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Factors associated with drug-free remission at 5 year in early onset axial spondyloarthritis patients: data from the DESIR cohort

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Abstract

Objectives : To assess the frequency of patients in drug-free remission at 5 years in a cohort of early axial SpA, and the factors associated with this remission.

Methods: *Patients:* Patients included in the DESIR (DEvenir des Spondyloarthropathies Indifférenciées Récentes) cohort undergoing the 5-year visit were selected for this analysis. *Definition of 5-year drug-free remission:* 1/ all patients in ASAS partial remission and/or ASDAS<1.3 at 5 year visit and 2/ taking no disease modifying anti-rheumatic drugs at the 5-year visit and 3/ with an ASAS-NSAID score≤25 at the 5-year visit. *Data analysis:* The proportion of patients in drug-free remission was described. The association between demographic, clinical, biological and imaging characteristics and drug-free remission at 5 years was assessed by logistic regression.

Results: Of the 412 patients included in this analysis, 73 (18%) were in drug-free remission at the 5-year visit. The baseline clinical factors associated with the chances to be in drug-free remission at the 5-year visit were symptom duration (OR=0.66[95%CI:0.44-0.97]), lower HAQ-AS score (OR=0.32 [0.12-0.78]), lower ASDAS score (OR=0.55[95%CI:0.34-0.86]), ASAS-NSAID score (OR=0.91[95%CI:0.82-0.99]). Furthermore, anti-TNF use (OR=0.20 [95%CI:0.08-0.42]) during the follow-up decreased the chances of being in 5-year drug-free remission.

Conclusion: The probability of being in drug free remission at 5 year when beginning an axial SpA is low and is associated with lower baseline disease activity and functional scores, while starting an anti-TNF is associated with poor chances of later being in drug-free remission.

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Keywords: spondyloarthritis, remission, anti-TNF, therapy

Introduction

Spondyloarthritis (SpA) is a chronic inflammatory rheumatism with heterogeneous presentation leading to inflammatory back pain, peripheral joint manifestations and often associated with extra-articular features. Over the last two decades, the prognosis for the disease has considerably improved with anti-TNF drugs approval in the early 2000's, and more recently with arrival of other biological disease-modifying antirheumatic drugs (bDMARDs) targeting the IL-17 pathway.[1-3]

According to ASAS-EULAR's (Assessment of SpondyloArthritis international Society – European League Against Rheumatism) recommendations,[4] inactive disease should be the ultimate goal to aim for when treating a SpA. The definition of remission in axial and peripheral SpA is quite challenging. Ideally, remission of a disease is achieved when no signs or symptoms are present. Although there is no widely accepted definition of remission for peripheral symptoms, we have several criteria to define axial SpA remission. The most widely used definition of remission in SpA is the ASAS partial remission criteria [5], composed of purely subjective measures without the presence of objective disease activity criteria such as CRP (C-reactive Protein) or inflammation in an MRI (Magnetic Resonance Imaging). More recently, an ASAS initiative endorsed an Ankylosing Spondylitis Disease Activity Score (ASDAS), which includes 4 clinical and one objective (CRP or erythrocyte sedimentation rate – ESR) disease activity parameters.[6] An ASDAS of <1.3 indicates inactive disease in SpA that could correspond to remission.[7]

In randomized trials, the proportions of patients reaching ASAS partial remission is about 15-30% for the non-steroidal anti-inflammatory drugs (NSAIDs) and about 15-60% for the TNF

(Tumor Necrosis Factors) inhibitors, while it is about 24% for NSAIDs and about 25-50% for TNF inhibitors when the ASDAS inactive disease criterion is used.[8]

Spontaneous remission has not been formally defined in the literature.[8] However, it is generally accepted that a resolution of the symptoms and signs of disease activity without the use of pharmacologic intervention would be consistent with a spontaneously remissive state. To date, little is known about the natural history of early axial spondyloarthritis and the probability of reaching drug-free remission.

We aimed to assess the proportion of patients with early axial SpA who reached drug-free remission 5 years after their inclusion in an early onset axial SpA cohort. We further investigated the baseline demographic, clinical, biological and imaging factors associated with 5-year drug-free remission, and secondly the impact of treatments received within the four first years of follow-up.

Methods

This study is an observational longitudinal cohort study.

Study population:

The DESIR (Devenir des Spondyloarthropathies Indifférenciées Récentes) cohort has already been described elsewhere. [9] Briefly, DE1SIR is a French prospective longitudinal cohort study, monitoring 708 patients (aged between 18 and 50 years) with inflammatory back pain suggestive of axial SpA, according to rheumatological opinion, over time, for ≥ 3 months and < 3 years in 25 centres across France, between 2007 and 2010. All patients included in the study had a collection of clinical data, blood samples, plain pelvis and spine X-rays, sacroiliac joints (SIJ) and spine MRI at baseline, and were prospectively followed at 6, 12, 18, 24, 36, 48

and 60 months. This work involved the whole population of patients with sufficient data to classify patients as being in drug-free remission at 5 year or not (n=412 patients, DESIR database locked on June 20th 2016). The patients with another condition than axSpA diagnosed during the follow-up were excluded.

Ethics, consent and permission:

The study complied with Good Clinical Practice Guidelines (clinicaltrials.gov: NCT01648907, <https://clinicaltrials.gov/ct2/show/NCT01648907>) and was approved by the appropriate medical ethic committee (CPP Ile-de-France III, submission number P070302). Patients gave informed consent before the start of the study, including permission to publish any individual data anonymously.

Definition of drug-free remission at 5 year

Patients were classified as being in drug free remission at 5 year if at the 5-year visit they were in ASAS partial remission and/or in ASDAS inactive disease, with no peripheral swollen joints at physical examination, and if they were taking neither corticosteroids nor DMARDs and had an ASAS-NSAID score $\leq 25\%$. [10]

A patient was classified as having an inactive disease if the ASDAS was < 1.3 at the 5-year visit. A patient was classified as being in ASAS partial remission if he/she had a value ≤ 2 (on a 0 to 10 scale) in each of the following 4 domains: patient global, pain, function (the Bath Ankylosing Spondylitis Functional Index – BASFI) and inflammation (mean of the Bath Ankylosing Spondylitis Disease Activity Index – BASDAI questions 5 and 6 – related to morning stiffness) at the 5-year visit.

A patient could have received DMARDs, corticosteroids or NSAIDs with a score $\geq 25\%$ in the first 4 years of follow-up in the DESIR cohort, but had to have stopped it before the 5-year visit to be considered in the drug-free remission group.

We also performed sensitivity analyses changing this definition. We thus investigated patients who fulfilled the previous definition at the 4-year visit and at the 5-year visit (patients in sustained drug-free remission). We also investigated patients who were in low disease activity or inactive disease according to the ASDAS (ASDAS <2.1) at the 4-year and 5-year visits (patients in sustained LDA).

Demographic, clinical, biological and imaging baseline data

For the present study, demographic and clinical characteristics including age, sex, body mass index, smoking, symptom duration at inclusion in the cohort, disease presentation at onset (axial only or presence of peripheral features – joint and/or enthesitis peripheral features; insidious, intermittent or acute presentation), level of confidence in the axial SpA diagnosis on a scale from 0 to 10, extra-articular features at baseline (including psoriasis, uveitis or inflammatory bowel disease), the *HLA-B27* status, the spondyloarthritis classification criteria (including ASAS 2009,[11] Amor criteria,[12] ESSG (European Spondylarthropathy Study Group) criteria [13] or modified New York criteria [14]), disease activity and functional impairment were analysed at baseline. The disease activity included the BASDAI and the ASDAS-C-Reactive Protein (ASDAS-CRP). The functional impairment at baseline was assessed by the BASFI, the Bath Ankylosing Spondylitis Metrology Index (BASMI), the Health Assessment Questionnaire for Ankylosing Spondylitis (HAQ-AS), the tender and swollen joint count, the Maastricht Ankylosing Spondylitis Enthesitis Score (MASSES) and CRP levels.

The following comorbidities were collected at baseline: gastric ulcer, digestive haemorrhage, major cardiovascular events (myocardial infarction, stroke), cardiac failure, lung disease, neoplasia, tuberculosis, diabetes and acquired immunodeficiency syndrome (AIDS).

Imaging data at baseline was also investigated and comprised the presence of a radiographic sacroiliitis (New York criteria [14]), the presence of structural changes on spine radiographs assessed by the mSASSS (modified Stoke Ankylosing Spondylitis Spinal Score) [15], the presence of MRI sacroiliitis according to the ASAS definition and the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring method (range 0–72) [16, 17], or the presence of MRI spine inflammation according to the Berlin score.[18] The details of the centralised scoring of imaging in the DESIR cohort, including its reliability, has already been reported elsewhere.[17, 19, 20]

Treatments during the five first years of follow-up

Treatments were analysed during the five first years of follow-up and included corticosteroids (oral, infusion, joint injections), analgesics, NSAIDs (ASAS-NSAID score (0-100)), [10] conventional synthetic DMARDs (csDMARDs) and anti-TNF.

Statistical analysis

Qualitative variables were described as numbers and percentages, quantitative variables were described as mean and standard deviation or median and interquartile range when appropriate. Comorbidities were grouped together, and the results are presented as the number of patients with at least one comorbidity.

Baseline demographic, clinical, biological and imaging characteristics, as well as treatments received during the four first years by patients in 5-year drug-free remission, were compared

to other patients with bilateral tests, using Chi2 test in case of in case of qualitative variables or with a Student t-test in case of quantitative variables with a significance threshold set at 5%. Associated variables with the 5-year drug-free remission criterion with a p value < 0.15 were selected for the multivariate model through a logistic regression, stepwise procedure. Co-linearity between the different variables was tested, and when co-linearity was identified, the most clinically relevant variable was kept in the final model. We also repeated the analyses with other definitions used for the sensitivity analyses, including patients in sustained drug-free inactive disease at the 4 and 5-year visits and patients in sustained drug-free low disease activity at the visit 4 et 5 years.

All statistics were performed by SAS 9.4 software.

Results

Of the 708 patients included in the DESIR cohort, 617 patients were still being followed in the DESIR cohort 5 years after inclusion, and 418 patients came to the 5-year visit and had sufficient data to be classified as being in drug-free remission at 5 year or not, of whom 73 (18%) were in 5-year drug-free remission. The comparison of clinical characteristics between patients included in this analysis and patients who missed the 5-year visit is detailed in supplementary material (table S1)[See the supplementary material associated with this article online].

The demographic, clinical, biological and imaging characteristics of patients in drug-free remission at 5 year compared to other patients are presented in table 1.

Patients in 5-year drug-free remission had shorter symptom duration, lower axial and peripheral disease activity, lower value of CRP and less functional impairment, while there

was no difference of extra-articular feature history between groups. There was no difference between groups in *HLA-B27* allele carriage nor baseline imaging data. Finally, patients in drug free remission at five years had lower baseline ASAS-NSAID scores (40.6 versus 58.4, $p=0.01$), lower analgesic use (64% versus 85%, $p<0.00001$) and anti-TNF (1% vs 53%, $p<0.0001$) use between baseline and 4-year visit compared to patients not in drug-free remission at 5 years.

The results of the multivariate analysis are presented in table 2.

Patients with longer disease duration, higher HAQ-AS and ASDAS scores and baseline NSAIDs intake scores had lower probability to be in drug-free remission at 5-year, while patient undergoing a DMARD during the follow-up had a very low probability to be in drug-free remission at 5 year (OR=0.20 [0.08-0.41]).

Sensibility analyses

We further analysed the data considering another definition of remission.

Firstly we identified patients with drug-free sustained inactive disease meaning with an ASDAS-CRP<1.3 at the 4-year AND 5-year visit. Among the 373 patient with available data at 4-year and 5-year visits, 34 (9%) were in drug-free inactive disease at 4 year and 5 year. After stepwise logistic regression, symptom duration and HAQ-AS score was associated with drug-free sustained inactive disease, while any DMARD use within the 3 first years of follow-up decreased the probability of being in sustained drug-free inactive disease (see supplementary file table S2)

Furthermore, we identified patients with drug-free inactive disease or low disease activity at 4-year and 5-year visits with an ASDAS-CRP<2.1. With this definition, 52 patients (15%) could

be classified in drug-free sustained inactive disease or low disease activity. After stepwise logistic regression, the male gender, the classification of axSpA according to the clinical arm increased the chances to be in sustained inactive disease without treatment while ASDAS-CRP, NSAIDs score at baseline and any DMARD intake during the 3 first years decreased the probability to be in low disease activity or inactive disease (table S2, supplementary data).

Discussion

In this study, 18% of patients with early onset axial SpA were in drug-free remission at the 5-year visit. Of the 182 patients who started an anti-TNF within the four first years of follow-up in the DESIR cohort, only one was able to interrupt it and was in remission at the 5-year visit. Patients with longer disease duration, higher ASDAS-CRP and HAQ-AS scores were less likely to be in drug-free remission at the 5-year visit.. A higher ASAS-NSAID score at baseline, and a DMARD initiation during the follow-up were strongly associated with a poor chance of being in 5-year drug free remission.

To our knowledge, this is the first study investigating factors associated with drug-free remission in early axSpA. Indeed, many randomised clinical trials reported drug-induced remission rates, but only few observational studies reported drug-free remission. Placebo arms of clinical trials can give information on remission in patients not receiving bDMARDs. For example, a recent meta-analysis showed that partial remission could be observed in 4% of patients taking a placebo of bDMARD at week 12, 7.4% of patients at week 16 and 3.7% of patients at week 24, while it was observed in 23% of patients treated by anti-TNF at week 12, 20.3% of patients taking anti-TNF or secukinumab at week 16 and 20.4% of patients

taking anti-TNF at week 24.[21] However, patients included in randomised clinical trials are highly selected, with the disease active, and the data observed cannot be extrapolated to all axial SpA patients. Very few studies reported a natural history of peripheral SpA or axial SpA and reported remission rates during the follow-up. However, in these studies, the patients could be on csDMARDs, NSAIDs or glucocorticoids, thus drug-free remission could not be assessed.[22-24] In the DESIR cohort, a recent study [25] investigated the rate of clinical remission after 2 years of follow-up, and found that 15% of patients achieved ASAS partial remission after 2 years, and 24% could be classified as having an inactive disease according to ASDAS. In this study patients in remission could also receive DMARDs or glucocorticoids. Their analysis also identified that analgesic use, ASAS clinical arm and baseline ASAS-NSAID score were predictors of remission as well as low CRP and low BMI. More recently the authors studied the factors associated with 5-year remission and showed that 17% of patients exposed to anti-TNF and 25% of patients not exposed were in 5 year remission.[26]

In this study, higher baseline disease activity scores, high functional impairment, and high NSAID consumption were associated with a poor prognosis, with a small chance of being in spontaneous remission during the follow-up. These factors are often the main predictors of starting an anti-TNF that would be continued over 5 years. Several studies reported the risk of relapse after stopping anti-TNF when remission is achieved. For example, in C-OPTIMISE, only 20% of patients who stopped certolizumab pegol had sustained remission 48 weeks later, compared to 88% of patients who continued anti-TNF[27]. More recently, the RE-EMBARK trial showed that only 57% of patients with non-radiographic axial SpA starting on etanercept could achieve ASDAS inactive disease after 24 weeks, of whom 37% will have a flare-up after interrupting etanercept,[28] while the recent SPACING trials showed that anti-TNF tapering with spacing injection strategy was feasible.[29] In a sensitivity analysis, we

tried to identify the factors associated with sustained inactive disease and low disease activity integrating the data of the 4-year and 5-year visits. Firstly we could notice that sustained inactive disease (only 9% of patients) or low disease activity (only 15% of patient) was rare in this cohort. Secondly the same predictive factors were identified, namely baseline symptom duration, ASDAS-CRP, HAQ-AS and baseline NSAID intake score. In patients with sustained drug-free inactive disease or low disease activity (ASDAS<2.1), male gender was predictive of sustained low disease activity. A previous work on DESIR cohort [30] had already showed that women had higher disease activity scores and functional scores despite having less radiographic or MRI sacroiliitis. Our findings suggest that women are less likely to have sustained low ASDAS-score without medication. However, when using a more stringent definition with an ASDAS-CRP<1.3, we could not identify any differences based on gender. We also identified in this analysis an association with the clinical arm of axSpA criteria. This association was not found with other analyses using a more stringent criterion of remission. Furthermore, we could not identify an association between any of the three outcomes and HLA-B27 or other features of the clinical arm. As objective sign of inflammation or a radiographic sacroiliitis are mandatory in France to introduce an anti-TNF, patients in clinical arm might be less likely treated with an anti-TNF, that increase the chances to reach the outcome of drug-free low disease activity or inactive disease.

This study has several limits. Firstly, only 412 patients out of 708 went to the 5-year visit and could be included in this analysis, leading to a risk of attrition bias: only patients with poorer outcomes were still followed in the clinical centers. We thus cannot exclude that the proportion of patients in drug-free clinical remission at 5 years could be higher. This is the major limit of all observational studies. We further compared the patients who underwent the 5-year visit to patients who missed this visit (table S1). Not surprisingly, patients who

missed the visit were less often treated with csDMARDs or anti-TNF, and used fewer analgesics during the follow-up. We could also observe that they less often carried *HLA-B27*, and a lower proportion of them were classified as axSpA with at least one SpA criterion. Indeed, the inclusion criteria in DESIR cohort was a high suspicion of axSpA according to physicians' opinion, and we cannot exclude that some patients were misclassified at inclusion in the cohort and were finally excluded during the follow-up. We could also observe that patients who missed the 5-year visit had higher BASDAI, BASFI and HAQ scores as well as higher tender joint scores compared to the patients who underwent the visit. Even if our rate of patients in drug-free clinical remission might be impaired by the missing data, the assessment of factors associated with remission remains consistent.

The second limit is the time of disease assessment. We only included the 5-year disease activity score in this analysis. We thus tried to perform a sensitivity analysis taking account to 4-year disease activity data and identified the same risk factors. Obviously, these two endpoints cannot reflect all disease activity fluctuation over time, and cannot be considered a proxy for sustained remission [31]. This is the limit of all observational studies with pre-defined end-points. New technologies, including new Apps, may better assess disease fluctuation over time. However, it is shown that patient adherence to such tools is low.[32]

Despite these limits, this study provides new data on the natural history of recent onset axial SpA in a large sample of patients, assessing a large dataset of demographic, clinical, biological and imaging characteristics.

For the first time in a large cohort of early axial SpA, this study reports the chance of being in drug-free remission after five years. The probability of one day being in drug-free remission when a decision to accept treatment with anti-TNF is taken seems very weak from these

observational data. Further research is necessary in longer follow-up studies to assess drug-free remission and sustained remission over time with nearby control endpoints.

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Competing interests:

The authors do not declare relevant competing interests related to this manuscript.

Online material. Supplementary data

Supplementary data (Tables S1-S2) associated with this article can be found in the online version at ...

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Table 1: Baseline demographic, clinical, biological and imaging characteristics and treatments over time of patients in 5-year drug free remission compared to other patients (univariate analyses)

Patient characteristics	Patients in 5-year drug-free remission N=73	Patients not in 5-year drug-free remission N=339
Age, mean (SD)	33.3 (8.1)	33.9 (8.7)
Gender, number of females (%)	36 (49.3)	187 (55.2)
Symptom duration, years, mean (SD)	1.3 (0.8)*	1.5 (0.9)
Current or past smokers, number (%)	21 (28.8)	128 (37.8)
Body mass index, mean (SD)	23.4 (3.8)	24.0 (4.2)
Patients classified as axSpA with at least one set of classification criteria, number (%)	57 (78.1)	287 (84.7)
Patients fulfilling ASAS axSpA criteria, number (%)	55 (75.3)	234 (69.0)
• in imaging arm, number (%)	27 (37.0)	143 (42.2)
• in clinical arm, number (%)	28 (38.4)*	91 (26.8)
Clinical presentation at onset		
“Explosive” (less than 24 hours)	12 (16.4)	59 (17.4)
Sub-acute (less than 1 week)	16 (21.9)	50 (14.8)
Insidious	44 (60.3)	215(63.4)
Intermittent	1 (1.4)	17 (5.0)
History of peripheral joint features, number (%)	36 (49.3)	195 (57.5)
History of peripheral enthesitis features	27 (37.0)	168 (49.6)
Extra-articular features at disease onset	19 (26.0)	97 (28.6)
Psoriasis	13 (17.8)	59 (17.4)
Inflammatory bowel disease	2 (2.7)	24 (7.1)
Uveitis	7 (9.6)	30 (8.9)
Patients with at least one comorbidity, number (%)	3 (4.1)	29 (8.6)
<i>HLA-B27</i> presence, number (%)	54 (73.9)	208 (61.4)

BASDAI, mean (SD)	29.1 (18.2)***	46.4 (19.6)
ASDAS-CRP, mean (SD)	1.94 (0.9)***	2.76 (0.9)
BASFI, mean (SD)	13.5 (16.7)***	32.1 (22.6)
HAQ-AS, mean (SD)	0.3 (0.4)***	0.7 (0.7)
BASMI, mean (SD)	1.9 (0.8)***	2.5 (1.0)
Tender joint count, mean (SD)	1.33 (3.6)***	4.22 (8.2)
Swollen joint count, mean (SD)	0.16 (0.8)	0.22 (1.4)
MASES, mean (SD)	2.03 (4.5)***	4.4 (5.6)
CRP, mg/L, mean (SD)	4.1 (4.8)**	8.8 (14.7)
Patients with radiograph sacroiliitis, number (%)	13 (17.8)	80 (23.6)
mSASSS, mean (SD)	1.2 (3.3)	1.6 (4.0)
Patients with MRI sacroiliitis, number (%)	20 (26.4)	121 (35.7)
SPARCC, mean (SD)	2.9 (6.5)	4.4 (8.2)
MRI spine Berlin score, mean (SD)	0.5 (1.2)	1.2 (3.1)
Baseline ASAS-NSAID score (0-100), mean, SD	30.7 (31.8)**	48.1 (39.1)
NSAID use between baseline and 4-year visits, number (%)	70 (95.9)	330 (97.4)
Analgesic use between baseline and 4-year visit, number (%)	47 (64.4)***	289 (85.3)
Corticosteroid use between baseline and 4-year visit, number (%)	7 (9.6)**	101 (29.8)
Any DMARD use between baseline and 4-year visit	10 (13.7)***	211 (62.2)
• csDMARD use	9 (12.3)	29 (8.6)
• Anti-TNF use	1 (1.4)	182 (53.7)

All comparisons were performed by logistic regression, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with CRP, BASFI: Bath Ankylosing Spondylitis Functional Index, HAQ-AS: Health Assessment

Questionnaire for Ankylosing Spondylitis, BASMI: Bath Ankylosing Spondylitis Mobility Index, MASES: Maastricht Ankylosing Spondylitis Enthesitis Score, mSASSS: modified Stoke Ankylosing Spondylitis Spine Score, SPARCC: Spondyloarthritis Research Consortium of Canada scoring system (Sacro-iliac joint MRI scoring system): MRI Berlin Score: Spine MRI scoring system, NSAID: Non-Steroidal Anti-Inflammatory Drug, csDMARD: conventional synthetic Disease-Modifying Antirheumatic Drug, *:p<0.05, **: p<0.001, ***: p<0.0001

Table 2: Results of the multivariate analysis assessing the factors associated with 5-year drug-free remission

Associated variables	OR [95%CI]
Symptom duration	0.66 [0.44-0.96]*
HAQ-AS	0.32 [0.12-0.78]*
ASDAS-CRP	0.55 [0.34-0.86]**
ASAS-NSAID score	0.99 [0.98-0.99]*
Use of any DMARD	0.20 [0.08-0.41]***

ASAS: Assessment of SpondyloArthritis international Society, HAQ-AS: Health Assessment Questionnaire for Ankylosing Spondylitis, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with CRP, NSAID: Non-Steroidal Anti-Inflammatory Drug,

The model included: smoking, *HLA- B27*, swollen joint count, tender joint count, MASES, acute presentation at disease onset, comorbidities, symptom duration, ASDAS-CRP, BASFI, BASMI, ASAS-NSAID score, corticosteroid use, anti-TNF use, analgesic use between baseline and 4-year visit. BASDAI and CRP were not included because of co-linearity with ASDAS-CRP. History of enthesitis features was not included because of redundancy with MASES.

*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.0001$