	142 (71.0%)	0.56	6 (66.7%)	148 (71.5%)	0.72
Age (yrs)	47.9 (12.2)	41.9 (12.5)	**<0.01**	48.5 (12.1)	42.4 (12.6)	**<0.01**	45.2 (13.6)	43.4 (12.6)	0.61	51.3 (10.0)	43.2 (12.7)	0.06
Symptom duration (yrs)	24.0 (11.9)	19.1 (11.5)	**<0.01**	25.4 (11.4)	19.3 (11.6)	**<0.01**	23.4 (13.2)	20.2 (11.7)	0.32	19.7 (14.3)	20.5 (11.7)	0.85
HLA-B27 positive (%)	48 (80.0%)	127 (86.3%)	0.26	36 (90.0%)	138 (83.1%)	0.28	11 (73.3%)	163 (85.3%)	0.26	4 (44.4%)	170 (86.3%)	**<0.01**
Hip involvement (%)	17 (28.8%)	28 (18.3%)	0.09	12 (30.0%)	33 (18.8%)	0.11	5 (33.3%)	40 (20.3%)	0.32	1 (11.1%)	44 (21.7%)	0.69
ASDAS-CRP	2.6 (1.0)	2.8 (1.1)	0.33	2.7 (0.8)	2.7 (1.1)	0.69	2.8 (1.2)	2.7 (1.1)	0.72	1.8 (0.7)	2.8 (1.1)	**<0.01**
BASDAI (0-10)	3.3 (2.1)	3.5 (2.1)	0.52	3.4 (2.0)	3.5 (2.2)	0.84	3.3 (2.5)	3.4 (2.1)	0.73	2.6 (1.9)	3.5 (2.1)	0.24
CRP (mg/L)	16.2 (19.2)	18.5 (26.1)	0.36	15.1 (14.9)	18.6 (26.2)	0.24	26.6 (30.0)	17.5 (24.1)	0.06	5.0 (3.2)	18.5 (24.8)	**<0.01**
ESR (mm/h)	12.2 (8.4)	15.4 (17.6)	0.89	11.6 (7.9)	15.3 (17.0)	0.87	17.0 (9.3)	14.4 (16.1)	0.07	8.0 (6.1)	14.9 (16.0)	0.19
Total swollen joint count (0-44)	1.6 (4.4)	0.5 (1.3)	**<0.01**	1.9 (5.2)	0.6 (1.5)	**<0.01**	1.1 (2.7)	0.8 (2.6)	0.71	0.3 (1.0)	0.8 (2.7)	0.57
BASFI (0-10)	3.4 (2.4)	3.4 (2.7)	0.99	3.2 (2.3)	3.4 (2.7)	0.71	4.1 (2.5)	3.3 (2.6)	0.26	2.6 (2.6)	3.4 (2.6)	0.41
BAS-G (0-10)	3.7 (2.6)	3.9 (2.6)	0.63	3.9 (2.7)	3.9 (2.5)	0.98	3.7 (2.4)	3.9 (2.6)	0.75	3.3 (2.5)	3.9 (2.6)	0.53
SF-36PCS (0-100)†	35.1 (12.0)	38.9 (10.7)	0.07	34.8 (12.1)	34.8 (10.9)	0.14	37.0 (10.6)	37.9 (11.3)	0.80	34.2 (13.8)	38.0 (11.1)	0.42
ASQoL (0-18)†	6.0 (4.4)	6.3 (4.5)	0.70	6.9 (4.4)	6.1 (4.5)	0.42	5.3 (4.1)	6.3 (4.1)	0.43	3.2 (3.2)	6.4 (4.5)	0.09
EuroQoL VAS (0-100)	70.9 (13.6)	68.0 (16.1)	0.22	69.2 (14.7)	68.9 (15.7)	0.85	72.1 (11.6)	68.5 (15.7)	0.41	75.2 (9.6)	68.5 (15.6)	0.21
BASMI (0-10)	4.0 (1.7)	3.8 (1.6)	0.34	4.1 (1.7)	3.8 (1.6)	0.35	4.3 (1.8)	3.8 (1.6)	0.25	3.1 (1.1)	3.9 (1.6)	0.19
mSASSS (0-72)	13.2 (15.7)	11.0 (16.4)	0.11	16.4 (18.0)	10.6 (15.6)	**0.04**	14.1 (13.0)	11.5 (16.4)	0.11	3.8 (3.8)	12.1 (16.5)	0.25

Mean (SD mean) or number of patients (%).
Analyses performed with ANOVA, Mann Whitney U-test (based on the median) for continuous outcomes and Chi-square test or Fisher's exact test for binary outcomes (**Bold:** statistically significant). †Results from month 36 are shown as this questionnaire was administered for the first time at month 36.

16.4 (SD 18.0) *vs*. 10.6 (SD 15.6), *p*=0.04). No differences between patients with and without a history of IBD were found. Patients with psoriasis were less often HLA-B27 positive compared with patients without psoriasis (4 (44.4%) *vs*. 170 (86.3%), *p*<0.01), and had a lower ASDAS-CRP compared with patients without psoriasis (1.8 (SD 0.7) *vs*. 2.8 (SD 1.1), *p*<0.01).

Association between extra-articular manifestations and functional disability over time

The association between the presence of EAMs and functional disability over time was investigated in two ways by using either the BASFI or the SF-36PCS as outcome.

With respect to the BASFI, in univariable analyses, no association between any EAM (B 0.37, 95%–CI -0.30 to 1.03, *p*=0.28), AAU (B 0.22, 95%–CI -0.45 to 0.90, *p*=0.52) or psoriasis (B 0.01, 95%–CI -1.59 to 1.62, *p*=0.99) with BASFI over time was found. Therefore, no multivariable analyses were performed. However, IBD was univariably significantly associated with BASFI over time (B=1.26, 95%–CI 0.13 to 2.39, *p*=0.03), but this disappeared in an adjusted multivariable model (B=0.66, 95%–CI -0.17 to 1.49, *p*=0.12) (Table II).

With respect to the SF-36PCS, no association over time was found between any EAM (B -1.41, 95%–CI -4.29 to 1.46, *p*=0.34), AAU (B -1.94, 95%-CI –4.96 to 1.09, *p*=0.21), IBD (B -2.05, 95%–CI -6.10 to 1.99, *p*=0.32) or pso-

Table II. Association between an EAM and BASFI over time.

Characteristic	Univariable analysis		Multivariable analysis inIBD	
	B (95%-CI)	*p*	B (95%-CI)	*p*
Any EAM	0.37 (-0.30 to 1.03)	0.28	-	
IBD	1.26 (0.13 to 2.39)	0.03	0.66 (-0.17 to 1.49)	0.12
AAU	0.22 (-0.45 to 0.90)	0.52	-	
Psoriasis	0.01 (-1.59 to 1.62)	0.99	-	
Male gender	0.11 (-0.61 to 0.83)	0.77	0.33 (-0.17 to 0.82)	0.20
Age (years)	0.04 (0.03 to 0.06)	<0.01	0.05 (0.03 to 0.07)	**<0.01**
Symptom duration (years)	0.04 (0.03 to 0.06)	<0.01	n.s.	n.s.
HLA-B27 positive	0.40 (-0.42 to 1.22)	0.34	-	
Hip involvement	1.52 (0.68 to 2.37)	<0.01	n.s.	n.s.
Smoking (current)	-0.37 (-0.76 to 0.02)	0.06	n.s.	n.s.
ASDAS-CRP	0.84 (0.73 to 0.95)	<0.01	0.80 (0.70 to 0.90)	**<0.01***
BASDAI (0-10)	0.54 (0.47 to 0.60)	<0.01	-	
CRP (mg/L)	0.01 (0.01 to 0.02)	<0.01	-	
ESR (mm/h)	0.03 (0.02 to 0.04)	<0.01	-	
Total swollen joint count (0-44)	0.03 (0.00 to 0.05)	0.04	n.s.	n.s
BASMI (0-10)	0.59 (0.49 to 0.69)	<0.01	0.37 (0.27 to 0.48)	**<0.01***
mSASSS (0-72)	0.03 (0.02 to 0.05)	<0.01	0.01 (-0.01 to 0.02)	0.26*
Use of biologicals	0.02 (-0.37 to 0.40)	0.93	-	
Use of DMARD	0.09 (-0.33 to 0.50)	0.69	-	
Use of NSAID	0.09 (-0.12 to 0.29)	0.43	-	
NSAID score	0.00 (0.00 to 0.00)	0.96	-	

Bold: statistically significant; n.s.: neither significant nor a confounder; - variable not included in the model because it was not statistically significant in the univariable analysis or another variable was preferred; *Confounder of incident IBD in this model.
IBD: inflammatory bowel disease; 95% CI: 95% confidence interval; HLA-B27: human leucocyte antigen- B27; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein (normal value <10 mg/dl); ESR: erythrocyte sedimentation rate; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; BASMI: Bath Ankylosing Spondylitis Metrology Index; DMARD: disease-modifying anti-rheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs.

riasis (B 1.89, 95%–CI -3.49 to 7.26, *p*=0.49) with the SF-36PCS either. Therefore, no multivariable analyses were performed.

Association between extra-articular manifestations and QoL over time

The association between the presence of EAMs and QoL was investigated using the disease-specific ASQoL and the generic EuroQoL as outcome. Univariably, no association between any EAM (B 0.05, 95%–CI -1.18 to 1.27, *p*=0.94), AAU (B 0.25, 95%–CI –1.08 to 1.57, *p*=0.72) or IBD (B 1.03, 95%–CI -0.97 to 3.03, *p*=0.31) with the ASQoL over time could be demonstrated. Therefore, no multivariable analyses were performed. Psoriasis was univariably associated with the ASQoL over time (B -1.94, 95%–CI -3.32 to -0.57, *p*<0.01), which disappeared in a multivariable analysis (B -0.38, 95%–CI -2.11 to 1.34, *p*=0.66) (Table III).

Similarly, no association between any EAM (B -0.68, 95%–CI -4.37 to 3.01, *p*=0.72), AAU (B 0.14, 95%–CI -3.54 to 3.82, *p*=0.94), or psoriasis (B -3.25, 95%–CI -11.84 to 5.33, *p*=0.46) with the EuroQoL over time was found. Because the univariable association between IBD and EuroQoL over time had a *p*-value <0.20, a multivariable analysis was done, which showed that IBD was associated with the EuroQoL over time (B 2.93, 95%–CI 0.14 to 5.72, *p*=0.04) (Table IV).

Association between extra-articular manifestations and radiographic damage over time

Table V shows the results of the association between the presence of EAMs and radiographic damage over time. Any EAM was univariably not associated with radiographic damage over time (B 3.31, 95%–CI -1.98 to 8.61, *p*=0.22). Therefore, no multivariable analysis was performed. Because the univariable association between AAU and radiographic damage over time had a *p*-value <0.20, a multivariable analysis was done, which showed that AAU was no longer associated with radiographic damage over time. Similar results were found for psoriasis. IBD was univariably not associated with radiographic damage over time (B 3.50, 95%–CI -3.84 to 10.84, *p*=0.35).

Table III. Association between an EAM and ASQOL over time.

Characteristic	Univariable analysis		Multivariable analysis inIBD	
	B (95%-CI)	*p*	B (95%-CI)	*p*
Any EAM	0.05 (-1.18 to 1.27)	0.94	-	
IBD	1.03 (-0.97 to 3.03)	0.31	-	
AAU	0.25 (-1.08 to 1.57)	0.72	-	
Psoriasis	-1.94 (-3.32 to -0.57)	**<0.01**	-0.38 (-2.11 to 1.34)	0.66
Male gender	-1.15 (-2.50 to 0.20)	0.09	-1.49 (-2.47 to -0.50)	**<0.01**
Age (years)	0.01 (-0.03 to 0.06)	0.58	-0.02 (-0.06 to 0.02)	0.39
Symptom duration (years)	0.02 (-0.02 to 0.07)	0.30	-	
HLA-B27 positive	-0.22 (-1.76 to 1.32)	0.78	-	
Hip involvement	0.71 (-0.82 to 2.24)	0.36	-	
Smoking (current)	-0.27 (-1.40 to 0.85)	0.64	-	
ASDAS-CRP	1.40 (1.07 to 1.74)	**<0.01**	0.69 (0.36 to 1.01)	**<0.01***
BASDAI (0-10)	1.19 (1.04 to 1.34)	**<0.01**	-	
CRP (mg/L)	0.00 (-0.02 to 0.02)	0.88	-	
ESR (mm/h)	0.02 (0.01 to 0.04)	**<0.01**	-	
Total swollen joint count (0-44)	1.15 (0.99 to 1.31)	**<0.01**	n.s.	n.s.
BASFI (0-10)	-0.05 (-0.13 to 0.03)	0.20	0.94 (0.76 to 1.13)	**<0.01***
BASMI (0-10)	0.50 (0.18 to 0.82)	**<0.01**	-0.08 (-0.40 to 0.26)	0.67*
mSASSS (0-72)	0.00 (-0.03 to 0.03)	0.98	-	
Use of biologicals	0.14 (-0.72 to 0.99)	0.75	-	
Use of DMARD	1.09 (0.06 to 2.12)	0.04	0.70 (-0.12 to 1.52)	0.10*
Use of NSAID	0.45 (-0.21 to 1.10)	0.18	0.46 (-0.07 to 1.01)	0.09*
NSAID score	0.00 (-0.01 to 0.01)	0.63	-	

Bold: statistically significant; n.s.: neither significant nor a confounder; -: variable not included in the model because it was not statistically significant in the univariable analysis or another variable was preferred; *Confounder of incident IBD in this model.

IBD: inflammatory bowel disease; 95% CI: 95% confidence interval; HLA-B27: human leucocyte antigen-B27; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein (normal value <10 mg/dl); ESR: erythrocyte sedimentation rate; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; BASMI: Bath Ankylosing Spondylitis Metrology Index; DMARD: disease-modifying anti-rheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs.

Discussion

This study in patients with longstanding AS and on average more than 8 years of follow up, showed that the presence of EAMs was not associated with more functional disability, QoL and radiographic damage over time, except for IBD, which was associated with a better EuroQoL.

In practice, it is often assumed that the presence of EAMs may contribute to the burden of disease and that they are predictors of a worse clinical outcome in patients with AS, however, the literature about this is limited and sometimes conflicting results are reported. With respect to AAU, one longitudinal study, with 5 years of follow-up in 74 patients with AS found that the presence of AAU was associated with more functional disability over time (13). In contrast, a cross-sectional study in 146 patients failed to demonstrate this association (31), which corresponds to the findings from our longitudinal study. Furthermore, we found no association between AAU and QoL over time, which is in line with an earlier cross-sectional study conducted in patients with spondyloarthritis (32). Conflicting results with respect to an association between AAU and radiographic damage have also been reported. Two cross-sectional studies failed to demonstrate an association between AAU and more severe radiographic damage in patients with AS (15) and spondyloarthritis (16), respectively, whereas another cross-sectional study found that a history of AAU was independently associated with more radiographic damage in patients with AS, besides a longer disease duration, male gender, and hip involvement (14). In the present study, we could not demonstrate an association between AAU and radiographic damage over time.

With respect to IBD, a cross-sectional study in 3,287 patients with AS showed

Table IV. Association between an EAM and EuroQoL over time.

Characteristic	Univariable analysis		Multivariable analysis inIBD	
	B (95%-CI)	*p*	B (95%-CI)	*p*
Any EAM	-0.68 (-4.37 to 3.01)	0.72	-	
IBD	-4.60 (-11.33 to 2.12)	0.18	2.93 (0.14 to 5.72)	**0.04**
AAU	0.14 (-3.54 to 3.82)	0.94	-	
Psoriasis	-3.25 (-11.84 to 5.33)	0.46	-	
Male gender	2.75 (-1.30 to 6.79)	0.19	1.46 (-1.24 to 4.16)	0.29
Age (years)	-0.11 (-0.22 to 0.00)	0.06	0.08 (-0.03 to 0.18)	0.16
Symptom duration (years)	-0.12 (-0.24 to 0.00)	0.06	n.s.	n.s.
HLA-B27 positive	1.03 (-4.03 to 6.09)	0.69	n.s.	n.s.
Hip involvement	-5.66 (-10.65 to -0.67)	**0.03**	0.95 (-2.73 to 4.62)	0.61*
Smoking (current)	0.82 (-1.91 to 3.55)	0.64		
ASDAS-CRP	-7.50 (-8.77 to -6.24)	**<0.01**	-4.35 (-5.79 to 2.91)	**<0.01***
BASDAI (0-10)	-4.16 (-4.77 to 3.55)	**<0.01**	-	
CRP (mg/L)	-0.14 (-0.22 to -0.07)	**<0.01**	-	
ESR (mm/h)	-0.23 (-0.31 to -0.16)	**<0.01**	-	
Total swollen joint count (0-44)	-0.23 (-0.47 to 0.01)	0.06	n.s.	n.s.
BASFI (0-10)	-4.25 (-4.79 to -3.72)	**<0.01**	-3.04 (-3.64 to -2.45)	**<0.01***
BASMI (0-10)	-.270 (-3.57 to 1.82)	**<0.01**	n.s.	n.s.
mSASSS (0-72)	-0.08 (-0.16 to 0.00)	**0.05**	0.03 (-0.06 to 0.11)	0.57*
Use of biologicals	0.97 (-2.30 to 4.24)	0.56	-	
Use of DMARD	-1.96 (-5.21 to 1.30)	0.24	-	
Use of NSAID	-1.87 (-3.53 to -0.21)	**0.03**	-2.32 (-4.21 to -0.43)	**0.02**
NSAID score	-0.01 (-0.03 to 0.01)	0.53	-	

Bold: statistically significant; n.s.: neither significant nor a confounder; -: variable not included in the model because it was not statistically significant in the univariable analysis or another variable was preferred; *Confounder of incident IBD in this model.

IBD: inflammatory bowel disease; 95% CI: 95% confidence interval; HLA-B27: human leucocyte antigen- B27; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein (normal value <10 mg/dl); ESR: erythrocyte sedimentation rate; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; BASMI: Bath Ankylosing Spondylitis Metrology Index; DMARD: disease-modifying anti-rheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs.

that patients with concomitant IBD had worse functioning than patients with AS alone (12). In our longitudinal study, IBD was not associated with more functional disability over time. Also, and similarly to another cross-sectional study (33), we did not find an association between the presence of IBD and more severe radiographic damage over time. Somewhat surprisingly we found that the presence of IBD in patients with AS was associated with a better score on the EuroQoL over time. This might be explained by several factors. First, the EuroQoL is a generic QoL questionnaire which might not sufficiently take into account the specific burden of IBD. Studies in patients with IBD have shown that IBD itself can interfere with daily activities and QoL (34). Second, the number of patients with IBD in our cohort was very small. The association, if at all, between IBD and EuroQoL may be different when larger cohorts are analysed. Our results should therefore be interpreted with caution.

With respect to psoriasis, a cross-sectional study in 3,287 patients with AS showed that patients with concomitant psoriasis had worse functioning than those without (12), and a cross-sectional study in 311 patients with AS found that patients with concomitant psoriasis who smoked had more functional disability than patients who had concomitant psoriasis but did not smoke or patients with AS who smoked without psoriasis (14). In the present longitudinal study, we could not demonstrate that psoriasis was associated with worse functioning over time. Furthermore, we did not find a relation between the presence of psoriasis and worse radiographic damage over time, which is in line with findings from a cross-sectional study (33). Other characteristics seem to be more important for radiographic damage over time. For example, in a previous study conducted within OASIS, we found that disease activity was associated with more radiographic damage over time (35). Other characteristics, such as male gender and smoking status have also been associated with radiographic damage over time (36, 37).

Some limitations of the present study need to be addressed. First, medical charts were not available in all patients. In the Netherlands, which represents most of the population (63.4%), information about the EAMs was collected from the rheumatology, internal medicine, ophthalmology, and dermatology charts. In Belgium and France, only the rheumatology charts were checked. Unfortunately, for some patients no medical charts could be retrieved. This could have resulted in an underestimation of the prevalence and incidence of EAMs. Second, the prevalence of psoriasis was low in our cohort, which might have limited the power of these analyses. For example the comparisons for the HLA-B27 status at baseline should be interpreted with caution. Third, we were not able to collect information on the degree or severity of a flare occurring in an EAM, which could be important information when we try to understand the association between EAMs and these outcomes over time. Fourth, this study was conducted in tertiary health care centres, which might include more severe patients with AS. Fifth, although the currently used instruments in this study focus on specific aspects of patients with AS, for example functioning and QoL, these instruments do not focus sufficiently on the overall picture of impairments, limitations and restrictions in activities or social participation of patients with AS. The recently developed ASAS Health Index addresses these aspects of health, based on the International Classification of Functioning, Disability, and Health (ICF) core-set for AS, in which patients and expert collaborated in its development (38). It might be relevant for future research to evaluate whether EAMs are associated with a worse outcome on these aspects of health using the ASAS Health Index.

The strength of this study is the long follow-up duration in which patients were regularly assessed, in a systematic way, with validated instruments.

In conclusion, EAMs do not seem to be a worse prognostic factor for functional

Table V. Association between an EAM and radiographic damage over time.

Characteristic	Univariable analyses		Multivariable analyses			
			Model 1 in AAU		Model 2 in psoriasis	
	B (95%-CI)	*p*	B (95%-CI)	*p*	B (95%-CI)	*p*
Any EAM	3.31 (-1.98 to 8.61)	0.22	-		-	
IBD	3.50 (-3.84 to 10.84)	0.35	-		-	
AAU	4.98 (-1.05 to 11.02)	0.11	-0.61 (-6.59 to 5.38)	0.84	-	
Psoriasis	-7.25 (-14.38 to -0.12)	**0.05**	-		-3.60 (-10.27 to 3.06)	0.29
Male gender	10.05 (5.50 to 14.59)	**<0.01**	8.51 (3.96 to 13.05)	**<0.01***	8.61 (3.99 to 13.23)	**<0.01***
Age (years)	0.86 (0.72 to 1.01)	**<0.01**	0.47 (0.14 to 0.80)	**<0.01***	0.43 (0.09 to 0.77)	**0.02***
Symptom duration (years)	0.88 (0.72 to 1.04)	**<0.01**	0.32 (-0.05 to 0.68)	**0.09***	0.35 (-0.02 to 0.72)	0.06*
HLA-B27 positive	4.87 (-1.54 to 11.28)	0.14	2.06 (-3.88 to 8.00)	0.50*	1.46 (-4.44 to 7.36)	0.63*
Hip involvement	17.94 (10.22 to 25.66)	**<0.01**	10.14 (0.70 to 19.59)	**0.04***	11.45 (1.93 to 20.96)	**0.02**
Smoking (current)	-3.76 (-6.90 to -0.61)	**0.02**	1,37 (-1.61 to 4.34)	**0.37***	1.20 (-1.47 to 3.87)	0.38*
ASDAS-CRP	-1.48 (-2.55 to -0.40	**<0.01**	-0.25 (-1.10 to 0.61)	0.58*	n.s.	n.s.
BASDAI (0-10)	-0.09 (-0.51 to 0.33)	0.69	-		-	
CRP (mg/L)	-0.09 (-0.15 to -0.03)	**<0.01**	-		-	
ESR (mm/h)	-0.01 (-0.08 to 0.06)	0.78	-		-	
Total swollen joint (0-44) count	0.15 (0.00 to 0.30)	**0.05**	-0.10 (-0.25 to 0.04)	0.17*	n.s.	n.s.
Use of biologicals	10.88 (7.67 to 14.09)	**<0.01**	5.43 (2.53 to 8.33)	**<0.01***	4.69 (1.91 to 7.83)	**<0.01**
Use of DMARDs	-0.62 (-2.95 to 1.71)	0.60	-		-	
Use of NSAIDs	-0.98 (-3.08 to 1.11)	0.36	-		-	
NSAID score	-0.02 (-0.06 to 0.01)	0.23	-		-	

Model 1: multivariable analysis with AAU as main variable; Model 2: multivariable analysis with psoriasis as main variable. Bold: significant; n.s.: neither significant nor a confounder; -: variable not included in the model because it was not statistically significant in the univariable analysis or another variable was preferred; *Confounder in this model.

EAM: extra-articular manifestation; IBD: inflammatory bowel disease; AAU: acute anterior uveitis; 95% CI: 95% confidence interval; HLA-B27: human leucocyte antigen-B27; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein (normal value <10 mg/dl); ESR: erythrocyte sedimentation rate; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; BASMI: Bath Ankylosing Spondylitis Metrology Index; DMARD: disease-modifying anti-rheumatic drugs; NSAIDs: non-steroial anti-inflammatory drugs.

disability, QoL and radiographic damage over time. Despite this, clinicians need to pay attention for the presence and new-onset of an EAM, because of its role in the diagnosis, classification, and treatment choice in patients with AS.

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