Extra-skeletal manifestations in axial spondyloarthritis are associated with worse clinical outcome despite the use of TNF blocking therapy.

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Abstract

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

Methods All consecutive patients included in the Groningen Leeuwarden Axial SpA (GLAS) cohort between 2004 and 2011 were analysed. 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 axial SpA patients, 31.5% had a positive history of one or more ESMs: 24.9% AAU, 9.4% IBD, and 4.4% psoriasis. History of psoriasis 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 with AAU, of which 3.6% had a first episode and 9.7% had recurrent AAU, 1.9% developed IBD, and 0.8% developed psoriasis.

Patients who newly developed ESMs (without history of ESMs) had worse ASQoL score (mean 10.0 vs. 5.9, p=0.001), larger occiput to wall distance (median 6.3 vs. 2.0, p=0.021) and more limited modified Schober test (mean 12.6 vs. 13.6, p=0.014) after 4 years of follow-up. The majority of patients developing an ESM used anti-TNF therapy.

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

Key messages

- One-third of axial SpA patients had a history of ESM at baseline and the 4-year incidence was 9.7% for recurrent AAU (3.6% for a first episode), 1.9% for IBD, and 0.8% for psoriasis.
- The majority of patients developing an ESM used anti-TNF therapy.
- The development of a new ESM was associated with less spinal mobility and worse quality of life during follow-up.

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Introduction

Spondyloarthritis (SpA) refers to a group of interrelated chronic auto-inflammatory rheumatic disorders including ankylosing spondylitis (AS), non-radiographic axial SpA), psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease (IBD), reactive arthritis (ReA), and undifferentiated SpA. (1,2) Overlapping features are often observed such as involvement of the axial skeleton, predominantly sacroiliitis and spondylitis, and the involvement of the peripheral skeleton such as peripheral arthritis, enthesitis and dactylitis. Furthermore, so-called extra-articular manifestations (EAMs) or more recently extra-skeletal manifestations (ESMs) can be present in SpA patients. The three most well-known ESMs are acute anterior uveitis (AAU), IBD, in particular Crohn's disease and ulcerative colitis, and psoriasis.

Recently published pooled data showed prevalence rates of 26% for uveitis, 7% for IBD and 9% for psoriasis in axial SpA. (3) The presence of these ESMs in patients with chronic inflammatory back pain or peripheral arthritis increased the likelihood of having SpA. (4–7) Therefore, these ESMs are included in the ASAS classification criteria. (8) Furthermore, the presence of one or more ESMs may influence treatment decisions. (9,10)

Although data on prevalence rates of ESMs are abundant, knowledge of incidence rates in axial SpA 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 psoriasis. This study started in 1996 and therefore none of the patients were treated with biologicals at baseline and approximately 20% started tumour necrosis factor-alpha (TNF-α) blocking therapy during follow-up after registration of these drugs. (11)

Until know, conflicting results with respect to the influence of ESMs on axial SpA disease outcome are published. It has been suggested that having an ESM contributes to the disease burden and may worsen clinical outcome measures. (12–15) As far as we know, 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 psoriasis in a large Dutch cohort of axial SpA patients and most important to explore associations of the history of ESMs and newly developed ESMs with axial SpA 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 on-going prospective longitudinal observational cohort study in the northern part of the Netherlands. Since November 2004, this cohort included consecutive AS outpatients who started TNF-α blocking therapy at the University Medical Centre Groningen (UMCG) or the Medical Centre Leeuwarden (MCL) due to active disease. (16) All patients were over 18 years of age, fulfilled the modified New York criteria for AS (17), and the ASAS criteria to start TNF-α blocking therapy (active disease defined as Bath AS 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 axial SpA patients irrespective 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, gender, symptom duration, HLA-B27 status, body mass index (BMI), smoking status (ever/never), smoking duration, swollen joint involvement (yes/no) and tender enthesis (yes/no) were collected. The use of pharmacological therapies were also recorded, including use of NSAIDs, conventional DMARDs, and TNF-α inhibitors. Clinical assessment of disease activity was performed at baseline and each follow-up visit using the Bath AS Disease Activity Index (BASDAI) (19) and AS Disease Activity Score (ASDAS). (20) Health-related quality of life of the patients was assessed at each visit using the AS Quality of Life (ASQoL), (21) physical function using the Bath AS Functional Activity Index (BASFI) (22), and spinal mobility using occiput to wall distance, chest expansion, lateral spinal flexion, modified Schober test and cervical rotation (since 2009 only). (23) Radiographic damage of the spine was scored only at baseline using the modified Stoke AS Spine Score (mSASSS). (24)

Extra-skeletal manifestations

At baseline and each follow up visit, standardized questions were used to gather information on AAU, IBD and psoriasis. 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 analysed. Descriptive statistics were used to calculate the mean ± SD or median (IQR) for normally or non-normally distributed continuous data respectively. Frequencies (n,%) were calculated for dichotomous data. Independent t-test, Mann Whitney U-test, Chi-Square test or Fisher's 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 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's Exact test were also performed when applivable 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 disease outcome measures ASQoL and mSASSS at 4 years for potential confounding could not be performed due to low incidence numbers of ESMs.
All statistical analysis were performed using SPSS 25.0 (IBM, Armonk, NY, USA). P-values ≤0.05 were considered statistically significant.

Results

414 axial SpA patients were included, with 360 (90%) classifying as Ankylosing Spondylitis (AS) and 40 (10%) as non-radiographic axial SpA The inclusion strategy is depicted in Supplementary Figure 1. 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 TNF-α

inhibitors at baseline. All patient characteristics are presented in Table 1. Of the 414 included patients, 362 had available 4-year follow-up data 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, less swollen joints, less NSAID and anti-TNF use and a lower ASDAS. There were no differences in prevalence of ESMs at baseline (Table 1).

Prevalence of ESMs

At baseline, 130 (31.4%) of 414 patients had a positive history of one or more 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 psoriasis. Twenty-nine (7.0%) patients had a history of two ESMs, of which 21 (5.1%) the combination of IBD and AAU, 4 (1.0%) AAU and psoriasis and 3 (0.7%) psoriasis and IBD. Only 1 (0.2%) patient had a history of all three ESMs combined.

History of ESMs associated with axial SpA characteristics and outcome

The 130 axial SpA patients with a history of any ESM were significantly older, had longer symptom duration, and used more often conventional DMARDs compared to patients without ESMs. According to the spinal mobility assessments, axial SpA patients with a history of any ESM had larger occipital 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 non-smokers compared to patient without AAU. Patients with IBD used significantly more often DMARDs and experienced worse quality of life (ASQoL) than patients without IBD. Patients with a history of psoriasis were more often HLA-B27 positive, experienced lower disease activity (BASDAI) and had more spinal radiographic damage, especially cervical mSASSS was higher (Table 2).

In multivariable regression analysis, we corrected the association with 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:*0.052). When analysing individual ESMs, we found that patients with a history of psoriasis had significantly more spinal radiological damage (mSASSS OR 6.88), especially at the cervical spine (cervical mSASSS OR 23.74).

4-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, 8 patients (1.9%) developed IBD and 3 patients (0.8%) developed psoriasis. The remaining 35 patients had recurrent AAU.

One patient developed two ESMs (IBD and AAU). Of the 48 patients with AAU, 17 (29.8%) developed more than one episode of AAU during the 4 year follow up period.

Development of ESMs associated with axial SpA characteristics and outcome

Patients who developed an ESM without a history of any ESMs at baseline (n=18) had worse quality of life (ASQoL), larger occiput to 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 significant longer symptom duration and were more often HLA-B27 positive. They also had significantly less often swollen joint involvement, worse quality of life (ASQoL), larger occiput to wall distance and more limited modified Schober. Since the number of patients who newly developed IBD and psoriasis was relatively small (n=8 and n=3 resp.), 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 who developed an ESM during follow up compared to 52 patients without a new ESM. Of those 15 patients, 10 patients had recurrent uveitis, who most frequently switched from etanercept to adalimumab.

Discussion

In our prospective cohort, a history of any ESM was present in one-third of the axial SpA patients. The highest prevalence was found for AAU (24.9%) followed by IBD (9.4%) and psoriasis (4.4%). Interestingly, history of ESMs at baseline was significantly associated with less spinal mobility and more spinal radiographic damage. Furthermore, 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 the ESM occurred. Finally, our multivariable analysis showed that history of ESMs, most prominent psoriasis, 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 psoriasis at baseline. [12] A systemic review and meta-analysis showed that prevalence rates of ESMs varied between studies due to clinical and methodological heterogeneity. The pooled prevalence rates were 25.8% (95% CI 24.1% to 27.6%) for uveitis, 6.8% (6.1% to 7.7%) for IBD, and 9.3% (8.1% to 10.6%) for psoriasis. (25) So far, conflicting results regarding the influence of ESMs on axial SpA disease outcome are published. In the DESIR cohort of 692 patients with inflammatory back pain suggestive for spondyloarthritis, patients with psoriasis had higher disease activity (BASDAI) and poorer functional status (BASFI). (26) In a cross-sectional cohort of 146 Chinese AS patients, higher disease activity (BASDAI) and worse physical functioning (BASFI, spinal mobility) was found in the 23 patients with a history of AAU, unfortunately no treatment data were available for these patients. (13) Also, a cross-sectional study including 131 AS, 110 PsA and 46 SAPHO patients reported higher disease activity (ASDAS, BASDAI and CRP) in patients with AAU, higher CRP in patients with IBD, but lower BASDAI in patients with skin psoriasis. (14) However, they did not report sub analysis for only AS patients.

On the other hand, a cross-sectional analysis of 20 AS patients with psoriasis and 201 AS patients without psoriasis with active disease (before starting TNF-α blocking therapy) did not show any significant differences in disease activity, physical function, spinal mobility, quality of life and radiographic damage between patients groups. (27) Also, a recent cross-sectional study of 352 AS patients and 193 nr-axial SpA patients showed that the presence of ESMs did not result in major differences in disease activity, physical function, spinal mobility status and quality of life in both

patient groups. (28) The patients in this cohort were mostly similar to ours, except a relatively low number of HLA-B27 positive patients (66%) and there was no data on treatment strategy.

Our group of AS patients starting anti-TNF therapy was relatively large, since the inclusion of the GLAS cohort started in 2004 with only including this subgroup of patients. In 2009, inclusion was extended to all axial SpA patients irrespective 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 to develop another episode of uveitis and also to be treated with a TNF inhibitor. In our cohort, patients with recurrent uveitis mainly switched to adalimumab, based on previous findings about the positive effect of adalimumab 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 conventional DMARDs. Our hypothesis is that the ESM of these patients mainly required the treatment with conventional DMARDs.

In our study, the association with more spinal radiographic damage was found especially in patients with a history of psoriasis. 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 AS patients 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 1023 AS patients did not demonstrate a significant association between psoriasis and radiographic damage. However, this study did not use the validated mSASSS scoring method, but classified patients in three groups (no damage, syndesmofytes, ankylosis), which is less sensitive to show differences. (30)

In respect to the incidence of ESM, during 4 years of follow-up, 39 (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 psoriasis. The incidence of ESMs was also associated with worse quality of life. Research on incidence rates of ESMs are scarce. The incidence rates of the different ESMs we found in our cohort match the rates previously reported in a few other axial SpA cohorts (3,11) One study performed in the framework of the OASIS cohort included 216 patients and had a mean follow up period of 8.3 (SD 4.3) 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 psoriasis. (11) Another study with AS patients 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% respectively for AAU, IBD and psoriasis. (3)

Our study was the first to demonstrate that the development of a new ESM does influence spinal mobility outcomes and disease-related quality of life. 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 also associated with less spinal mobility and worse quality of life. Although we also observed a lower quality of life in patients who developed IBD or psoriasis during follow-up (with similar differences as for uveitis; data not shown), this difference did not reach statistical significance probably due to the small number of patients who developed IBD (n=8) and psoriasis (n=3). In the previously mentioned 216 AS patients from the OASIS cohort, longitudinal associations between incidence of ESMs and disease outcome have also been investigated. In univariable analysis, psoriasis 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 over time and no association with ASQoL. The EuroQoL 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 axial SpA patients, reflecting the population in current daily clinical practice. Furthermore, data of ESMs were verified in the medical records for diagnosis by an ophthalmologist, dermatologist or gastroenterologist.

To conclude, history of ESMs at baseline was present in one-third of the 414 axial SpA patients: 24.9% AAU, 9.4% IBD, and 4.4% psoriasis. The prevalence of ESMs was significantly associated with older age, longer symptom duration, more conventional DMARD use, less spinal mobility and more spinal radiographic damage. There was an independent association between psoriasis 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 psoriasis. The majority of patients developing an ESM used anti-TNF therapy. Patients who developed a new ESMs demonstrated worse spinal mobility and worse quality of life.

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Conflict of interest

S.A. has received research grants from Pfizer. F.W. has received consulting fees from Abbvie and Janssen. A.S. has received research grants from Abbvie, Pfizer and Novartis and consulting fees from Abbvie, Pfizer, MSD, Novartis and UCB. They had no influence in design and conduct of the study. All other authors have declared no conflicts of interest in relation to this article.

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Table 1: Characteristics at baseline of 414 included axial SpA patients

	Baseline (n=414)	4-year follow up (n=362)	Lost to follow up (n=52)	*P-value*
Patient characteristics				
Age (yrs)	43.1 (12.5)	43.4 (12.2)	41.1 (14.2)	*0.785*
Male gender (%)	265 (64%)	238 (66%)	27 (52%)	***0.021***
Symptom duration (yrs)	15.0 (8.0-24.0)	17.0 (8.0-25.0)	11.0 (7.1-18.0)	***0.046***
HLA-B27+ (%)	313 (77%)	278 (78%)	35 (69%)	*0.353*
BMI (kg/m2)	26.2 (4.4)	26.6 (4.4)	24.0 (3.8)	***0.005***
Smoking status (never smoked) (%)	113 (31%)	98 (30%)	15 (33%)	*0.951*
Swollen joint involvement (%)	53 (13%)	51 (15%)	2 (3.8%)	***0.022***
Tender entheses (%)	253 (62%)	221 (62%)	32 (62%)	*0.961*
NSAID use (%)	314 (80%)	283 (82%)	31 (65%)	***0.018***
DMARD use (%)	57 (14%)	53 (15%)	4 (7.7%)	*0.203*
Start TNF-α inhibitors (%)	276 (67%)	251 (69%)	24 (47%)	***0.000***
Disease activity				
BASDAI	5.4 (2.1)	5.5 (2.1)	4.8 (2.1)	*0.053*
ASDAS	3.3 (1.0)	3.3 (1.0)	2.9 (1.0)	***0.021***
Disease outcome				
ASQoL	8.8 (4.7)	8.9 (4.8)	8.4 (4.2)	*0.541*
BASFI	4.9 (2.4)	4.9 (2.4)	4.6 (2.6)	*0.911*
Occiputal wall distance	3.0 (0-9.9)	3.0 (0-10.0)	0.0 (0.0-8.0)	*0.585*
Cervical rotation mean†	57.5 (24.5)	56.5 (25.1)	62.9 (20.8)	*0.417*
Chest expansion	4.0 (2.2)	4.0 (2.2)	4.3 (2.4)	*0.313*
Lateral spinal flexion mean	10.5 (5.6)	10.3 (5.4)	11.5 (5.6)	*0.417*
Modified schober test	13.1 (1.7)	13.0 (1.7)	13.1 (1.8)	*0.923*
mSASSS at baseline	4.5 (1.0-15.5)	4.8 (1.0-15.6)	3.2 (1.0-13.5)	*0.181*
- Cervical mSASSS at baseline	3.0 (0.5-9.6)	3.5 (0.5-10.1)	2.0 (0.5-5.1)	*0.079*
- Lumbar mSASSS at baseline	1.5 (0.0-7.5)	2.0 (0-8.0)	1.0 (0-5.5)	*0.183*

Data presented as mean (SD), number of patients (%) or median (p25-p75). Patients lost to follow up compared to patient in follow op (362 vs 52)

† available since 2009, n=216

Table 2: The Prevalence of ESMs in relation to axial SpA disease characteristics and outcome

	Any ESM		Acute anterior uveitis		Inflammatory bowel disease		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)	**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 gender (%)	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)	**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/m2)	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)
Smoking status: never smoked	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%)
Diseas activity								
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	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	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 to wall distance	**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	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	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	**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	**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)

Data presented as mean (SD), number of patients (%) or median (p25-p75). * = p<0.05. BMI = body-mass index. NSAID = non-steroid anti-inflammatory drug. DMARD = Disease modifying anti-rheumatic drug. BASDAI = Bath Ankylosing Spondylitis Disease Activity Index. ASDAS = Ankylosing Spondylitis Disease Activity Score. ASQoL = AS Quality of Life. BASFI = Bath Ankylosing Spondylitis Functional Index. mSASSS = modified Stoke AS Spine Score

Table 3: The prevalence of ESMs in relation to axial SpA disease outcome in multivariable models

	Any ESM		Acute anterior uveitis		Inflammatory bowel disease		Psoriasis	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Disease outcome	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
ASQoL	0.996 (0.952-1.041)	0.948 (0.878-1.024)	0.984 (0.937-1.032)	0.932 (0.856-1.015)	**1.081 (1.005-1.164)**	1.077 (0.977-1.187)	0.938 (0.847-1.039)	0.930 (0.801-1.081)
Total mSASSS	**1.836 (1.214-2.774)**	2.261 (0.994-5.146)	**1.573 (1.114-2.441)**	0.978 (0.412-2.320)	1.723 (0.933-3.181)	2.033 (0.893-4.632)	**2.708 (1.076-6.813)**	**6.876 (1.622-29.156)**
- Cervical mSASSS	1.767 (0.998-3.130)	3.077 (0.859-11.022)	1.454 (0.788-2.685)	1.166 (0.338-4.026)	1.311 (0.564-3.044)	2.200 (0.725-6.680)	**4.504 (1.187-17-095)**	**23.274 (1.809-299.486)**
- Lumbar mSASSS	1.322 (0.793-2.205)	0.992 (0.327-3.006)	1.337 (0.769-2.326)	0.534 (0.152-1.881)	0.648 (0.220-1.906)	0.648 (0.220-1.906)	1.878 (0.654-5.397)	3.151 (0.668-14.862)

Data presented OR with 95% CI. Data for all ESMs and AAU corrected for sex, symptom duration, HLA-B27 status, BMI, smoking status, NSAID use, DMARD use and ASDAS. IBD data corrected for symptom duration, DMARD use and ASDAS. Psoriasis data corrected for symptom duration, HLA-B27 status and ASDAS.

Table 4: Patient characteristics after 4-years 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)	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 gender (%)	14 (77.8%)	152 (65.2%)	3 (43%)	233 (66%)	2 (67%)	234 (66%)	11 (84%)	225 (65%)	24 (69&)	212 (65%)
Symptom duration (yrs)	21 (11-24)	13.5 (7-24)	17 (2-23)	16 (8-25)	19 (12-)	16.5 (8-25)	**24 (19-26)**	**16 * (8-25)**	**22 (12-26)**	**16 * (8-25)**
HLA-B27+ (%)	16 (88.9%)	174 (76.3%)	4 (57%)	272 (79%)	3 (100%)	273 (78%)	**13 (100%)**	**263 * (77.4%)**	29 (83%)	247 (78%)
BMI (kg/m2)	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)
Smoking status: never smoked	3 (19%)	60 (29%)	1 (20%)	97 (31%)	0	98 (31%)	2 (17%)	96 (31%)	9 (29%)	89 (31%)
Swollen joint involvement (%)	0	6 (3%)	0	13 (4%)	0	13 (4%)	0	13 (4%)	2 (6%)	11 (3%)
Tender enthesis (%)	5 (29%)	83 (37%)	1 (17%)	129 (38%)	2 (67%)	128 (37%)	4 (31%)	126 (37%)	14 (42%)	116 (37%)
NSAID use (%)	8 (53%)	122 (56%)	4 (67%)	175 (53%)	2 (67%)	177 (53%)	4 (36%)	175 (53%)	13 (41%)	166 (54%)
DMARD use (%)	1 (6%)	12 (5%)	2 (29%)	27 (8%)	1 (33%)	28 (8%)	1 (8%)	28 (8%)	3 (9%)	26 (8%)
Anti-TNF use (%)	15 (83%)	154 (66%)	6 (86%)	242 (69%)	2 (67%)	246 (69%)	11 (85%)	237 (68%)	27 (77%)	221 (68%)
Disease activity										
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	**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	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 to wall distance	**6.3 (2-16)**	**2 * (0-8)**	3 (0-7)	3 (0-10)	14 (2-)	3 (0-10)	**8.0 (5-16)**	**2.5 * (0-9)**	7 (0-14)	3 (0-9)
Cervical rotation mean	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	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	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	**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)**

Activity Index. ASDAS = Ankylosing Spondylitis Disease Activity Score. ESR = Erythrocyte sedimentation rate. CRP = C-reactive protein. ASQoL = AS Quality of Life. BASFI = Bath Ankylosing Spondylitis Functional Index.