Health and Imaging Outcomes in Axial Spondyloarthritis

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'Choose a job you love,

and you will never have to work a day in your life.'

Confucius, 551 - 479 BC

To my parents

To my brother and sister

To Alexandra and Leonardo

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Chapter 1

General Introduction

GENERAL INTRODUCTION

Background

Spondyloarthritis (SpA) is a heterogeneous disease that can either have a predominantly axial (cardinal manifestation: chronic back pain) or a predominantly peripheral (cardinal manifestation(s): arthritis, enthesitis or dactylitis) phenotype. The range of clinical features of SpA is broad and includes chronic (typically inflammatory) back pain, arthritis, enthesitis, dactylitis, as well as extra-articular manifestations such as psoriasis, uveitis and inflammatory bowel disease.[1]

Susceptibility to SpA is largely genetically determined, and its heritability has been estimated to be as high as 90%.[2] The disease is strongly linked to the Human Leukocyte Antigen B27 (HLA-B27), with HLA-B27 explaining 30-50% of the overall genetic risk. However, the influence of HLA-B27 on disease phenotype is controversial, with conflicting results published in the literature.[3,4] The contribution of environmental factors to the disease phenotype remains poorly characterised, with limited data published on dietary habits,[5] enteric and upper respiratory tract infections,[6,7] and cigarette smoking,[8] at the time the work presented in this thesis was developed. Therefore, the influence of genetic factors, such as HLA-B27, and environmental factors, such as smoking, on the phenotype and outcome of patients with axial SpA warranted further research.

In the last few years there has been a remarkable progress in our understanding of SpA among which the development and validation of classification criteria for axial and peripheral SpA by an international group of experts in the field, the Assessment of SpondyloArthritis international Society (ASAS), is probably the most eye-catching. Axial SpA can be further divided into radiographic (ie. ankylosing spondylitis [AS]) and non-radiographic axial SpA. This new classification approach has the advantage of better describing the disease, allowing an earlier identification and treatment of the disease and potentially leading to improved health outcomes.[9,10]

The development of validated tools (table 1) for measuring patient outcome has been a major contribution of ASAS to the field of axial SpA. These tools have stimulated clinical research in axial SpA and contributed to the success of a large number of drug development programmes and drug registration programmes.[11] Despite these remarkable developments, the way the various health outcomes in axial SpA relate to each other is still a matter of debate. The development of new methods of assessment, such as magnetic resonance imaging (MRI), which is capable of detecting acute and chronic lesions of the spine and the sacroiliac joints,[12-14] added more complexity to these relationships. Better understanding of the relationships between health outcomes in axial SpA, including imaging outcomes (those related to radiographic and MRI assessments, such as the development of syndesmophytes and MRI lesions), would result in better understanding of the disease and of the assessment

tools that are available for use in clinical practice and research studies.

Table 1. Assessment of SpondyloArthritis international Society (ASAS) core sets[10,11]

Domain	Instrument	For SMARD and PT	For CRK	For DCART
Function	BASFI	X	X	X
Pain	NRS/VAS (spine, at night, last week, due to AS) NRS/VAS (spine, last week, due to AS)	X	X	X
Spinal mobility	Chest expansion, modified Schober, occiput to wall distance, cervical rotation, lateral spinal flexion or BASMI	X	X	X
Patient global	NRS/VAS* (global disease activity, last week)	X	X	X
Stiffness	NRS/VAS* (spine, duration of morning stiffness, last week)	X	X	X
Fatigue	Fatigue question of BASDAI (NRS/VAS*)	X	X	X
Peripheral joints and entheses	Number of swollen joints (44-joint count) Validated entheses score		X	X
Acute phase reactants	CRP or ESR		X	X
Radiographs of the spine	Lateral lumbar and cervical spine			X

*ASAS prefers the use of a NRS. AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRK, clinical record keeping; CRP, C-reactive protein; DCART, disease-controlling anti-rheumatic treatments; ESR, erythrocyte sedimentation rate; NRS, numerical rating scale (0–10); PT, physical therapy; SMARD, symptom modifying anti-rheumatic drugs; VAS, visual analogue scale (0–10cm).

The ASAS core set of domains and instruments to assess and monitor patients with axial SpA includes several disease activity measures (table 1). In addition to the core set tools a composite index named the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) has been extensively used to assess disease activity in axial SpA.[15] BASDAI combines six individual variables (fatigue, axial pain, joint pain and swelling, tender areas, intensity and duration of morning stiffness) into one single score and is a fully patient-oriented measure. However, it is well-described that patients and physicians have different perspectives about disease activity in axial SpA.[16] For example, patients may give more value to subjective symptoms like pain and fatigue, while physicians may give more value to objective signs like the number of swollen joints or to laboratory findings like the presence of elevated acute phase reactants. Therefore the correlation between patient and physician global assessments of disease activity is typically weak in axial SpA and the same applies to the correlation between BASDAI and physician global assessment.[16] Furthermore, BASDAI lacks specificity for inflammatory disease processes and does not take the redundancy and dependence of individual variables

Table 2. Measures of disease activity in axial spondyloarthritis

Instrument	Questions and calculation rules
BASDAI[15]	How would you describe the overall level of fatigue/tiredness you have experienced? How would you describe the overall level of AS neck, back or hip pain you have had? How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had? How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure? How would you describe the overall level of morning stiffness you have had from the time you wake up? How long does your morning stiffness last from the time you wake up? Calculation: ((Q1 + Q2 + Q3 + Q4) + (Q5 + Q6) ÷ 2) ÷ 5
BAS-G[23]	Please place a mark on the scale below to indicate the effect your disease has had on your well-being over the last week. Please place a mark on the scale below to indicate the effect your disease has had on your well-being over the last six months. Calculation: Each question represents a different timeframe and should be interpreted individually.
Spinal pain[10]	On average, last week, how much pain of your spine due to AS did you have? On average, last week, how much pain of your spine due to AS did you have at night? Calculation: Each question is usually interpreted individually.
Mini-BASDAI[18]	How would you describe the overall level of fatigue/tiredness you have experienced? How would you describe the overall level of AS neck, back or hip pain you have had? How would you describe the overall level of morning stiffness you have had from the time you wake up? How long does your morning stiffness last from the time you wake up? Calculation: ((Q1 + Q2) + (Q3 + Q4) ÷ 2) ÷ 3
ASDAS[20]	How would you describe the overall level of AS neck, back or hip pain you have had? How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had? How would you describe the overall level of morning stiffness you have had from the time you wake up? How active was your spondylitis on average during the last week? C-reactive protein level (mg/L) or erythrocyte sedimentation rate level (mm/h) Calculation ASDAS-CRP: 0.12 x Q1 + 0.07 x Q2 + 0.06 x Q3 + 0.11 x Q4 + 0.58 x Ln(CRP+1) Calculation ASDAS-ESR: 0.08 x Q1 + 0.09 x Q2 + 0.07 x Q3 + 0.11 x Q4 + 0.29 x √(ESR)

BASDAI questions relate to the past week, response is either on a 0-10 NRS or on 0-10cm VAS, from 'none' to 'very severe', except for the duration of morning stiffness in which the anchors are 'zero hours' and '2 or more hours'. The same applies to mini-BASDAI and ASDAS questions extracted from the BASDAI. The anchors for the spinal pain questions are 'no pain' and 'most severe pain'. ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BAS-G, Bath Ankylosing Spondylitis Patient Global Score; NRS, numerical rating scale; VAS, visual analogue scale; √(ESR), square root of the erythrocyte sedimentation rate (mm/h); Ln(CRP+1), natural logarithm of the C-reactive protein (mg/L) + 1.

into account. A modified version of the BASDAI (mini-BASDAI) without the questions about tender areas and joint pain/swelling has also been tested and did not perform better than the BASDAI.[17,18] BASDAI, mini-BASDAI, Bath Ankylosing Spondylitis Patient Global Score (BAS-G), spinal pain and ASDAS questions and calculation rules are presented in table 2.[10,19]

BASDAI has served the SpA community well for many years but its limitations led the ASAS group to develop a new composite measure for disease activity in axial SpA: the Ankylosing Spondylitis Disease Activity Score (ASDAS).[20,21] After this initial step, further validation and the development of clinically relevant cut-offs for the ASDAS became an important item on the axial SpA research agenda.

MRI has gained increasing importance over the last few years in the field of axial SpA due to its ability to show acute and chronic lesions that relate to axial SpA disease processes. Acute (inflammatory) lesions on MRI are best visualised by a short tau inversion recovery (STIR) sequence (bone oedema) or by a T1 post-gadolinium sequence (osteitis), while chronic lesions (fatty deposition/fat metaplasia, erosions, syndesmophytes and ankylosis) are best visualised by a T1-weighted turbo spin-echo sequence (Figure 1 and 2).[10,14] The recent MRI literature in axial SpA has focused on various disease aspects, namely the role of MRI for improved diagnosis, assessment of treatment effects, and predicting structural progression in patients with axial SpA.[22] New bone formation is a key feature of axial SpA that at the spinal level is represented by syndesmophyte formation/bridging, a type of lesion that is best seen on conventional radiographs. The possible association between MRI lesions of inflammation and fat metaplasia in the spine in relation to syndesmophyte formation/bridging (progression of structural damage) has emerged as one of the most intriguing and challenging research questions in the modern era of axial SpA.

Aims of this thesis

The work presented in this thesis has four objectives:

1. To improve and facilitate the assessment of disease activity in axial SpA using the ASDAS.
2. To increase our knowledge about the mutual relationships between health outcomes in axial SpA.
3. To increase our knowledge about the factors that influence phenotypic variability in axial SpA.
4. To clarify the relationship between MRI lesions and radiographic progression in axial SpA.

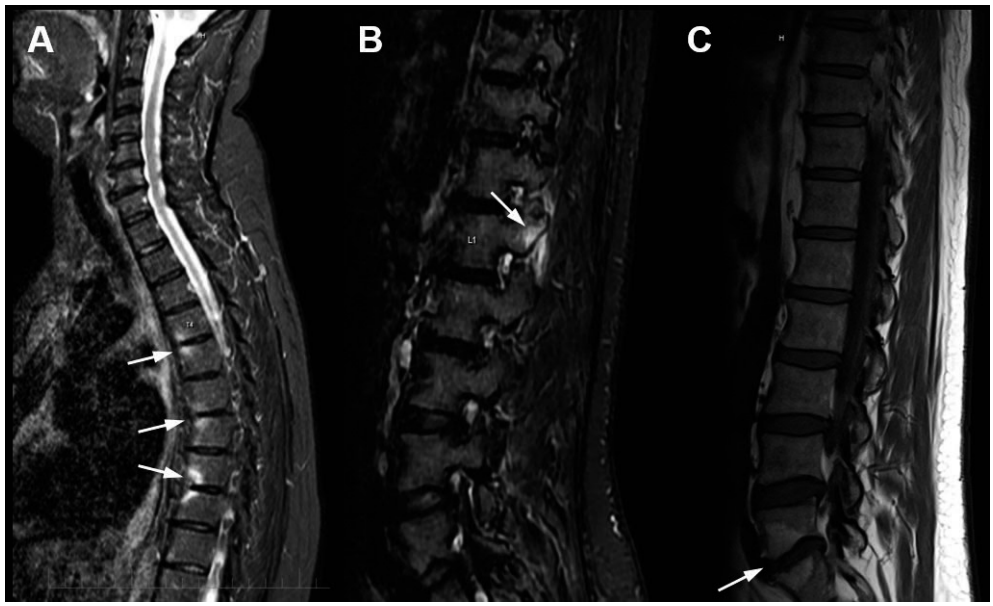

Figure 1. Anterior spondylitis (1A), STIR image showing corner bone marrow oedema at T4/5, T6/7 and T8/9. Arthritis of the zygoapophyseal joints (1B), STIR image showing inflamed facet joints at L1/2. Fatty deposition (1C), T1 image showing high signal intensity due to fatty deposition at L5/S1 anterior vertebral corners.[24]

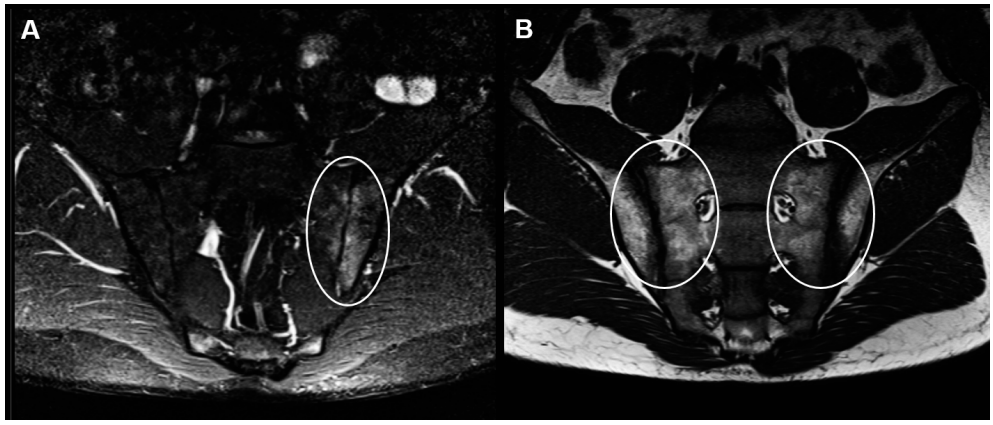

Figure 2. Left sacroiliitis (bone marrow oedema) in a patient with non-radiographic axial spondyloarthritis (2A), affected bone marrow areas (oval line) are located periarticularly (STIR). Fatty deposition in the same patient (2B), T1 image showing high signal intensity due to fatty deposition (oval lines) at both sacroiliac joints.[24]

This thesis focuses on the axial SpA subgroup, mainly on patients with AS. Three cohorts of patients have been studied:

1. The AS Study for the Evaluation of Recombinant infliximab Therapy (ASSERT) cohort[25]: ASSERT was a 24-week randomized controlled trial comparing infliximab monotherapy and placebo in patients with active AS, with an open extension until 102 weeks with all patients on infliximab. The ASSERT population includes patients with AS according to the modified New York criteria[26] with a BASDAI[15] and a spinal pain score ≥4 (range 0–10). Data from the ASSERT cohort is presented in **chapters 2, 4, 5, 6, 9, 10 and 11.**
2. The Norwegian Disease Modifying Anti-Rheumatic Drug (NOR-DMARD)[27] cohort: NOR-DMARD is a Norwegian register from 5 centers that includes consecutive patients with axial SpA (according to the treating rheumatologist) starting a new synthetic or biological DMARD regimen. Patients from the NOR-DMARD register are considered an appropriate representation of patients with axial SpA as seen by rheumatologists in Norway. Data from the NOR-DMARD cohort is presented in **chapter 2**.
3. The *Devenir des Spondyloarthropathies Indifférenciées Récentes* (DESIR) cohort[28]: DESIR is a longitudinal prospective cohort that includes adults aged over 18 and less than 50 years from 25 regional centers in France. Patients are required to have inflammatory back pain fulfilling either the Calin or Berlin criteria[29,30] with symptom duration more than 3 months and less than 3 years and symptoms suggestive of SpA according to the opinion of the local investigator. Data from the DESIR cohort is presented in **chapters 3, 7 and 8.**

Assessment of disease activity in axial SpA using the ASDAS

Due to the phenotypic heterogeneity of axial SpA and the possibility of the coexistence of several clinical manifestations, the use of single variables for disease activity assessment may lead to misrepresentation of disease activity. This is why composite indices can be useful tools for disease activity assessment in axial SpA. Composite scores integrate several different aspects of disease activity into one single numerical value, resulting in a more precise estimate of the construct 'disease activity' in comparison to the single variables of the composite score. Indices may also have the advantage of increased statistical power in clinical trials and observational studies. Furthermore, they improve the consistency of patient assessment and care across different clinical and research settings, and may help patients and doctors better understand the disease and its impact.[19,31-34]

The BASDAI has been the most widely used disease activity composite index in axial SpA.[15] However, it has limitations as mentioned above. The ASDAS is an algorithm that

combines elements of the BASDAI and patient global assessment with a laboratory measure of inflammation, either the C-reactive protein (CRP) level (preferred formula) or the erythrocyte sedimentation rate (ESR) (alternative formula).[20,21] The inclusion of an acute phase reactant in the ASDAS formula brings an objective component into the score. Moreover, ASDAS variables have different weights that take potential redundancy and dependency of variables into account, as a result of the statistical methods used to develop it (principal component analysis and discriminant function analysis).

The ASDAS has been developed by ASAS and several aspects of the truth, feasibility and discrimination of the score had already been tested when the work described in this thesis started.[20,21] However, clinically relevant cut-off values for disease activity states and response criteria using the ASDAS were still lacking. Such cut-offs are crucial to improve the interpretability and the clinical applicability of a continuous measure. The development of appropriate ASDAS cut-offs for disease activity states and response criteria and its validation in an independent dataset are described in **Chapter 2**.

ASDAS was developed and validated making use of conventional CRP (cCRP) tests. Lately, cCRP tests have increasingly been replaced by so-called high sensitivity (hs) CRP tests, both in clinical practice and in the research setting. However, it was unclear how differences between cCRP tests (with high detection limit) and hsCRP tests (with low detection limit) worked out with regards to the performance of the ASDAS. In **Chapter 3,** detailed analyses of how the ASDAS-CRP formula performs, of how low CRP values obtained by hsCRP influence the ASDAS-CRP, and of the agreement between different ASDAS formulae and imputation strategies, are presented. In addition, we have also determined the best way to calculate ASDAS-CRP when the cCRP level is below the limit of detection.

Knowledge about the mutual relationships between health outcomes in axial SpA

Measuring and monitoring health outcomes is of paramount importance in rheumatology and in medicine in general. Yet, quantifying health outcomes is a complex and challenging process. As mentioned above, the ASAS group has proposed several instruments to assess health outcomes in axial SpA.[11] These instruments cover distinct domains and are subdivided into core sets to be applied in different settings (table 1). These core sets include measures of physical function,[35] spinal mobility,[36] radiographic damage,[37,38] and several disease activity variables such as the assessment of spinal pain, patient global assessment of disease activity, the number of swollen joints, an enthesitis count, the duration of morning stiffness, the level of fatigue and acute phase reactants. Composite indices for measuring disease activity[19,33] and instruments to measure the level of MRI inflammation have also been developed for the assessment of axial SpA.[39,40] Understanding how health outcomes relate to each other in axial SpA and fit in a framework that allows their interpretation in a structured and integrated manner

would help to better understand the disease and the tools that we use to assess and monitor it.

Progressive limitation of spinal mobility is a hallmark of axial SpA and a predictor of poor long-term outcome. In **Chapter 4** we studied the determinants of limitation of spinal mobility in a large cohort of AS patients. An important novel aspect of this study was the inclusion of MRI spinal inflammation as one of the assessments/measures. Taking into account the possibility that spinal (MRI) inflammation may be an important and potentially reversible factor determining spinal mobility, we investigated the relationship between spinal mobility, radiographic damage of the spine and MRI spinal inflammation in patients with AS. This analysis was the starting point for further analyses looking at a broader spectrum of health outcomes. In **Chapter 5**, using a conceptual framework shared between several chronic diseases,[41,42] we investigated the relationship between health-related quality of life, physical function, clinical disease activity, spinal mobility and structural damage in detail and proposed a stratified model for health outcomes in AS.

MRI is currently considered a powerful tool to document treatment effects and the inflammatory burden of the disease; however, studies looking at the relationship between MRI inflammation scores and clinical and laboratorial disease activity assessments were scarce. In **Chapter 6**, using clinical and imaging cross-sectional and longitudinal data, we investigated the relationship between MRI inflammation and measures of clinical disease activity as well as treatment responses in patients with AS treated with a tumour necrosis factor alpha (TNF) blocker.

Knowledge about the factors that influence phenotypic variability in axial SpA

As mentioned above, the influence of HLA-B27 on the phenotype of axial SpA is controversial.[3,4] Furthermore, the contribution of HLA-B27 to the diagnosis, prognosis and management of axial SpA had previously been investigated mainly in AS but not in non-radiographic axial SpA. In **Chapter 7** we have analysed a cohort of patients with early axial SpA consisting of mainly patients with the non-radiographic form of the disease and investigated the contribution of HLA-B27 to phenotypic variability.

In addition to genetic factors, environmental factors may contribute to phenotypic variability. For example, in rheumatoid arthritis, smoking has reproducibly been linked to an increased risk of developing the disease and a gene-environment interaction between smoking and HLA-DRB1 shared epitope alleles´ has been described in several cohorts. This gene-environment interaction was only demonstrated in anti-citrullinated peptide antibody (ACPA)-positive and not in ACPA-negative disease, indicating that smoking may contribute to the pathway that is associated with ACPA-positive rheumatoid arthritis.[43,44]

Information on smoking influencing the outcome of axial SpA was scarce and the hypothesis that smoking could impact the outcome of patients with axial SpA had just been launched when the analyses reported in **Chapter 8** were published. This study aimed to determine the prevalence of smoking and its association with various clinical, functional and imaging outcomes in early axial SpA, including potential gene-environment interactions such as the interaction between smoking and HLA-B27 positivity.

Extra-articular manifestations belong to the typical picture of axial SpA, help the physician to recognize the disease and make a diagnosis, and may determine the prognosis and influence health outcomes in axial SpA. In **Chapter 9** we have focused on one extra-articular manifestation in particular - psoriasis. The main reason for doing that was that there had been few studies assessing the differences between axial SpA patients with and without concomitant psoriasis, and in this chapter we compared demographic, clinical and imaging characteristics between AS patients with and without this extra-articular manifestation.

Relationship between MRI lesions and radiographic progression in axial SpA

Structural damage in axial SpA is characterised by excessive bone formation, with syndesmophytes being the typical lesions.[45,46] The processes driving syndesmophyte formation are not completely understood.[47,48] One theory postulates that inflammation and osteoproliferation are related, and that initially, inflammation triggered by unknown stimuli (eg. mechanical stress or infectious agents) drives a bone catabolic process where the Wnt pathway and dickkopf-1 (Dkk-1) upregulation play a prominent role; later on, as inflammation fluctuates and is intermittently dampened, the bone catabolic process may give rise to a bone anabolic response characterized by reactive osteoproliferation.[49,50] Another theory suggests that inflammation and repair are unrelated phenomena and that the same triggers can independently activate inflammatory and stromal cells, with the activation of stromal cells leading to endochondral bone formation.[51] If inflammation is indeed the principal trigger of repair responses, a strong case can be made for early and/or prolonged anti-inflammatory treatment, namely with TNF-blockers. On the other hand, if inflammation and repair are independent pathways triggered by common factors, specific therapies targeting stromal pathways may be needed to prevent new bone formation in AS.

MRI provides an indirect and non-invasive method of investigating elements of the pathophysiology of new bone formation in AS. Fat deposition can be seen on T1-weighted sequences and bone marrow edema (reflecting inflammation) can be seen on T2-weighted sequences with fat suppression, such as the STIR sequence.[13,52,53] However, conventional radiography is still the gold-standard method to assess syndesmophyte formation/bridging[54] because tissues with low proton density such as cortical bone and paravertebral ligaments exhibit low or no signal intensity in all pulse sequences and are

difficult to differentiate on MRI scans.[55]

Understanding the axial SpA pathophysiological processes and elucidating the relationship between MRI lesions (particularly bone marrow oedema/osteitis - which is an inflammatory lesion - and fat deposition – which is a chronic lesion) and new bone formation have attracted much attention from the SpA scientific community. There is a large debate about whether stopping structural progression in axial SpA is therapeutically possible.[47,48]

In **Chapter 10**, we have initially investigated the relationship between inflammation on MRI and the formation/growth of syndesmophytes. We did so by looking at inflammation at the vertebral unit level and at the patient level and investigating its potential contribution to new bone formation in patients with AS treated with a TNF-blocker. This analysis was prompted by the results of two previous smaller studies showing an association between MRI inflammation and new bone formation in AS.[56,57] Subsequently, one additional study addressing this topic showed consistent results with previous publications.[58] After the publication of these 4 studies, advancing insight pointed to the potential importance of fat deposition in the sequel of inflammation and syndesmophyte formation.[59-61] We therefore decided to re-read all MRIs of the patients in the ASSERT study and to do a far more detailed assessment in order to be able to investigate the role of fatty lesions in this process. We scored all the ASSERT images at the vertebral corner level according to the presence or absence of MRI inflammation as well as fat deposition. In **Chapter 11,** we have analysed multiple combinations of MRI lesions at three different time points, including a sequence analysis, specifically addressing the hypothesis that vertebral corner inflammation could contribute to fat deposition which in turn could contribute to new bone formation.

A summary and general discussion about the findings of this thesis is presented in **Chapter 12**. A summary of this thesis in Dutch is provided in **Chapter 13**.

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Chapter 2

Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores

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ABSTRACT

Background

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a new composite index to assess disease activity in ankylosing spondylitis (AS). It fulfils important aspects of truth, feasibility and discrimination. Criteria for disease activity states and improvement scores are important for use in clinical practice, observational studies and clinical trials and so far have not been developed for the ASDAS.

Objectives

To determine clinically relevant cut-off values for disease activity states and improvement scores using the ASDAS.

Methods

For the selection of cut-offs data from the Norwegian disease modifying antirheumatic drug (NOR-DMARD) registry, a cohort of patients with AS starting conventional or biological DMARDs, were used. Receiver operating characteristic analysis against several external criteria was performed and several approaches to determine the optimal cut-offs used. The final choice was made on clinical and statistical grounds, after debate and voting by Assessment of SpondyloArthritis international Society members. Cross-validation was performed in NOR-DMARD and in Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy, a database of patients with AS participating in a randomised placebo-controlled trial with a tumour necrosis factor blocker.

Results

Four disease activity states were chosen by consensus: inactive disease, moderate, high and very high disease activity. The three cut-offs selected to separate these states were: 1.3, 2.1 and 3.5 units. Selected cut-offs for improvement were: change ≥1.1 units for clinically important improvement and change ≥2.0 units for major improvement. Results of the cross-validation strongly supported the cut-offs.

Conclusion

Cut-off values for disease activity states and improvement using the ASDAS have been developed. They proved to have external validity and a good performance compared to existing criteria.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that affects the axial skeleton. It is characterised by inflammatory back pain, bony fusion of the spine, decreased mobility, functional impairment and decreased quality of life. Other clinical features of AS include asymmetric peripheral oligoarthritis, enthesitis, fatigue and specific organ involvement such as anterior uveitis, psoriasis and chronic inflammatory bowel disease.[1]

The concept of disease activity, a reflection of the underlying inflammation, encompasses a wide range of domains and measures.[2] Since currently used single component measures or indices have limitations because they measure only one aspect of the disease, are fully patient or doctor oriented, or lack face and/or construct validity, the Assessment of SpondyloArthritis international Society (ASAS) has developed a new disease activity score for use in AS: the 'Ankylosing Spondylitis Disease Activity Score' (ASDAS).[3]

Designed in analogy of the DAS[4] for rheumatoid arthritis (RA), the ASDAS is a composite index with continuous measurement properties. The development process resulted in four candidate ASDAS scores,[3] all of them fulfilling important aspects of truth, feasibility and discrimination.[3,5] The ASAS membership has selected the ASDAS with C-reactive protein (CRP) as the preferred version and with erythrocyte sedimentation rate (ESR) as the alternative version.[3]

In order to increase interpretability, a disease activity measure requires criteria for identifying 'disease activity states' (or 'status') and 'improvement' (or 'response criteria'). Improvement scores help to determine whether treatments really work, that is whether they actually produce clinically important improvement, allowing investigators, clinicians, regulators and patients to determine the efficacy (or lack thereof) of a given intervention and to communicate about response using the same metric.[6] Disease activity states measure clinical disease activity at specific timepoints. They are important for supporting decisions about entry into clinical trials, for supporting treatment changes and for defining therapeutic goals. Furthermore, in light of recent therapeutic advances and the increasing potential to improve the outcomes of patients with AS, the definition of criteria for disease states according to the ASDAS is highly relevant, as the prognosis may be different in patients depending on the disease activity states they attain, even if the same level of improvement is achieved. This observation highlights the importance of reporting disease activity states and not just absolute and categorical therapeutic responses, an important concept that has been clearly demonstrated in RA.[7]

Criteria for disease activity states and improvement scores are therefore important for use in clinical practice, observational studies and clinical trials and so far have not

been developed for the ASDAS. In the present study, we evaluated clinically relevant cut-off values for disease activity states and improvement scores using both forms of the ASDAS.

PATIENTS AND METHODS

ASDAS calculation

The ASDAS formulae[3] are as follows:

ASDAS-CRP (the preferred version):

0.12 × Back Pain + 0.06 × Duration of Morning Stiffness + 0.11 × Patient Global + 0.07 × Peripheral Pain/Swelling + 0.58×Ln(CRP+1)

ASDAS-ESR (the alternative version):

0.08 × Back Pain + 0.07 × Duration of Morning Stiffness + 0.11 × Patient Global + 0.09 × Peripheral Pain/Swelling + 0.29 × √(ESR)

CRP is in mg/litre, ESR is in mm/h; the range of other variables is from 0 to 10; Ln represents the natural logarithm; √ represents the square root.

Nomenclature for ASDAS disease activity states and improvement scores

During the 2010 ASAS workshop in Berlin, Germany, upon presentation of results and discussion, four disease activity states and two improvement scores were chosen by consensus: (1) disease activity states: 'inactive disease', 'moderate disease activity', 'high disease activity' and 'very high disease activity'; and (2) improvement scores: 'minimal clinically important improvement' (MCII) and 'major improvement'.

Study population used for the selection of cut-offs

For the selection of cut-offs we used data from the Norwegian disease modifying antirheumatic drug (NOR-DMARD) register[8,9] a Norwegian five-centre register that includes consecutive patients with AS (according to the treating doctor) starting a new conventional or biological DMARD regimen. Measures of disease activity and health status are assessed at baseline, 3, 6, 12 months and yearly thereafter. Patients from the NOR-DMARD register are an appropriate representation of patients with AS in general, as seen by rheumatologists in Norway. Of the patients from NOR-DMARD that we analysed, 69% were men, 90% were positive for human leucocyte antigen (HLA)-B27, the mean (SD) age was 43.3 (10.7) years and the mean disease duration since diagnosis

was 12.0 (10.6) years. Detailed characteristics of patients included in NOR-DMARD have been described previously.[8,9]

In order to have the best representation of the disease activity states being studied, 3-month data (n=331–336) were used to select the cut-off for 'inactive disease' and between 'moderate' and 'high disease activity', while baseline data (n=467–477) were only used to select the cut-off for 'very high disease activity'. The reason for this choice was because the large majority of patients from NOR-DMARD had (very) active disease at baseline (eg, none of the patients fulfilled ASAS partial remission criteria). Change scores between baseline and 3-month assessment (n=295) were used to select the cut-offs for improvement. The development of cut-offs was performed using ASDAS-CRP, the preferred ASDAS version.

Study populations used for cross-validation of the cut-offs

Cross-validation was performed in NOR-DMARD (with an additional timepoint at 6 months) and in an 80% random sample of the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) cohort (n=219–223).[10] In brief, ASSERT was a randomised 24-week placebo-controlled trial with infliximab that included patients with AS (according to the modified New York criteria[11]) with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[12] and a spinal pain score ≥4 (range 0–10). The ASSERT population was typical of patients with moderate to severe AS. Of the patients from ASSERT that we analysed, 79% were men, 89% were positive for HLA-B27, the mean (SD) age was 39.3 (10.1) years and the mean disease duration was 10.6 (8.7) years. Detailed characteristics of patients in the ASSERT trial have been described previously.[10] For the validation we used baseline, 12-week and 24-week data.

The validation of the cut-offs was performed for ASDAS-CRP and ASDAS-ESR. Owing to the statistical approach used in the development of the ASDAS formulae,[3] it was expected that the cut-offs developed with ASDAS-CRP would also be applicable to ASDAS-ESR.

Measurement instruments

Patient assessment of global disease activity and the six individual questions of the BASDAI were available in NOR-DMARD and ASSERT. The range of all scores is from 0 to 10. CRP (mg/litre) was also available in both databases, while ESR (mm/h) and physician's global assessment of disease activity were only available in NOR-DMARD. With these assessments, ASDAS-CRP could be calculated in both databases while ASDAS-ESR could only be calculated in NOR-DMARD.

In previous studies concerning the ASDAS,[3,5] no description has been given as to how values below the CRP threshold of detection should be handled. This has now been

studied and we recommend that in such cases half of the value of the threshold should be used (eg, if the limit of detection is 4 mg/litre, a value of 2 should be used). The use of the high sensitivity CRP assay is preferred.

The Bath Ankylosing Spondylitis Functional Index (BASFI)[13] was also available in both databases, allowing us to calculate ASAS partial remission and ASAS response criteria.[14 15] Moreover, having BASDAI total score available, we were also able to calculate response measures used for the evaluation of efficacy of anti-tumour necrosis factor (TNF) treatment in clinical practice, based on the BASDAI, that is the proportion of patients who had at least 2 units improvement (ΔBASDAI≥2) or at least 50% improvement (BASDAI50).

Use of the receiver operating characteristic analysis for the selection of cut-offs in NOR-DMARD

As there is no universal gold standard to assess disease activity in AS, we performed receiver operating characteristic (ROC) analysis against predefined external criteria considered to be representative of the various diseases activity states. Because ASDAS cut-offs should be representative of the perspectives of patients and doctors, we used the patient and physician global assessments at predefined levels (<1, <3 and >6 cm) as external constructs for 'inactive disease', to separate 'moderate' from 'high disease activity' and for 'very high disease activity', respectively. Additionally, for determining the cut-off for 'inactive disease' we also used ASAS partial remission as an external criterion (table 1).

One of the questions from ASAS members was about estimating the relationship between BASDAI and ASDAS as the BASDAI cut-off of 4 has been extensively used in trials with TNF blockers to determine 'high disease activity'. Therefore, we compared BASDAI (<3, <3.5 and <4 cm) with the cut-off between 'moderate' and 'high disease activity' (table 1).

Regarding improvement, the most frequently recommended external criterion for ROC analysis (an anchor-based approach) is the 'global rating of change' (GRC), a Likert-type scale scored for change by the patient.[16–18] In NOR-DMARD such a scale is available in the form of a unique question where patients score the change in their health status according to five categories: 'much better', 'better', 'unchanged', 'worse' and 'much worse'. For the ROC analysis, external anchors were constructed by dichotomising the rating scale for change in two different ways: a cut-off between 'much better/better' and 'unchanged/worse/much worse' in order to determine 'MCII', and a cut-off between 'much better' and 'better/unchanged/worse/much worse' to determine 'major improvement'. Moreover, we used the entire cohort in the ROC analysis, rather than just the two groups adjacent to the dichotomisation point because it has been shown that

this procedure maximises precision and yields a more logical estimate of the cut-offs.[19] The same principle was used in the ROC analysis for disease activity states.

We applied three methods of 'optimal' cut-off determination: (1) fixed 90% specificity, (2) the Youden index and (3) the closest point to (0,1), that is the point where the shoulder of the ROC curve is closest to the left upper corner of the graphic. The first method is particularly important in the clinical context (you try to avoid that patients in low/moderate disease activity are misclassified as inactive), while the last two methods provide the best balance between sensitivity and specificity.[20–22]

Comparison of the cut-off for 'MCII' obtained by the ROC method with 'minimal detectable improvement' obtained by other methods

The ROC method assesses which change on the measurement instrument corresponds with an important/meaningful change defined by the anchor, in this case the patient.[23] This is higher in hierarchy than 'minimal detectable improvement' based on measurement precision.[18] However, it is important to assure that the 'MCII' lies within boundaries that can be assessed beyond measurement error.[23] Therefore, we compared 'MCII' obtained by the ROC method with various methods of determining 'minimal detectable improvement' and used this to benchmark the choice of the cut-off value for 'MCII'.

Comparison was made with the 'mean change' (a less reliable anchor-based approach)[24] and several distribution based approaches: the 'Wyrwich standard error of measurement',[25] the 'Jacobson's reliable change index',[26] the '0.5*SD approach',[27] and the 'smallest detectable change approach'[28] (supplementary table 1).

Cross-validation study

Cross-validation was performed in NOR-DMARD and ASSERT for ASDAS-CRP and in NOR-DMARD for ASDAS-ESR. In order to allow comparisons between ASDAS-CRP and ASDAS-ESR, only patients with both values available were used for cross-validation in NOR-DMARD. However, including all patients with obtainable data for each ASDAS version (approximately 10% more patients) the results were similar (data not shown). Several cross-validation approaches were used:

1. Calculation of sensitivity and specificity of ASDAS cutoff values in comparison with several other criteria at different timepoints.
2. Assessment of the longitudinal distribution of patients over ASDAS disease activity states before and after start of treatment.
3. Mean values of BASDAI and ASDAS across the four ASDAS disease activity states.
4. Percentage of patients achieving ASDAS improvement criteria ('MCII' and 'major improvement') in comparison to other widely used improvement

criteria (ΔBASDAI≥2, BASDAI50, ASAS20 and ASAS40), 3 and 6 months after start of treatment.

5. In order to assess discriminative power, χ^2 and p values were calculated for the differences between placebo and infliximab in ASSERT. SPSS V.17.0 (SPSS, Chicago, Illinois, USA) was used in all statistical analysis.

RESULTS

Selection of the optimal cut-offs for disease activity states and improvement scores

The cut-offs for the various external criteria, according to fixed 90% specificity, Youden index and closest point to (0,1) are presented in table 1. The 90% specificity criterion was considered to be the most clinically relevant cut-off for 'inactive disease', to separate 'moderate' from 'high disease activity' and for improvement scores. In these cases, specificity is clinically more important in order to reduce the risk of misclassifying patients whose disease remains active (or who have not really improved) according to the external construct. Regarding the cut-off for 'very high disease activity', we considered that it would be better to have the best balance between sensitivity and specificity.

The definite choice for appropriate cut-offs was facilitated by consistent results across all external criteria (table 1). Such concordance between patient and physician global scores (and ASAS partial remission criteria, in the case of 'inactive disease') adds to the robustness of our results.

The three cut-offs for disease activity states selected after debate and voting by ASAS members were as follows: <1.3 between 'inactive disease' and 'moderate disease activity', <2.1 between 'moderate' and 'high disease activity' and >3.5 between 'high' and 'very high disease activity' (figure 1A). The cut-off between 'moderate' and 'high disease activity' (<2.1 units) corresponded to a BASDAI cut-off of <3.5 cm (table 1).

The cut-offs selected for improvements were: change of ≥1.1 units for 'MCII' and change of ≥2.0 units for 'major improvement' (figure 1B). Importantly, the cut-off for 'MCII' exceeded the 'minimal detectable improvement' based on measurement error, which ranged from 0.4 to 1.1 (supplementary table 1).

Cross-validation results

Regarding ASDAS-CRP, the cut-offs developed in NOR-DMARD at 3 months showed similar results in terms of sensitivity and specificity against the same (and other)

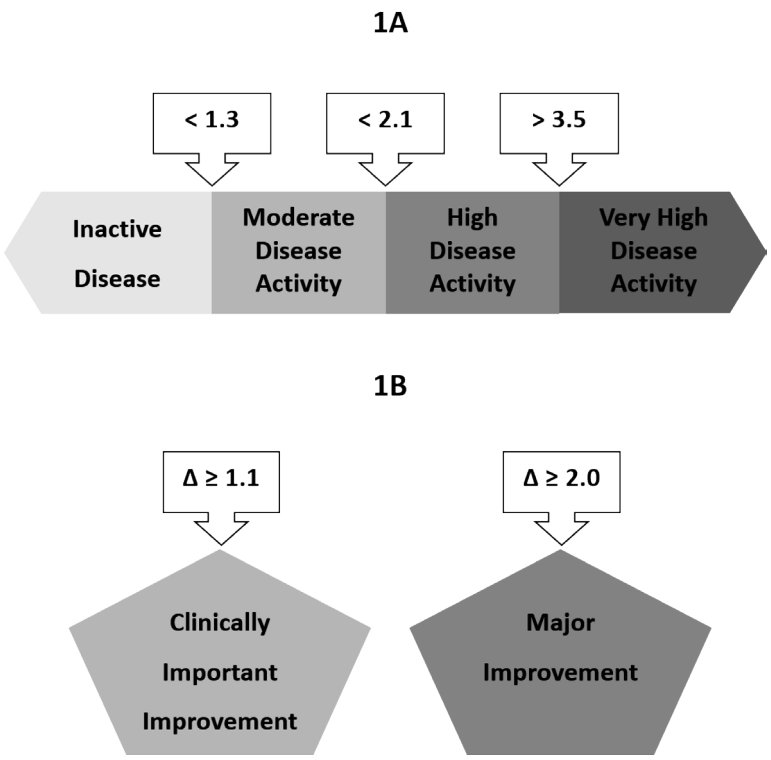

Figure 1. Selected cut-offs for (A) disease activity states and (B) improvement scores according to the Ankylosing Spondylitis Disease Activity Score (ASDAS). Every improvement beyond the 'minimal clinically important improvement' is a 'clinically important improvement'.

external constructs in NOR-DMARD at 6 months and in ASSERT at 3 and 6 months (table 2). Noticeably, results in ASSERT often surpassed the results in NOR-DMARD, yielding higher sensitivities (above 80%) while retaining the same level of specificity (approximately 90%). For the cut-off between 'high' and 'very high disease activity' (analysis only preformed at baseline) the slightly lower concordance probably reflects the higher subjectivity of the cut-off and a different selection criterion for the 'optimal' cut-off.

The longitudinal distribution of ASDAS-CRP disease activity states in both databases (table 3) showed a clinically and statistically significant shift of treated patients from higher disease activity states towards lower disease activity states. Interestingly, in the longitudinal analysis of ASSERT, the differences between the infliximab and placebo groups clearly discriminate between the two treatment arms: at 6-month follow-up 31.9% (infliximab) versus 0% (placebo) of the patients had 'inactive disease' ($p<0.001$), while 12.3% (infliximab) versus 53.6% (placebo) had 'very high disease activity' ($p<0.001$).

Table 1. ROC analysis: ASDAS cut-offs for disease activity states and improvement scores according to several external criteria and according to three different methods of 'optimal' cut-off determination

ASDAS cut-offs and external criteria	n (P+N)	90% SP (SE/SP)	Youden (SE/SP)	(0,1) (SE/SP)	AUC (95% CI)
Cut-off between 'inactive disease' and 'moderate disease activity':					
ASAS partial remission	336 (74+262)	**<1.29** (64.9/90.1)	<1.60 (90.5/81.3)	<1.54 (89.2/82.4)	0.91 (0.88 to 0.94)
Patient global <1	336 (77+259)	**<1.35** (75.3/90.0)	<1.52 (87.0/84.1)	<1.52 (87.0/84.2)	0.91 (0.88 to 0.94)
Physician global <1	331 (113+218)	**<1.29** (44.2/89.9)	<1.95 (77.0/71.1)	<1.95 (77.0/71.1)	0.79 (0.74 to 0.84)
Cut-off between 'moderate' and 'high disease activity':					
Patient global <3	336 (179+157)	**<2.08** (79.3/89.8)	<2.46 (93.3/77.7)	<2.36 (89.9/80.9)	0.94 (0.92 to 0.96)
Physician global <3	331 (258+73)	**<2.14** (59.7/90.4)	<2.58 (75.2/80.8)	<2.58 (75.2/80.8)	0.84 (0.79 to 0.89)
BASDAI <3	337 (154+183)	<1.94 (86.4/90.1)	<1.83 (85.1/92.3)	<2.05 (88.3/88.5)	0.94 (0.92 to 0.97)
BASDAI <3.5	336 (181+155)	**<2.17** (85.1/89.7)	<2.14 (83.4/91.6)	<2.17 (85.1/89.7)	0.95 (0.92 to 0.97)
BASDAI <4	336 (202+134)	**<2.24** (82.7/90.3)	<2.15 (79.7/94.8)	<2.34 (86.1/88.1)	0.94 (0.92 to 0.97)
Cut-off between 'high' and 'very high disease activity':					
Patient global >6	477 (220+257)	>3.75 (61.4/89.9)	**>3.58** (71.8/84.4)	**>3.53** (73.6/82.5)	0.86 (0.83 to 0.89)
Physician global >6	467 (55+412)	>4.62 (30.9/90.1)	**>3.33** (87.3/52.4)	**>3.50** (80.0/60.0)	0.74 (0.67 to 0.81)
Cut-off for 'clinically important improvement':					
Better or much better*	295 (209+86)	**≥1.12** (63.6/89.5)	≥1.12 (63.6/89.5)	≥0.68 (76.1/76.7)	0.84 (0.79 to 0.88)
Cut-off for 'major improvement':					
Much better*	295 (91+204)	**≥2.01** (56.0/90.2)	≥1.32 (83.5/75.0)	≥1.32 (83.5/75.0)	0.85 (0.80 to 0.90)

ASAS partial remission criteria are fulfilled if the value of the following four domains is below 2 (range 0–10): spinal pain, physical function measured by the BASFI, patient global assessment and inflammation measured as the mean of the last two BASDAI questions (severity and duration of morning stiffness).
*External criterion based on a unique NOR-DMARD question, in which patients rated the perceived change in their health status since the start of treatment on a five-point Likert-type scale (much better, better, unchanged, worse, much worse). The chosen cut-offs are highlighted in bold. Range of BASDAI and patient and physician global assessment is 0–10.
(0,1), cut-off according to the closest point to (0,1) criterion; 90% SP, cut-off according to the 90% specificity criterion; ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; AUC, area under the curve; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; P+N, number of positive+negative results according to the external criterion; ROC, receiver operating characteristic; SE, sensitivity; SP, specificity; Youden, cut-off according to the Youden index criterion.

Table 2. Sensitivity and specificity of ASDAS cut-off values for disease activity states and levels of improvement against several external criteria in NOR-DMARD and ASSERT

		NOR-DMARD (ASDAS-CRP)			NOR-DMARD (ASDAS-ESR)			ASSERT (ASDAS-CRP)		
ASDAS cut-offs and external criterion	**Timepoint**	**SE**	**SP**	**n**	**SE**	**SP**	**n**	**SE**	**SP**	**n**
ASDAS <1.3:										
ASAS partial remission	3 Months	66.7	88.8	310	78.3	86.3	310	80.6	92.3	219
	6 Months	60.0	91.2	192	82.2	91.2	192	87.2	90.0	219
Patient global <1	3 Months	69.9	90.7	310	71.2	85.2	310	82.1	89.6	220
	6 Months	67.5	85.6	207	80.0	82.6	207	81.3	86.1	219
Physician global <1	3 Months	44.4	88.3	305	56.5	87.8	305	–	–	–
	6 Months	71.9	85.6	199	84.4	82.6	199	–	–	–
ASDAS <2.1:										
Patient global <3	3 Months	80.4	87.3	310	91.7	80.3	310	81.7	90.6	220
	6 Months	83.6	89.7	207	93.6	85.6	207	87.2	83.5	220
Physician global <3	3 Months	59.3	88.7	305	70.0	83.9	305	–	–	–
	6 Months	84.3	89.7	199	94.1	85.6	199	–	–	–
ASDAS >3.5:										
Patient global >6	Baseline	74.8	79.2	442	59.4	88.3	442	85.2	58.0	223
Physician global >6	Baseline	79.2	59.4	432	67.9	71.5	432	–	–	–
ΔASDAS ≥1.1:										
Better or much better	3 Months	62.7	86.7	252	63.8	80.0	252	–	–	–
	6 Months	61.7	96.8	164	60.2	90.3	164	–	–	–
ASAS20	3 Months	84.5	83.8	258	86.2	80.3	258	83.6	87.0	220
	6 Months	83.3	79.3	165	85.9	81.6	165	84.1	90.3	219
ΔASDAS ≥2.0:										
Much better	3 Months	56.4	90.2	252	59.0	93.7	252	–	–	–
	6 Months	53.8	90.2	164	50.0	91.1	164	–	–	–
ASAS40	3 Months	64.9	93.9	258	61.0	94.5	258	86.5	80.8	220
	6 Months	60.4	93.8	165	54.7	93.8	165	83.7	90.2	219

ASAS20 and ASAS40 response criteria are based on four independent domains: spinal pain, physical function measured by the BASFI, patient global assessment and inflammation measured as the mean of the last two BASDAI questions (severity and duration of morning stiffness); ASAS20 treatment response is defined as improvement of ≥20% and ≥1 unit (range 0–10) in at least three of the four above domains, and no worsening of ≥20% and ≥1 unit in the remaining fourth domain; ASAS40 treatment response is defined as improvement of ≥40% and ≥2 units in at least three of the four above domains, and no worsening in the remaining fourth domain; ASAS partial remission criteria are fulfilled if the value for all four domains is below 2. Range of patient and physician global assessment is 0–10. ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASSERT, Ankylosing Spondylitis Study for the Evaluation of Recombinant Infl iximab Therapy; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NOR-DMARD, Norwegian register of disease modifying antirheumatic drugs.

Table 3. Longitudinal distribution of ASDAS disease activity states (%) in NOR-DMARD and ASSERT

Timepoint	N	ASAS partial remission	ASDAS<1.3	1.3≤ASDAS<2.1	2.1≤ASDAS≤3.5	ASDAS>3.5
NOR-DMARD (ASDAS-CRP):						
Baseline	442	1.6	1.6	7.2	45.7	45.5
3 Months	310	22.3	23.5	25.8	32.6	18.1
6 Months	192	23.4	20.8	25.0	35.9	18.2
NOR-DMARD (ASDAS-ESR):						
Baseline	442	1.6	2.0	11.3	53.2	33.5
3 Months	310	22.3	28.1	30.6	31.0	10.3
6 Months	192	23.4	26.0	27.1	33.9	13.0
ASSERT (ASDAS-CRP):						
Baseline	223	0	0	1.3	29.1	69.5
3 Months	219	16.4	19.6	20.5	38.8	21.0
6 Months	219	17.8	23.7	20.5	32.9	22.8
ASSERT (ASDAS-CRP) infliximab vs placebo (χ^2, p value):						
Baseline	166 vs 57	0 vs 0 (NA)	0 vs 0 (NA)	1.2 vs 1.8 (0.1, 0.756)	30.1 vs 26.3 (0.3, 0.586)	68.7 vs 71.9 (0.2, 0.645)
3 Months	163 vs 56	21.5 vs 1.8 (11.8, 0.001)	25.8 vs 1.8 (15.2, <0.001)	26.4 vs 3.6 (13.3, <0.001)	38.7 vs 39.3 (0.01, 0.933)	9.2 vs 55.4 (53.5, <0.001)
6 Months	163 vs 56	23.3 vs 1.8 (13.2, <0.001)	31.9 vs 0 (23.4, <0.001)	23.3 vs 12.5 (3.0, 0.084)	32.5 vs 33.9 (0.04, 0.846)	12.3 vs 53.6 (40.6, <0.001)

ASAS partial remission criteria are fulfilled if the value of the following four domains is below 2 (range 0–10): spinal pain, physical function measured by the BASFI, patient global assessment and inflammation measured as the mean of the last two BASDAI questions (severity and duration of morning stiffness).
ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASSERT, Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NOR-DMARD, Norwegian register of disease modifying antirheumatic drugs.

Moreover, 'inactive disease' according to the ASDAS had higher discriminatory capacity (χ^2=23.4, p<0.001) than ASAS partial remission criteria (χ^2=13.2, p<0.001).

Comparison of BASDAI and ASDAS mean values across the four ASDAS activity states during follow-up (table 4) showed that ASDAS disease activity states were in agreement with clinically relevant numerical differences in BASDAI mean values: BASDAI mean value for ASDAS 'inactive disease' ranged from 0.78 to 1.12, while for ASDAS 'very high disease activity' it ranged from 6.93 to 7.29 (scale 0–10).

Finally, in both databases, ASDAS 'MCII' (ΔASDAS≥1.1) was able to identify more patients with clinically meaningful improvement than the classical criteria: for example in ASSERT at 6-month follow-up, 57.5% of patients achieved ASDAS 'MCII', while 51.6%, 41.6% and 52.5% achieved ΔBASDAI≥2, BASDAI50 and ASAS20, respectively (table 5). ASDAS 'MCII' was also able to discriminate better between infliximab and placebo groups when compared to classical response criteria (higher χ^2 values). Regarding ASDAS 'major improvement' (ΔASDAS≥2.0) it was often a more stringent criterion than ASAS40, supporting its validity as a measure of large improvement. Moreover, similarly to the 'MCII' cut-off, it showed a higher capacity to discriminate between active and placebo groups compared to usual response criteria (higher χ^2 values).

Regarding ASDAS-ESR, overall the results of the cross-validation in NOR-DMARD were very similar to ASDAS-CRP (tables 2–5). No relevant differences were observed for 'improvement cut-offs', while regarding the cut-off values for disease activity states, ASDAS-ESR showed a trend to categorise slightly more patients in lower disease activity states compared to ASDAS-CRP (eg, in NOR-DMARD at 6 months 26.0% had 'inactive disease' according to ASDAS-ESR and 20.8% according to ASDAS-CRP) and slightly less patients in higher disease activity states (13.0% had 'very high disease activity' according to ASDAS-ESR and 18.2% according to ASDAS-CRP).

Table 4. BASDAI and ASDAS mean values and SD across the four ASDAS disease activity states in NOR-DMARD (n=310 at 3 months, n=192 at 6 months) and ASSERT (n=219 at 3 and 6 months)

	NOR-DMARD (ASDAS-CRP)		NOR-DMARD (ASDAS-ESR)		ASSERT (ASDAS-CRP)	
Disease activity states	**BASDAI (mean±SD)**	**ASDAS (mean±SD)**	**BASDAI (mean±SD)**	**ASDAS (mean±SD)**	**BASDAI (mean±SD)**	**ASDAS (mean±SD)**
ASDAS <1.3 (3 months)	1.09±0.87	0.94±0.26	1.12±0.79	0.92±0.21	0.97±0.65	0.94±0.22
ASDAS <1.3 (6 months)	1.01±0.67	0.90±0.29	1.04±0.73	0.91±0.22	0.78±0.60	0.95±0.20
1.3≤ASDAS<2.1 (3 months)	2.17±1.26	1.62±0.22	2.60±1.30	1.66±0.24	2.38±0.99	1.65±0.23
1.3≤ASDAS<2.1 (6 months)	2.37±1.23	1.64±0.22	2.78±1.15	1.67±0.20	2.53±1.06	1.70±0.24
2.1≤ASDAS≤3.5 (3 months)	4.40±1.55	2.67±0.38	5.29±1.51	2.75±0.41	4.87±1.55	2.78±0.40
2.1≤ASDAS≤3.5 (6 months)	4.59±1.73	2.75±0.41	5.23±1.62	2.73±0.42	4.92±1.40	2.80±0.39
ASDAS>3.5 (3 months)	6.93±1.33	4.12±0.63	7.29±1.34	4.31±0.62	7.07±1.57	4.31±0.57
ASDAS>3.5 (6 months)	7.04±1.42	4.23±0.58	7.24±1.53	4.20±0.52	7.19±1.31	4.33±0.63

ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASSERT, Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NOR-DMARD, Norwegian register of disease modifying antirheumatic drugs.

Table 5. Percentage of patients achieving ASDAS improvement criteria and classical improvement criteria in NOR-DMARD and ASSERT

	NOR-DMARD (ASDAS-CRP)		NOR-DMARD (ASDAS-ESR)		ASSERT (ASDAS-CRP)		ASSERT (ASDAS-CRP) infliximab vs placebo			
Improvement criterion	**3 Months (n=258)**	**6 Months (n=165)**	**3 Months (n=258)**	**6 Months (n=165)**	**3 Months (n=220)**	**6 Months (n=219)**	**3 Months (n=164 vs 56)**	**χ^2 (p value)**	**6 Months (n=163 vs 56)**	**χ^2 (p value)**
ΔASDAS≥1.1	46.9	50.3	49.6	50.3	58.2	57.5	71.3 vs 19.6	45.9 (<0.001)	69.3 vs 23.2	36.3 (<0.001)
ΔASDAS≥2.0	23.6	23.6	22.1	21.8	33.6	39.3	43.9 vs 3.6	30.4 (<0.001)	50.9 vs 5.4	36.3 (<0.001)
ΔBASDAI≥2	43.0	43.6	43.0	43.6	50.9	51.6	60.4 vs 23.2	23.1 (<0.001)	62.6 vs 19.6	30.8 (<0.001)
BASDAI50	36.8	39.4	36.8	39.4	40.5	41.6	50.6 vs 10.7	27.6 (<0.001)	51.5 vs 12.5	26.1 (<0.001)
ASAS20	45.0	47.3	45.0	47.3	54.1	52.5	64.0 vs 25.0	25.6 (<0.001)	63.2 vs 21.4	29.2 (<0.001)
ASAS40	29.8	32.1	29.8	32.1	41.8	38.8	50.6 vs 16.1	20.5 (<0.001)	47.2 vs 14.3	19,1 (<0.001)

ASAS20 and ASAS40 response criteria are based on four independent domains: spinal pain, physical function measured by the BASFI, patient global assessment and inflammation measured as the mean of the last two BASDAI questions (severity and duration of morning stiffness); ASAS20 treatment response is defined as improvement of ≥20% and ≥1 unit (range 0–10) in at least three of the four above domains, and no worsening of ≥20% and ≥1 unit in the remaining fourth domain; ASAS40 treatment response is defined as improvement of ≥40% and ≥2 units in at least three of the four above domains, and no worsening in the remaining fourth domain; ASAS partial remission criteria are fulfilled if the value for all four domains is below 2.

ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASSERT, Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NOR-DMARD, Norwegian register of disease modifying antirheumatic drugs.

DISCUSSION

This study sought to determine cut-off values for disease activity states and improvement scores in AS based on the ASDAS. The definition of such criteria is of clinical and scientific importance.[6,7] We developed the cut-offs in a routine care population of patients with AS (NOR-DMARD) and validated them in the same population at a different timepoint and in a TNF blocker trial population (ASSERT). The fact that the cut-offs preformed at least as good in the trial population enhances their potential for application in both settings. Noticeably, the results of the cross-validation with ASDAS-CRP and ASDAS-ESR were very similar, supporting the use of the same cut-offs with both ASDAS versions.

The cut-offs were developed on clinical and statistical grounds and showed a remarkable consistence between the various external constructs that were used. Regarding improvement cut-offs, the availability of a GRC questionnaire in NOR-DMARD allowed us to use the most adequate gold standard for this purpose.[17,18,29] Importantly, the cut-off for 'MCII' was beyond borders of measurement error according to all tested methods.

ASDAS categories will facilitate studying the impact of disease activity states on prognosis. Furthermore, the cut-off for 'inactive disease' may be an important guideline for achieving a therapeutic aim. Compared to ASAS partial remission criteria, ASDAS 'inactive disease' has the advantage of being independent of BASFI: patients with a lot of structural damage that (as a consequence) have a high BASFI[30] may never achieve ASAS partial remission, while they may more easily achieve 'inactive disease'. In light of the results of the cross-validation, the new ASDAS-based improvement cut-offs may also facilitate the discrimination between treatment arms in clinical trials, and therefore result in smaller sample sizes.

The major limitation of our study is probably the lack of a universal and broadly accepted 'gold standard' for clinical disease activity in AS. However, we believe that the use of patient and physician global assessments as external constructs and their remarkable consistence for the selection of cut-offs overcomes this limitation. The use of arbitrary cut-offs for the external constructs may also be argued, but this was the only possible approach and the predefined cut-offs were discussed and accepted by ASAS members as representative of the disease activity states under study.

In summary, cut-off values for disease activity states and levels of improvement have been developed for the ASDAS. These cut-offs have proven to have external validity and a good performance in cross-validation. They have been endorsed by ASAS and are now ready to be used in clinical practice, observational studies and clinical trials.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. ASDAS minimal detectable improvement

Method for calculating MDI	Measurement error
Mean change of stable patients between 0-3 months	1.05
Wyrwich SEM	0.41
Jacobson's RCI	1.13
0.5*SD of change between 0-3 months	0.62
SDC of stable patients between 0-3 months	1.06

MDI, minimal detectable improvement; ASDAS, Ankylosing Spondylitis Disease Activity Score; SEM, standard error of measurement; RCI, reliable change index; SD, standard deviation; SDC, smallest detectable change. Mean change: the minimal detectable improvement (MDI) is the mean Δscore of patients who had small improvement ('better' on the global rating of change). Wyrwich SEM: MDI= SD_{BL} x (√[1-r]). Jacobson's RCI: MDI= 1.96 x SD_{BL} x (√(2 x [1-r])). 0.5 SD approach: the MDC is 0.5 SD of the Δscore of the instrument between 2 time-points. SDC approach: MDI= 1.96 x (SD of Δscore in 'unchanged' patients between 2 time-points)/√2. For the Wyrwich SEM, the test-retest intraclass correlation coefficient of stable patients was used for 'r'; BL, baseline.

Chapter 3

Calculating the ankylosing spondylitis disease activity score if the conventional C-reactive protein level is below the limit of detection or if high-sensitivity C-reactive protein is used: an analysis in the DESIR cohort

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ABSTRACT

Objectives

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite measure of disease activity in axial spondyloarthritis. The aims of this study were to determine the most appropriate method for calculating the ASDAS using C-reactive protein (CRP) level when the conventional CRP level is below the limit of detection, to determine how low CRP values obtained by high-sensitivity CRP (hsCRP) measurement influence ASDAS-CRP results, and to test agreement between different ASDAS formulae.

Methods

Patients with axial spondyloarthritis who had a conventional CRP level below the limit of detection (5 mg/liter) were selected (n=257). The ASDAS-conventional CRP with 11 different imputations for the conventional CRP value (range 0-5 mg/liter, at 0.5 mg/liter intervals) was calculated. The ASDAS-hsCRP and ASDAS using the erythrocyte sedimentation rate (ESR) were also calculated. Agreement between ASDAS formulae was tested.

Results

The ASDAS-hsCRP showed better agreement with the ASDAS-CRP calculated using the conventional CRP imputation values of 1.5 and 2.0 mg/liter and with the ASDAS-ESR than with other imputed formulae. Disagreement occurred mainly in lower disease activity states (inactive/moderate disease activity). When the CRP value was <2 mg/liter, the resulting ASDAS-CRP scores may have been inappropriately low.

Conclusion

When the conventional CRP level is below the limit of detection or when the hsCRP level is <2mg/liter, the constant value of 2 mg/liter should be used to calculate the ASDAS-CRP score. There is good agreement between the ASDAS-hsCRP and ASDAS-ESR; however, formulae are not interchangeable.

INTRODUCTION

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index to assess disease activity in axial spondyloarthritis (SpA).[1-3] It combines five single disease activity variables in such a manner that it optimally conveys information, resulting in one single score with better validity, enhanced discriminative capacity, and improved ability to detect change as compared to separate variables.[1-5] ASDAS cut-off values have been developed to define disease activity states and response criteria.[2]

The ASDAS has been endorsed by the Assessment of SpondyloArthritis international Society (ASAS) and by the Outcome Measures in Rheumatology study group and validated in various populations worldwide.[5-10] The ASAS membership has selected the ASDAS using the C-reactive protein (CRP) levels as the preferred version and the ASDAS using the erythrocyte sedimentation rate (ESR) as an alternative.[1-3] The same validated cut-off values apply to both the ASDAS-CRP and the ASDAS-ESR.[2]

The development and validation of the ASDAS was based on conventional CRP values. It has been suggested that when the conventional CRP is below the limit of detection and high-sensitivity CRP (hsCRP) is not available, 50% of the threshold value should be used to calculate the ASDAS-CRP.[2] However, this recommendation is not based on data-driven testing and the effect of using the hsCRP has not been determined. Further testing is required.

The aims of this study were to determine the best way to calculate the ASDAS when the conventional CRP is below the limit of detection, to study the influence of low CRP values obtained by hsCRP in the ASDAS-CRP, and to test agreement between different ASDAS formulae.

PATIENT AND METHODS

Patients

Baseline data from the Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort was used. Details of the DESIR cohort have been previously described.[11] Briefly, DESIR is a French multicenter, prospective study of patients with early (<3 years´ duration) inflammatory back pain (IBP) suggestive of SpA. A total of 708 patients were included in the DESIR cohort at baseline. For the present study, we selected all patients who fulfilled the ASAS classification criteria for axial SpA[12] and who had a conventional CRP value below the limit of detection as well as the results of hsCRP testing; we used data from baseline assessments only. We used the dataset locked on 12 December 2011.

ASDAS Calculation

ASDAS-CRP and ASDAS-ESR scores were calculated based on 5 variables: acute-phase reactant levels (either CRP or ESR) and 4 patient-reported variables,[1,2] namely back pain (question 2 on the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI][13]), duration of morning stiffness (question 6 on the BASDAI), peripheral pain/swelling (question 3 on the BASDAI), and patient global assessment of disease activity. All the patient-reported variables were scored on a scale of 0-10. ASDAS scores were also categorised according to previously published cut-off values for disease activity: an ASDAS score of <1.3 = inactive disease, ≥1.3-<2.1 = moderate activity, ≥2.1-3.5 = high activity, and >3.5 = very high disease activity.[2] Disease activity was quantified using the following equations:

ASDAS-CRP = (0.12*back pain) + (0.06*duration of morning stiffness) + (0.11*patient global) + (0.07*peripheral pain/swelling) + (0.58*ln[CRP +1])

or

ASDAS-ESR = (0.08*back pain) + (0.07*duration of morning stiffness) + (0.11*patient global) + (0.09*peripheral pain/swelling) + (0.29*√ESR)

The limit of detection by the conventional CRP assay was 5 mg/liter. The ASDAS-conventional CRP with 11 different imputations (from 0 mg/liter [ASDAS-CRP(0)] to 5 mg/liter [ASDAS-CRP(5)], at 0.5 mg/liter intervals) to replace the undetermined conventional CRP value was calculated. High-sensitivity CRP was measured by particle-enhanced immunoturbidimetry on a Cobas Integra 800 or Modular Analytics P800 device according to the instructions of the manufacturer (Roche Diagnostics). (Measurement was performed at Paris Bichat, a biologic resource center, by Dr. Joëlle Benessiano).

To gain insight into how low CRP values influence the total ASDAS-CRP score, we plotted CRP values against the CRP term 0.58*ln(CRP+1) from the ASDAS-CRP formula and displayed the ASDAS-CRP scores that were calculated using multiple CRP values (from 0 to 5 mg/liter) and different fixed values (from 0 to 5 units) for the 4 other variables included in the ASDAS-CRP formula (back pain, duration of morning stiffness, peripheral pain/swelling, and patient global assessment of disease activity).

Statistical analysis

The two-way mixed single-measures (absolute agreement) intraclass correlation coefficient (ICC) was used to assess agreement between the ASDAS-hsCRP and other ASDAS formulae (ASDAS-conventional CRP with different imputation strategies and ASDAS-ESR). The ICC can have values between 0 (no agreement) and 1 (perfect agreement).

Scatterplots were created to provide an additional view of the deviation of ASDAS-conventional CRP and ASDAS-ESR from ASDAS-hsCRP. Mean differences (and 95% confidence intervals) between ASDAS-hsCRP and other ASDAS formulae were also calculated.

Agreement between ASDAS-determined disease activity states was assessed using the kappa statistic. The kappa statistic represents the actual agreement beyond chance as a proportion of the potential agreement beyond chance. Since disease activity states are ordered categories, we used the weighted kappa value. The kappa statistic can have values between 0 (agreement equivalent to chance) and 1 (perfect agreement). The strenght of agreement was determined as follows: kappa values of <0.20 indicate poor agreement, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good, 0.81-1.00 very good. SPSS version 22 and MedCalc version 13.1 were used in the statistical analyses.

RESULTS

Patient characteristics

A total of 260 patients fulfilled the inclusion criteria. Three patients had missing ASDAS results; therefore, data from 257 patients were available. Demographic and clinical characteristics of the study population are shown in supplementary table 1.

Agreement between ASDAS formulae

Table 1 shows the level of agreement between the results obtained using the different ASDAS formulae, both in terms of continuous variables (scores on the ASDAS) and in terms of the categorical variable (the disease activity state as determined by the score).

Quantitatively, the best agreement between the ASDAS-hsCRP and ASDAS-conventional CRP scores occurred with the imputed CRP values 1.0, 1.5, 2.0 and 2.5 mg/liter (ICC=0.94, 0.95, 0.94 and 0.92, respectively, representing very good agreement). Agreement between ASDAS-hsCRP and ASDAS-ESR was also very good (ICC=0.91) (table 1). As shown in the scatterplots presented in figure 1, use of conventional CRP imputation values ≤1.0 mg/liter systematically resulted in lower scores of the ASDAS-conventional CRP as compared to the ASDAS-hsCRP, while conventional CRP imputation values ≥2.5 mg/liter systematically resulted in higher scores on the ASDAS-conventional CRP compared to the ASDAS-hsCRP.

Table 1. Agreement between results obtained using the ASDAS-hsCRP and results obtained using other ASDAS formulae (ASDAS-conventional CRP with multiple imputation and ASDAS-ESR)*

	ASDAS-hsCRP vs. ASDAS calculated using other formulae (continuous variable)		ASDAS-hsCRP vs. ASDAS disease activity states calculated using other formulae (categorical variable)
	ICC (95% CI)	**Mean (95% CI) difference in ASDAS score**	**Weighted kappa (95% CI)**
ASDAS-CRP(0)	0.78 (-0.06 to 0.94)	-0.52 (-1.02 to -0.03)	0.51 (0.44 to 0.57)
ASDAS-CRP(0.5)	0.89 (0.33 to 0.96)	-0.29 (-0.79 to 0.21)	0.73 (0.67 to 0.79)
ASDAS-CRP(1)	0.94 (0.89 to 0.96)	-0.12 (-0.62 to 0.38)	0.73 (0.67 to 0.79)
ASDAS-CRP(1.5)	0.95 (0.93 to 0.96)	0.01 (-0.49 to 0.51)	0.75 (0.69 to 0.81)
ASDAS-CRP(2)	0.94 (0.90 to 0.96)	0.11 (-0.38 to 0.61)	0.76 (0.70 to 0.81)
ASDAS-CRP(2.5)	0.92 (0.70 to 0.96)	0.20 (-0.29 to 0.70)	0.71 (0.65 to 0.77)
ASDAS-CRP(3)	0.89 (0.37 to 0.96)	0.28 (-0.22 to 0.78)	0.66 (0.60 to 0.73)
ASDAS-CRP(3.5)	0.86 (0.11 to 0.96)	0.35 (-0.15 to 0.85)	0.64 (0.58 to 0.70)
ASDAS-CRP(4)	0.83 (0.00 to 0.95)	0.41 (-0.09 to 0.91)	0.61 (0.54 to 0.67)
ASDAS-CRP(4.5)	0.81 (-0.04 to 0.94)	0.47 (-0.03 to 0.96)	0.59 (0.53 to 0.65)
ASDAS-CRP(5)	0.78 (-0.06 to 0.94)	0.52 (0.02 to 1.01)	0.50 (0.44 to 0.57)
ASDAS-ESR	0.91 (0.85 to 0.94)	0.13 (-0.52 to 0.79)	0.69 (0.63 to 0.76)

*The Ankylosing Spondylitis Disease Activity Score (ASDAS) using the conventional C-reactive protein (CRP) level with 11 different imputations [ASDAS-CRP(0) to ASDAS-CRP(5), representing CRP values from 0 to 5 mg/liter, at 0.5 mg/liter intervals] and the ASDAS using the erythrocyte sedimentation rate (ESR) were calculated. Two hundred fifty-seven patients were used in all analyses except for the analyses of ASDAS-ESR (n= 246). hsCRP: high-sensitivity CRP; ICC: intraclass correlation coefficient; 95% CI: 95% confidence interval.

Qualitatively, the best agreement between ASDAS-hsCRP and ASDAS-conventional CRP disease activity states occurred with the conventional CRP imputation values of 1.5 and 2 mg/liter (weighted kappa=0.75 and 0.76, respectively, representing good agreement) (table 1). Agreement between ASDAS-hsCRP and ASDAS-ESR disease activity states was also good (weighted kappa=0.69). Disease activity states according to ASDAS-CRP(1.5) and ASDAS-CRP(2) had 78.2% and 78.1% agreement with ASDAS-hsCRP disease activity states, respectively. This percentage decreased to 53.3-75.6% when other CRP values were imputed. Disagreement was evident in lower disease activity states, namely shifts between inactive disease and moderate disease activity (supplementary table 2).

Effect of low CRP values on ASDAS-CRP scores

The values corresponding to y=0.58*ln(CRP+1), the CRP term from the ASDAS-CRP formula, according to CRP values between 0 and 5 mg/liter, were calculated. The function approximates y=0 asymptotically. For higher values, the relationship between

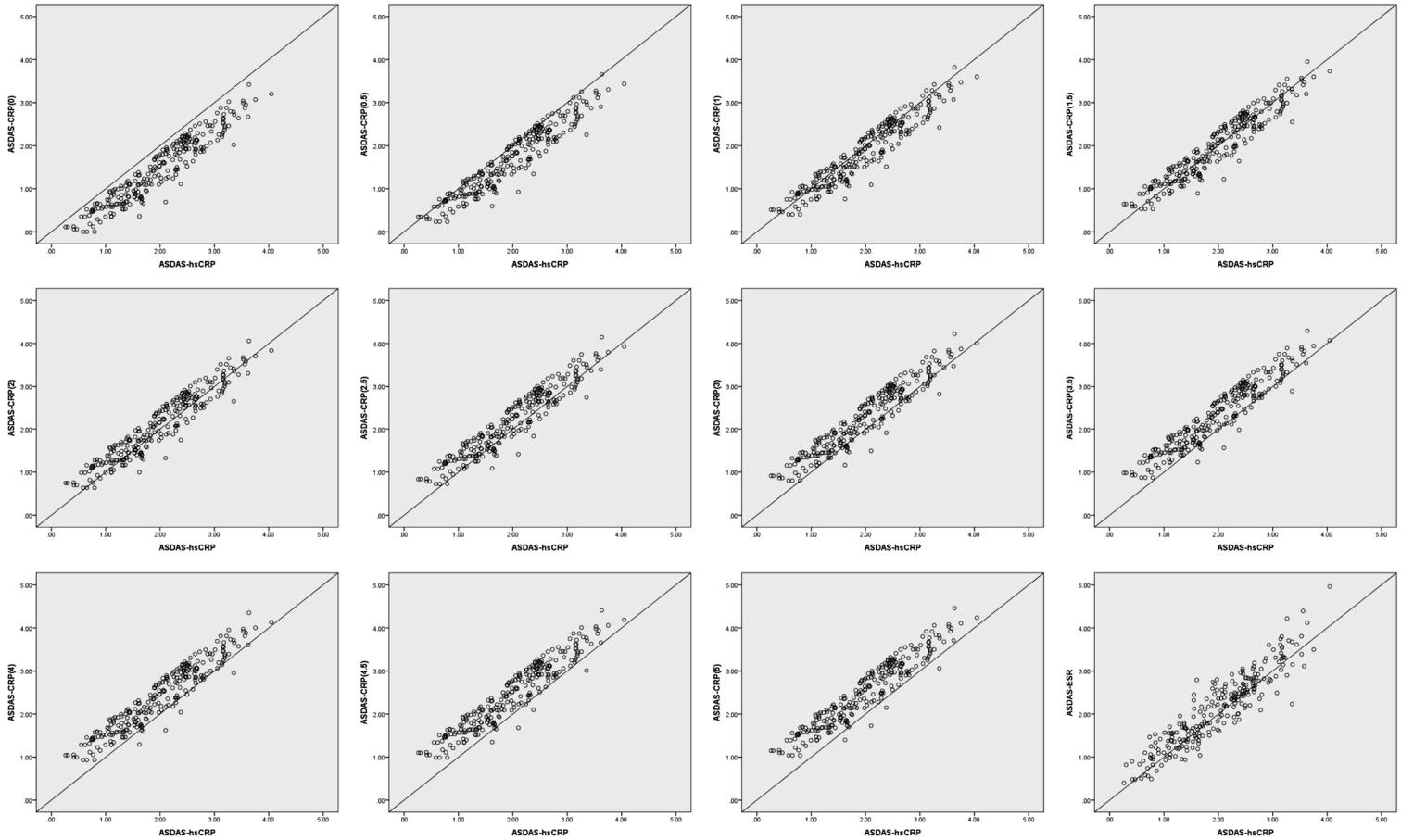

Figure 1. Scatterplots showing the relationship between the Ankylosing Spondylitis Activity Score (ASDAS) using high-sensitivity C-reactive protein (hsCRP) measurement and other ASDAS formulae (ASDAS-conventional CRP [ASDAS-CRP] with multiple imputation of CRP values [ranging from 0 to 5 mg/liter, at 0.5 mg/liter intervals] and ASDAS using the erythrocyte sedimentation rate [ESR]). The line indicates exact agreement between the ASDAS formulae. Data on 257 patients were used for all analyses except for analysis on the relationship between ASDAS-hsCRP and ASDAS-ESR, where data on 246 patients were used.

CRP and 0.58*ln(CRP+1) is roughly linear. However, for lower values, small differences in the CRP value represent larger steps in the term 0.58*ln(CRP+1) because the steepness of the curve increases in this area, which may result in inappropriately low ASDAS scores. This implies that it may be better not to use very low CRP values when calculating the ASDAS-CRP. The decision about the optimal CRP threshold value can be made by examining hypothetical case scenarios. A graphic representation of the results of this analysis, illustrating that this threshold should be between 1.5 and 2.5 mg/liter, is presented in supplementary figure 1.

Table 2 is a matrix showing ASDAS-CRP scores for hypothetical scenarios in which different CRP values and different fixed values for the other 4 items used in the ASDAS-CRP formula were imputed. The 1.5, 2.0 and 2.5 mg/liter imputation strategies perform well with very subtle differences. However, looking at individual cases is particularly informative. If all the other variables are equal to 4, disease activity is rated as moderate when a CRP constant value of 1.5 is used (ASDAS 2.0) but high when a CRP constant value of 2 is used (ASDAS 2.1). Clinically, the latter scenario makes more sense. Further, if all the other variables are equal to 1.5, disease activity is rated as moderate when a constant value of 2.5 is used (ASDAS 1.3) but inactive when a CRP constant value of 2 is used (ASDAS=1.2). Again, clinically the latter scenario makes more sense. These two examples favour the use of the constant value of 2 mg/liter rather than 1.5 or 2.5 mg/liter as the ideal imputation strategy for very low CRP levels.

Table 2. ASDAS-conventional CRP results for different CRP values and different fixed values for all the other four variables used in the calculation of the ASDAS-CRP formula

CRP (mg/liter)	ASDAS-CRP									
	All other variables=0	All other variables=1	All other variables=1.5	All other variables=2	All other variables=2.5	All other variables=3	All other variables=3.5	All other variables=4	All other variables=4.5	All other variables=5
0	0.0	0.4	0.5	0.7	0.9	1.1	1.3	1.4	1.6	1.8
0.5	0.2	0.6	0.8	1.0	1.1	1.3	1.5	1.7	1.9	2.0
1	0.4	0.8	0.9	1.1	1.3	1.5	1.7	1.8	2.0	2.2
1.5	0.5	0.9	1.1	1.3	1.4	1.6	1.8	2.0	2.2	2.3
2	0.6	1.0	1.2	1.4	1.5	1.7	1.9	2.1	2.3	2.4
2.5	0.7	1.1	1.3	1.4	1.6	1.8	2.0	2.2	2.3	2.5
3	0.8	1.2	1.3	1.5	1.7	1.9	2.1	2.2	2.4	2.6
3.5	0.9	1.2	1.4	1.6	1.8	2.0	2.1	2.3	2.5	2.7
4	0.9	1.3	1.5	1.7	1.8	2.0	2.2	2.4	2.6	2.7
4.5	1.0	1.3	1.5	1.7	1.9	2.1	2.2	2.4	2.6	2.8
5	1.0	1.4	1.6	1.8	1.9	2.1	2.3	2.5	2.7	2.8

*The Ankylosing Spondylitis Disease Activity Score (ASDAS) using the conventional C-reactive protein (CRP) level was calculated using multiple CRP values (ranging from 0 to 5 mg/liter, at 0.5 mg/liter intervals) and multiple fixed values (from 0 to 5 units, at 0.5-unit intervals) for the other 4 variables used in the calculation of the ASDAS-CRP (back pain, duration of morning stiffness, peripheral pain/swelling, and patient global assessment of disease activity). ASDAS scores were categorized as follows: <1.3 = inactive disease (lightly shaded), ≥1.3-<2.1 = moderate disease activity (shaded), ≥2.1-3.5 = high activity (darkly shaded), and >3.5 = very high disease activity.

DISCUSSION

The availability of conventional CRP and hsCRP determinations in the DESIR cohort allowed us to perform this analysis in a large population of patients with early IBP who fulfilled the ASAS classification criteria for axial SpA. Our study shows that when the conventional CRP value is below the limit of detection, the value of 2 mg/liter should be used to calculate the ASDAS-CRP. Furthermore, when the hsCRP value is below 2 mg/L, the constant value of 2 mg/liter should also be used to calculate the ASDAS-CRP.

We have shown that for very low hsCRP values, small differences represent larger steps in the CRP term of the ASDAS formula and therefore larger steps in the total ASDAS-CRP score. The final choice of the best imputation value was made by looking at a matrix of clinical scenarios (table 2) according to different imputation strategies. Differences between the imputation of the 1.5, 2.0 and 2.5 mg/liter CRP values were small, but the analysis of individual cases regarding the repercussion of these different imputation strategies in ASDAS disease activity states allowed us to conclude that the best option was not to use hsCRP values below 2 mg/liter.

Disagreement between the ASDAS-hsCRP and other ASDAS formulae was mainly evident among lower disease activity states (inactive/moderate disease activity), a shift that has fewer therapeutic implications than the shift between moderate and high/very high disease activity. This is particularly important given recent evidence that the ASDAS cut-off for high disease activity (ASDAS ≥2.1) is likely to be the most appropriate ASDAS cut-off value for use in the selection of patients for tumor necrosis factor blocker treatment.[14,15] Further evidence supports the replacement of the commonly used BASDAI selection cut-off of 4 units (on a 0-10 scale) by the ASDAS high disease activity cut-off.[16] There was also a high level of agreement between the ASDAS-hsCRP and ASDAS-ESR. However, it is important to highlight that formulae are not interchangeable.

One of the limitations of our study is the fact that this is a selected population with early disease. Therefore results might not be generalisable to the entire spectrum of axial SpA patients, in particular to patients with advanced disease/ankylosing spondylitis. However, a lack of generalisability is unlikely given the fact that CRP is more frequently elevated in ankylosing spondylitis than in non-radiographic axial SpA, so the need to substitute conventional CRP values below the limit of detection or very low hsCRP values will occur more often in early disease than in late disease.[17]

The ASDAS is increasingly being used as a measure of disease activity in clinical practice, clinical trials and observational studies[16]. This study contributes to further standardisation of the ASDAS and to a more homogeneous and reproducible application of this new index.

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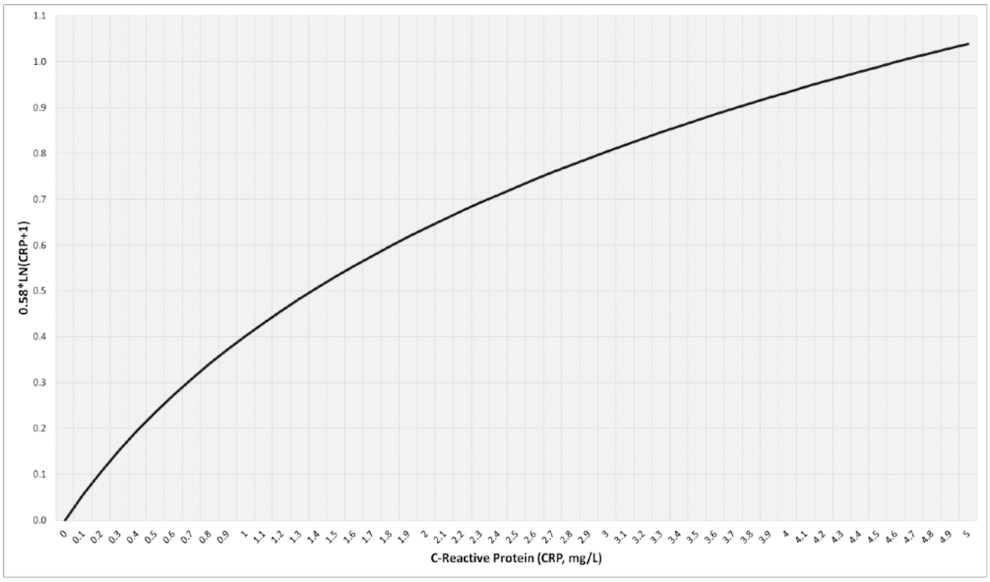
SUPPLEMENTARY MATERIAL

Supplementary table 1. Summary of the baseline clinical and demographic characteristics of the study population (n=257)*

Male, no (%)	121 (47.1)
Caucasian, no (%)	234 (91.1)
Age, years	33.2 (8.8)
HLA-B27 positive, no (%)	191 (89.7)
ASDAS-hsCRP	2.0 (0.8)
ASDAS-ESR[a]	2.2 (0.9)
hsCRP, mg/liter	1.7 (1.4)
ESR†, mmHg	8.2 (6.9)
BASDAI (0-10 scale)	4.0 (2.1)
Patient global assessment (0-10 scale)	4.6 (2.7)
Physician global assessment (0-10 scale)	3.9 (2.2)
BASMI (0-10 scale)	2.2 (0.9)
BASFI (0-10 scale)	2.6 (2.2)

*Except were indicated otherwise, values are the mean (standard deviation). [a]ESR was not available in 4.3% (11/257) of the patients. ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; hsCRP: high sensitivity CRP; ESR: erythrocyte sedimentation rate.



Supplementary figure 1. Graphic displaying the results of the C-reactive protein (CRP) component of the ASDAS-CRP formula (0.58*ln(CRP+1)) according to the CRP value, from 0 to 5 mg/liter, at 0.1 mg/liter intervals.

Supplementary table 2. Percentage and causes of disagreement in ASDAS disease activity states using ASDAS-hsCRP and other ASDAS formulae (ASDAS-conventional CRP with multiple imputation strategies* and ASDAS-ESR)

ASDAS formulae	ASDAS-hsCRP
	ASDAS disease activity states, percentage and causes of disagreement
ASDAS-CRP(0)	**Disagreement: 46.7%** MDA → ID: 21.0%; HDA → ID: 2%; HDA → MDA: 20.6%; VHDA → HAD: 3.1%
ASDAS-CRP(0.5)	**Disagreement: 25.0%** ID → MDA: 0.4%; MDA → ID: 12.5%; MDA → HAD: 0.4%; HDA → MDA: 8.6%; HAD → ID: 0.4%; VHDA → HAD: 2.7%
ASDAS-CRP(1)	**Disagreement: 24.4%** ID → MDA: 3.1%; MDA → ID: 10.1%; MDA → HAD: 2.3%; HDA → MDA: 6.2%; HAD → ID: 0.4%; VHDA → HAD: 2.3%
ASDAS-CRP(1.5)	**Disagreement: 21.9%** ID → MDA: 5.1%; MDA → ID: 5.4%; MDA → HAD: 4.7%; HDA → MDA: 4.7%; HAD → ID: 0.4%; HDA → VHDA: 0.4%; VHDA → HAD: 1.2%
ASDAS-CRP(2)	**Disagreement: 21.8%** ID → MDA: 6.6%; MDA → ID: 2.7%; MDA → HAD: 6.6%; HDA → MDA: 4.3%; HDA → VHDA: 1.2%; VHDA → HAD: 0.4%
ASDAS-CRP(2.5)	**Disagreement: 25.3%** ID → MDA: 10.9%; MDA → ID: 1.6%; MDA → HAD: 8.2%; HDA → MDA: 2.3%; HDA → VHDA: 1.9%; VHDA → HAD: 0.4%
ASDAS-CRP(3)	**Disagreement: 29.1%** ID → MDA: 13.2%; MDA → ID: 0.4%; MDA → HAD: 10.1%; HDA → MDA: 1.9%; HDA → VHDA: 3.1%; VHDA → HAD: 0.4%
ASDAS-CRP(3.5)	**Disagreement: 31.6%** ID → MDA: 14.8%; MDA → ID: 0.4%; MDA → HAD: 11.3%; HDA → MDA: 0.8%; HDA → VHDA: 4.3%
ASDAS-CRP(4)	**Disagreement: 34.3%** ID → MDA: 15.6%; MDA → ID: 0.4%; MDA → HAD: 13.2%; HDA → MDA: 0.8%; HDA → VHDA: 4.3%
ASDAS-CRP(4.5)	**Disagreement: 35.8%** ID → MDA: 17.5%; MDA → HAD: 10.1%; HDA → MDA: 2%; HDA → VHDA: 6.2%
ASDAS-CRP(5)	**Disagreement: 43.6%** ID → MDA: 17.9%; MDA → HAD: 18.7%; HDA → MDA: 0.4%; HDA → VHDA: 6.6%
ASDAS-ESR	**Disagreement: 28.1%** ID → MDA: 7.7%; MDA → ID: 3.3%; MDA → HAD: 8.5%; HDA → MDA: 3.3%; HDA → VHDA: 4.1%; VHDA → HAD: 1.2%

*ASDAS-CRP(0) to ASDAS-CRP(5) represents the ASDAS-CRP results with 11 imputation strategies for the conventional CRP, from 0 to 5 mg/liter, at 0.5 mg/liter intervals. ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; hsCRP: high sensitivity CRP; ID: inactive disease; MDA: moderate disease activity; HAD: high disease activity; VHDA: very high disease activity. Data on 257 patients were used for all analyses except for the ASDAS-ESR, where data on 246 patients were used.

Chapter 4

Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis

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ANN RHEUM DIS. 2010 AUG;69(8):1465-70

ABSTRACT

Objective

To study the relationship between spinal mobility, radiographic damage of the spine and spinal inflammation as assessed by MRI in patients with ankylosing spondylitis (AS).

Methods

In this subanalysis of the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy cohort, 214 patients, representing an 80% random sample, were investigated. Only baseline data were used. MRI inflammation was assessed by the AS spinal MRI activity (ASspiMRI-a) score, structural damage by the modified Stoke AS Spine Score (mSASSS) and spinal mobility by the linear definition of the Bath Ankylosing Spondylitis Metrology Index (BASMI). Univariate correlations were calculated on baseline values using Spearman rank correlation. Independent associations between the variables of interest were investigated by multivariate linear regression analysis. Associations with clinical disease activity, C-reactive protein, disease duration, age, gender, body mass index and HLA-B27 status were also investigated. Subanalyses were performed according to disease duration.

Results

BASMI correlated moderately well with mSASSS (Spearman's $\rho=0.6$) and weakly with ASspiMRI-a ($\rho=0.3$). A best-fit model for BASMI included both mSASSS (regression coefficient (B)=0.865, $p<0.001$) and ASspiMRI-a (B=0.236, $p=0.018$). In patients with a disease duration ≤3 years, B was greater for ASspiMRI-a than for mSASSS (0.595 vs 0.380), while in patients with a disease duration >3 years B was greater for mSASSS than for ASspiMRI-a (0.924 vs 0.156).

Conclusion

Spinal mobility impairment in AS is independently determined both by irreversible spinal damage and by reversible spinal inflammation. Spinal mobility impairment is more influenced by spinal inflammation in early disease, and by structural damage in later disease.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic progressive inflammatory disorder characterised by inflammatory back pain. Many axial anatomical structures may be involved in AS. Sacroiliitis may occur as well as spondylitis, spondylodiscitis, (spinal) enthesitis and arthritis of the zygoapophyseal, costovertebral and costosternal joints. The disease is characterised by bony fusion of the axial skeleton, which can be detected best on plain radiographs of the spine.[1]

MRI has emerged in recent years as an assessment tool because of its ability to detect inflammation in the sacroiliac joints, the spine and other joints affected by AS.[2,3] Only specialised MRI techniques, such as the short tau inversion recovery (STIR) technique, the T2-weighted gradient-echo sequence after fat suppression (T2-FS) and the T1 weighted turbo spin-echo sequence after administration of contrast agent (gadolinium diethylenetriaminepentaacetic acid (T1/Gd-DTPA)), can detect inflammation with a high level of specificity.[2,4] Increased signal on T2-FS and STIR images reflect bone marrow oedema (BMO), while signal enhancement after contrast administration on T1 images reflects hypervascularisation,[5] both undetectable with conventional radiography.[6,7]

The association between radiographic damage of the spine and spinal mobility impairment in AS has been unequivocally demonstrated at the group level.[8–12] However, at the individual level, the association between spinal mobility and radiographic damage is not so strong that spinal mobility can be used as a proxy for radiographic evaluation,[12] an observation that does not dispute the concept that radiographic damage is associated with decreased spinal mobility. One of the possible explanations for the discordance between the level of spinal mobility impairment and the degree of radiographic damage (eg, patients with severe impairment despite absent or mild radiographic damage) might be that spinal inflammation contributes to spinal mobility impairment in patients with AS. This hypothesis is underlined by the observation in clinical trials that anti-tumour necrosis factor α (TNFα) therapy may increase spinal mobility after only a few months of treatment,[13–15] which is in accordance with the suppression of active spinal inflammation as seen on MRI.[16–19]

Taking into account the possibility that spinal inflammation may be an important and potentially reversible factor determining spinal mobility, the aim of this study was to investigate the relationship between spinal mobility, radiographic damage of the spine and spinal inflammation as assessed by MRI in patients with AS, taking other possible factors such as clinical disease activity and gender into account.

PATIENT AND METHODS

Patients with AS

This study is an investigator-performed subanalysis of the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) cohort.[14] In total 214 patients were investigated. Only baseline data were used. These 214 patients were part of a representative 80% random sample (224 patients) of the ASSERT cohort. Ten patients were excluded from the analysis owing to incomplete radiographic assessment (n=7), incomplete MRI assessment (n=1) or both (n=2). In brief, ASSERT was a double-blind, placebo-controlled clinical trial with infliximab that included patients with AS (according to the modified New York criteria[20]) for at least 3 months before screening, with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4 (range 0–10), and with a spinal pain assessment score ≥4 on a visual analogue scale (range 0–10 cm). Patients were excluded from the study if they had total ankylosis of the spine, other inflammatory rheumatic disease or fibromyalgia. Detailed inclusion and exclusion criteria of patients in the ASSERT trial have been described previously.[14]

Disease severity assessments

Spinal mobility was assessed by the Bath Ankylosing Spondylitis Metrology Index (BASMI), a combined index comprising five measures of spinal mobility and hip involvement in patients with AS. It includes measures of lateral lumbar flexion, tragus-to-wall distance, lumbar flexion, intermalleolar distance and cervical rotation.[21,22] The Assessment of SpondyloArthritis international Society (ASAS) has adopted the BASMI as one of the measures of their core set for spinal mobility assessment in AS.[23] The recently proposed linear definition of the BASMI[24] showed greater sensitivity to change than the BASMI with 3 and 11 grades and was used in this study; moreover, it is more appropriate to statistical analysis. Range is from 0 to 10, with higher scores representing greater spinal mobility impairment. Disease activity was assessed both by the BASDAI[25] and by the newly developed ASAS-endorsed Disease Activity Score for use in AS, the ASDAS.[26] The BASDAI (range 0–10) is a self-administered, patient- based questionnaire and consists of six questions completed on a 10 cm visual analogue scale, related to particular symptoms of the disease (fatigue/tiredness, axial pain, pain/swelling in joints, pain/discomfort in entheses, stiffness severity and duration). The following ASDAS formula was used in this study: (0.121 × back pain) + (0.058 × duration of morning stiffness) + (0.110 × patient global) + (0.073 × peripheral pain/swelling) + (0.579 × ln (C-reactive protein (CRP) + 1)). For both the BASDAI and ASDAS, higher scores represent higher disease activity.

Radiographic assessment and scoring method

Lateral radiographic views of the cervical and lumbar spine were used and scored according to the modified Stoke AS Spine Score (mSASSS) scoring system.[27] The total mSASSS is the sum (range 0–72) of the numerical scores for the anterior corners of the cervical spine from the lower border of C2 to the upper border of T1, and the anterior corners of the lumbar spine from the lower border of T12 to the upper border of S1 (total of 24 corners). Each vertebral corner is scored as follows: 0=normal; 1=erosions, sclerosis or squaring; 2=syndesmophytes; 3=bridging syndesmophytes. The mSASSS was chosen by ASAS and the international Outcome Measurement in Rheumatoid Arthritis Clinical Trials (OMERACT) group as the preferred measure for measuring structural damage and progression in AS.[28] Patients who had more than three vertebral corners missing were excluded; if ≤3 corners were missing, the mean of the other scoring corners was used for imputation, as previously reported.[29] Two qualified and well-trained readers who were blinded to the patient's identity and treatment evaluated each radiograph independently. The mean of both readers' scores was used in the analysis.

MRI assessment and scoring method

Images were scored according to the AS spinal MRI activity (ASspiMRI-a) score,[30,31] a widely used MRI scoring system, recently validated in a multi-reader exercise.[32,33] With the ASspiMRI-a score, activity is assessed at the level of the discovertebral unit (DVU). A DVU is defined as the area between two virtual horizontal lines through the middle of two adjacent vertebrae. The combined information provided by T1/Gd-DTPA and STIR sequences was used for scoring the MR images and each DVU was given an MRI activity score based on the amount of BMO or erosions, as follows: 0=no abnormalities, 1=minor BMO involving ≤25% of the DVU; 2=moderate BMO involving >25% but ≤50% of the DVU; 3=major BMO involving >50% of the DVU; 4=BMO and minor erosion involving ≤25% of the DVU; 5=BMO and moderate erosion involving >25% but ≤50% of the DVU; 6=BMO and major erosion involving >50% of the DVU. Thus, the ASspiMRI-a score for each DVU ranges from 0 to 6. Since 23 DVUs are assessed (from C2 to S1), the total ASspiMRI-a score for the spine ranges from 0 to 138. In studies concerning the ASspiMRI-a score, no description has been given as to how missing DVU scores should be handled. In this study, we chose to exclude patients who had >2 DVU scores missing; if ≤2 DVU scores were missing, the mean of the other DVU scores was used for imputation. Two qualified and well-trained readers, different from the readers of the radiographs, who were blinded to the patient's identity and treatment evaluated each sequence independently. The mean of both readers' scores was used in the analysis.

Statistical analysis

All data are expressed as median (IQR) or proportion if applicable. Simple univariate

correlations were calculated on baseline values using Spearman rank correlation. Independent associations between the variables of interest were investigated by linear regression analysis, using BASMI as the dependent variable. The relationship between spinal mobility as measured by the BASMI, MRI inflammation as assessed by the ASspiMRI-a score and structural damage according to the mSASSS was first investigated. Second, the contributory or confounding effect of other independent variables was investigated one by one: disease activity as assessed by the ASDAS or the BASDAI, CRP, disease duration, age, gender, body mass index and HLA-B27 status. Finally, a best-fit model with the relevant variables was built. Non-normally distributed variables (mSASSS, ASspiMRI-a score, CRP and disease duration) underwent a normalization procedure using the van der Waerden technique before being entered into the linear regression analysis. Interactions between mSASSS, ASspiMRI-a, CRP, age, disease duration and gender were tested. Because of a relevant statistical interaction between disease duration and ASspiMRI-a/mSASSS, a subanalysis was performed for patients with low (≤3 years) versus high (>3 years) disease duration (the 3-year cut-off point corresponding to the first quartile). All the statistical analyses were performed using SPSS 16 (SPSS, USA).

RESULTS

Baseline clinical, imaging and demographic characteristics of the study population

We analysed data of 214 patients, for whom all baseline variables were available. Table 1 shows the baseline clinical, imaging and demographic characteristics of the study population. The study population was typical of patients with moderate-to-severe AS. Most patients were men (78.5%) and were HLA-B27 positive (89.7%). At baseline, 79.9% of the patients had elevated CRP levels (CRP >0.5 mg/dl), 82.2% of the patients had evidence of spinal inflammation (ASspiMRI-a score >0 by any reader) and 98.6% of the patients had evidence of radiographic damage of the spine (mSASSS >0 by any reader).

Relationship between spinal mobility, radiographic damage of the spine and spinal inflammation

BASMI correlated moderately well with mSASSS (Spearman's $\rho=0.6$, $p<0.001$) and weakly with ASspiMRI-a ($\rho=0.3$, $p<0.001$), disease duration ($\rho=0.3$, $p<0.001$), CRP ($\rho=0.2$, $p=0.006$) and age ($\rho=0.2$, $p=0.001$). Multivariate linear regression analysis showed that the mSASSS and ASspiMRI-a scores were independently associated with BASMI (table 2, model 1). We further investigated whether the association between spinal mobility, radiographic damage of the spine and spinal inflammation was independent of

Table 1. Summary of the baseline clinical, imaging and demographic characteristics of the study population (n=214)*

Characteristics	Value
Male (n (%))	168 (78.5)
Age (years)	40 (32, 46)
Disease duration (years)	9 (3, 16)
BMI (kg/m^2)	25.5 (22.6, 27.9)
History of uveitis (n (%))	135 (63.1)
History of psoriasis (n (%))	20 (9.3)
History of IBD (n (%))	15 (7.0)
HLA-B27 positive (n (%))†	191 (89.7)
BASMI	4.6 (3.6, 5.8)
ASDAS	4.0 (3.4, 4.6)
BASDAI	6.5 (5.3, 7.0)
CRP level (mg/dl)‡	1.5 (0.7, 2.9)
mSASSS	13.8 (4.5, 29.1)
ASspiMRI-a	4.5 (0.5, 9.8)

*Except were indicated otherwise, values are the median (IQR); †one patient was not assessed for HLA-B27 status; ‡normal range 0–0.5 mg/dl. ASDAS, Ankylosing Spondylitis Disease Activity Score; ASspiMRI-a, Ankylosing Spondylitis spinal MRI activity; BASDAI, Bath Anklyosing Spondylitis Disease Activity Index; BASMI, linear definition of the Bath Ankylosing Spondylitis Metrology Index; BMI, body mass index; CRP, C-reactive protein; IBD, inflammatory bowel disease; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.

differences in clinical and demographic variables (table 2, models 2–9). The regression coefficient (B) for the relationship between BASMI and mSASSS (B=0.841; p<0.001) and for the relationship between BASMI and ASspiMRI-a (B=0.213; p=0.031) was only significantly influenced by adding gender to the model (>10% change in the value of B). A best-fit model for BASMI (table 3) included mSASSS (B=0.865; p<0.001), ASspiMRI-a (B=0.236; p=0.018) and gender (B=−0.305; p=0.165). Results were similar if disease duration (almost significant in the exploratory analysis shown in table 2) was included in the model: mSASSS (B=0.809; p<0.001), ASspiMRI-a (B=0.244; p=0.014), disease duration (B=0.171; p=0.065) and gender (B=−0.275; p=0.210). Of note, the analysis using the untransformed variables produced similar results to the analysis with normalised variables, which adds to the robustness of the results (data not shown). Figure 1 plots the relationship between spinal mobility and radiographic damage of the spine for three different preset values of spinal inflammation (figure 1A) and the relationship between spinal mobility and spinal inflammation for three different preset values of radiographic damage of the spine (figure 1B), using the regression equation obtained from the untransformed data. From the graphs, it is clear that both mSASSS and ASspiMRI-a are independently determining the value of BASMI.

Owing to a relevant statistical interaction, patients were then separated according to disease duration (table 3). In patients with a disease duration ≤3 years, B was greater

Table 2. Investigation of contributory and confounding effects of baseline variables on the relationship between spinal mobility (dependent variable), radiographic damage of the spine and spinal inflammation (n=214)

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9
mSASSS	0.841* (0.655 to 1.027)	0.836* (0.650 to 1.022)	0.849* (0.663 to 1.036)	0.833* (0.646 to 1.020)	0.784* (0.591 to 0.977)	0.834* (0.627 to 1.040)	0.865* (0.677 to 1.054)	0.842* (0.654 to 1.031)	0.841* (0.653 to 1.028)
ASspiMRI-a	0.213** (0.020 to 0.406)	0.205** (0.011 to 0.399)	0.219** (0.026 to 0.413)	0.198** (0.001 to 0.395)	0.223** (0.031 to 0.416)	0.215** (0.020 to 0.411)	0.236** (0.041 to 0.432)	0.214** (0.020 to 0.409)	0.216** (0.023 to 0.410)
ASDAS		0.093 (–0.110 to 0.296)							
BASDAI			0.052 (–0.061 to 0.166)						
CRP				0.072 (–0.115 to 0.259)					
Disease duration					0.180 (–0.002 to 0.362)				
Age						0.001 (–0.018 to 0.021)			
Gender (male)							–0.305 (–0.738 to 0.127)		
BMI								–0.003 (–0.046 to 0.041)	
HLA-B27									–0.045 (–0.611 to 0.520)

Values are the regression coefficients (95% CI) for the dependent variable 'spinal mobility' as assessed by the 'BASMI'. Baseline variables were tested for contributory or confounding effects on the relationship between 'radiographic damage of the spine' as assessed by the 'mSASSS' and 'spinal inflammation' as assessed by the 'ASspiMRI-a'. Each variable was added to the initial model (model 1), one after the other (models 2–9). This method allows an investigation of the effect of each independent variable on the stability of the capacity of 'mSASSS' and 'ASspiMRI-a' to predict 'BASMI'. *p<0.001; **p<0.05. ASDAS, Ankylosing Spondylitis Disease Activity Score; ASspiMRI-a, Ankylosing Spondylitis spinal MRI activity; BASDAI, Bath Anklyosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C-reactive protein; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.

Table 3. Best-fit model for spinal mobility (BASMI)

	Entire ankylosing spondylitis population (n=214)	Disease duration ≤3 years (n=53)	Disease duration >3 years (n=161)
mSASSS			
B	0.865	0.380	0.924
95% CI	0.677–1.054	−0.099 to 0.858	0.715–1.134
p Value	<0.001	0.117	<0.001
ASspiMRI-a			
B	0.236	0.595	0.156
95% CI	0.041–0.432	0.173–1.016	−0.070 to 0.383
p Value	0.018	0.007	0.174
Gender (male)			
B	−0.305	−0.454	−0.299
95% CI	−0.738 to 0.127	−1.338 to 0.429	−0.796 to 0.198
p Value	0.165	0.307	0.237

Results are shown for the entire AS population and according to disease duration. ASspiMRI-a, Ankylosing Spondylitis spinal MRI activity; B, regression coefficient; BASMI, linear definition of the Bath Ankylosing Spondylitis Metrology Index; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.

for ASspiMRI-a than for mSASSS (0.595 vs 0.380), while in patients with a disease duration >3 years, B was greater for mSASSS than for ASspiMRI-a (0.924 vs 0.156).

DISCUSSION

The results of this study show that spinal mobility impairment in AS is independently determined by irreversible spinal damage as well as by reversible spinal inflammation. These findings are consistent with clinical data reporting the improvement of both spinal inflammation and spinal mobility after treatment with anti-TNFα[13–15] and with studies confirming the association between radiographic damage of the spine and spinal mobility impairment at the group level[8–12] but not always at the individual level.[12] It confirms that spinal inflammation may explain those cases of discordance between the level of spinal mobility impairment and the degree of radiographic damage.

Moreover, the results of this study also show that spinal mobility impairment is more influenced by spinal inflammation in early disease, and by structural damage in later disease, which may imply that spinal mobility can better be maintained by early as compared with delayed intervention.

To our knowledge, only one study has assessed the relationship between MRI spinal inflammation and spinal mobility. Rudwaleit *et al*[34] reported a Spearman r coefficient of 0.238 between the Berlin MRI spine score[19] and the BASMI. This correlation coefficient was not statistically significant, which may be owing to the small sample size of the study (46 patients with active AS who participated in randomized controlled trials). In

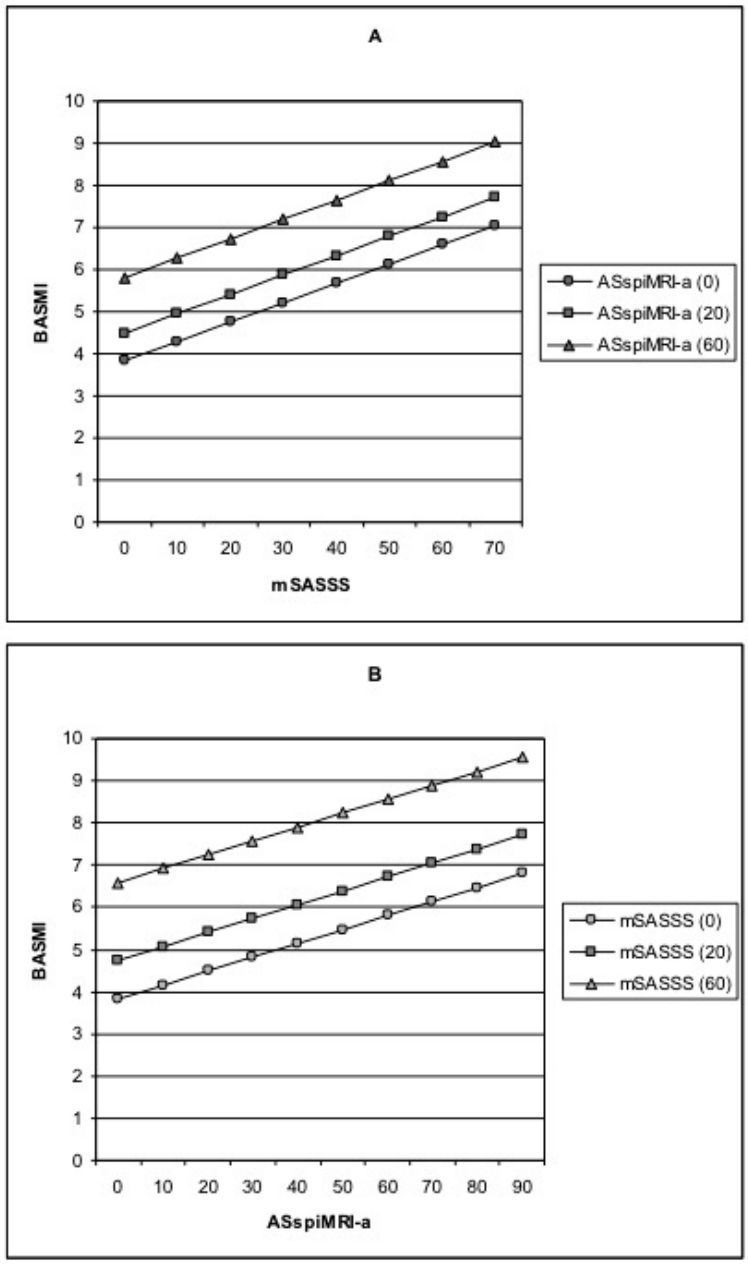

Figure 1. (A) Relationship between spinal mobility and radiographic damage of the spine for three different preset values of spinal inflammation; (B) relationship between spinal mobility and spinal inflammation for three different preset values of radiographic damage of the spine. An increase of 10 units in mSASSS (range 0–72) leads to an increase of 0.46 in BASMI (range 0–10) independent of the effect of ASspiMRI-a; similarly, an increase of 10 units in ASspiMRI-a (range 0–138) leads to an increase of 0.33 in BASMI. ASspiMRI-a, ankylosing spondylitis spinal MRI activity; BASMI, linear definition of the Bath Ankylosing Spondylitis Metrology Index; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.

the same study, the authors reported that the MRI scores of the spine did not correlate at all with other disease activity markers, including BASDAI, patient global, morning stiffness, CRP and erythrocyte sedimentation rate. However, this study also showed that widespread inflammation in the spine as detected by MRI contributes to predicting a major clinical response in patients with active AS treated with anti-TNFα agents.

Owing to its ability to detect inflammatory changes, and in light of the paucity of reliable objective measures to quantify disease activity in AS, MRI has been increasingly used as a surrogate end point in clinical trials of TNFα blocking agents. MRI has also evolved as an important diagnostic tool in patients without definite radiographic sacroiliitis, because it visualizes active (acute) inflammation in the sacroiliac joints and the spine and may therefore be a relevant tool for the early diagnosis of axial spondyloarthritis (SpA), including AS.[35,36] By showing that inflammatory changes (and not only structural changes) contribute to spinal mobility impairment, this study gives a new and original meaning to MRI spinal inflammation, further elucidating its role in the burden of disease.

Most likely, spinal inflammation prevails in the early phase of AS, whereas at later stages, the disease burden is often caused both by inflammatory and secondary changes. Given that anti-TNFα therapy is highly anti-inflammatory and effective in the long-term suppression of active spinal inflammation as seen on MRI,[16–19] the finding that spinal mobility impairment is more influenced by spinal inflammation in early disease supports the concept of a 'window of opportunity' to treat patients before they develop irreversible bony changes and suggests that early treatment of reversible inflammatory lesions may be of great importance in recovering mobility and achieving better patient outcomes. The relationship between ankylosis and spinal inflammation is still a matter of debate. In fact, there is now evidence that anti-TNFα therapy will not influence radiographic progression in patients with established AS.[37,38] Irrespective of this relationship, the findings from this study have immediate implications for patient care and patient outcome, since they show a relationship between spinal inflammation and spinal mobility, which, in turn, has direct implications for the function and quality of life.[39,40] Ultimately, the findings from this study may also be of relevance to a group of patients with a substantial disease burden but unmet need: the patients with non-radiographic axial SpA,[41] for whom the recent publication of validated classification criteria for axial SpA[35,36] will facilitate the conduct of clinical trials and observational studies. In addition, the finding that in established disease spinal mobility is mainly explained by structural damage indicates that spinal mobility can also be seen as a surrogate measure for long-term outcome. The 3-year cut-off point used in this study is arbitrary and should not be used as a reference value. Moreover, spinal inflammation cannot be neglected in later disease as many of these patients have significant spinal inflammation. Furthermore, the benefit of anti-TNFα therapy in later disease is indisputable and goes beyond the reduction of spinal inflammation and improvement of spinal mobility.

Some limiting factors should be taken into account. One of them may be the fact that mSASSS only accounts for structural damage in the anterior corners of the cervical and lumbar spine. Exclusion of the thoracic spine and of the posterior sites of the spine may result in an underestimation of the structural damage, as may the exclusion of the vertebral ligaments and facet joints, which also have an important role in spinal mobility. This study, however, gives justice to the hypothesis that involvement of the structures not measured directly by mSASSS is in line with structures measured by mSASSS. Another limiting factor may be the fact that the ASspiMRI-a score only captures spinal inflammatory activity (bone oedema and discitis) at the DVU level, excluding the surrounding soft tissues and facet joints, which may underestimate inflammatory activity. However, none of the other available scoring methods for structural damage or spinal inflammation performs better than the mSASSS and ASspiMRI-a,[29,32] respectively, and it is unlikely that this can influence the overall conclusions of this study, although at the individual level it may be of some importance. The above arguments would be mainly of importance if we did not establish a relationship. Another theoretical limitation pertains to lack of generalisability, or that the results of this study are only valid within the ASSERT population. However, we do not believe that external validity is compromised because the population includes the entire range of spinal mobility impairment, radiographic damage and spinal inflammation.

In summary, this study suggests that both the assessment of MRI spinal inflammation and radiographic damage of the spine have an independent and additive value in the outcome measurement of AS, both contributing to spinal mobility impairment. This study also suggest that spinal mobility impairment is more influenced by spinal inflammation in early disease, and by structural damage in later disease, which may imply that spinal mobility can better be maintained by early rather than late intervention.

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Chapter 5

A stratified model for health outcomes in ankylosing spondylitis

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ABSTRACT

Objectives

To investigate the relationships between several health outcomes in ankylosing spondylitis (AS).

Methods

Baseline pretreatment data from 214 patients with AS participating in the AS Study for the Evaluation of Recombinant Infliximab Therapy were analysed. Measures of health-related quality of life (HRQoL) and physical function were used as dependent variables in linear regression analysis. Associations between HRQoL (36-Item Short Form (SF-36)), physical function, clinical disease activity, spinal mobility, structural damage, MRI inflammation, disease duration, age, gender, body mass index and HLA-B27 were explored. Univariate associations were retested in multivariate models. The robustness of the models was evaluated by sensitivity analyses.

Results

The physical component of SF-36 was independently associated with measures of physical function and disease activity (adjusted R^2 ($adjR^2$)=0.39–0.40). The mental component of SF-36 was independently associated with physical function ($adjR^2$=0.07). Physical function was independently associated with measures of spinal mobility and disease activity ($adjR^2$=0.39–0.45). Spinal mobility was hierarchically shown to be an intermediate variable between structural damage and physical function, while physical function was shown to be intermediate between spinal mobility and the physical component of SF-36.

Conclusion

According to the proposed stratified model for health outcomes in AS, HRQoL is determined by physical function and disease activity, physical function is determined by spinal mobility and disease activity, and spinal mobility is determined by structural damage and inflammation of the spine. As more is learnt about how to measure AS, knowledge about the disease improves and better decisions can be made on the assessment and treatment of this disease.

INTRODUCTION

Health outcomes include different aspects of health and illness and their consequences on a person's life. These include health status (symptom severity and degree of functional limitation), impairment (alteration of normal body structure or biofunction), quality of life (subjective appraisal of health status), costs (monetary costs of obtaining care and costs of lost work productivity) and mortality.[1]

The Assessment of SpondyloArthritis international Society (ASAS) has recommended a core set of validated ankylosing spondylitis (AS) measures of impairment and health status to be used in clinical trials and clinical practice.[2-4] Measurement instruments for radiographic damage[5,6] and for MRI inflammation[7,8] have also been developed and, recently, a new index for measuring disease activity - the AS Disease Activity Score (ASDAS) - was proposed and validated in AS.[9-11]

The spectrum of AS is heterogeneous and the relationships between health outcomes are complex and incompletely understood. Presumably, there is a generic hierarchical order of domains, with health-related quality of life (HRQoL) at the top and signs and symptoms (and MRI inflammation) at the bottom. HRQoL can be thought of as the highest multidimensional goal dependent on other domains (eg, health status and impairment), reflecting the overall impact of the illness (including signs and symptoms) and its treatment on patients and their response to these impacts. However, we do not know exactly how these domains interrelate. Improved understanding about these relationships will deepen our knowledge of AS and its management, treatment and impact on patients and society.

This theoretical concept is not new to rheumatic diseases (or to most chronic diseases), and goes back to the writings of Tennant[12] and Fries[13] and to what was to become the International Classification of Impairments, Disabilities, and Handicaps of the World Health Organization. In this schema, as described by Tennant,[12] disease gives rise to impairment, defined as 'any loss or abnormality of psychological, physiological, or anatomical structure or function'; impairment itself may lead to disability, defined as 'any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being'; impairments and disabilities, by interacting with the physical and social environment, can result in handicap, defined as a 'disadvantage for the given individual that limits or prevents the fulfilment of a role that is normal'; and at the end of the disease–handicap continuum we can find quality of life, a broader outcome that can be influenced by a whole series of other factors such as self-esteem, coping skills, age, gender and ethnicity.[12]

Despite being a conceptual frame shared between several chronic diseases, the evidence for AS is lacking as the number of previous reports analysing the relationship

between outcomes is small, they included small numbers of patients and focused on a limited number of outcomes. A more broad analysis - adjusting for potential confounders and including a large number of health outcomes simultaneously - is lacking, and is of utmost importance as it may offer a more solid conceptual basis for thinking about outcomes in AS and for understanding what we are measuring when assessing patients with this disease. In particular, the availability of inflammation assessed on MRI of the spine in a large number of patients is a unique feature of the current dataset.

In this study we investigated the relationships between HRQoL, physical function, disease activity, spinal mobility and structural damage in detail and propose a stratified model for health outcomes in AS.

PATIENT AND METHODS

AS patient population

This study investigated a representative baseline 80% random sample (224 patients) of the AS Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) cohort.[14] Ten patients were excluded from the analysis owing to incomplete radiographic assessment (n=7), incomplete MRI assessment (n=1) or both (n=2). The final number of patients included in this study was 214.

In brief, ASSERT was a double-blind placebo-controlled clinical trial with infliximab that included patients with AS (according to the modified New York criteria)15 for at least 3 months prior to screening, with a Bath AS Disease Activity Index (BASDAI) ≥4 (range 0–10) and a Spinal Pain Assessment Score ≥4 (range 0–10 cm, visual analogue scale). Detailed inclusion and exclusion criteria of patients in the ASSERT trial have been described previously.[14]

Measures of health outcomes

Two patient-reported outcomes were used as measures of HRQoL and physical function: the 36-Item Short Form (SF-36) health survey questionnaire[16] (both the SF-36 Physical Component Summary Score (SF-36 PCS) and the SF-36 Mental Component Summary Score (SF-36 MCS)) and the Bath AS Functional Index (BASFI).[17] It should be noted that, although often mislabelled as a quality of life measure, the SF-36 is in fact a health status measure and it should be interpreted as such when we use the term HRQoL.

The BASDAI,[18] the ASDAS[9-11] and the level of C-reactive protein (CRP) were included as measures of clinical disease activity. Spinal mobility was assessed using the Bath AS Metrology Index (BASMI),[19-21] structural damage was assessed by the modified

Stoke AS Spine Score (mSASSS)[5,6] and MRI spinal inflammation was assessed by the AS spinal MRI Activity (ASspiMRI-a) score.[7,8] All these measurement tools have been validated and are recommended for use in AS.[4,22]

Statistical analysis

All data are expressed as median (IQR) or proportion if applicable. Pearson (normally distributed variables) and Spearman correlation coefficients (not normally distributed variables) were used to build a correlation matrix between health outcomes.

Possible associations between BASFI, SF-36 (physical and mental component scores) and a large number of outcome measures (ASDAS, BASDAI, CRP, BASMI, mSASSS, ASspiMRI-a) and clinical-demographic variables (disease duration, age, gender, body mass index (BMI) and HLA-B27) were first explored by univariate linear regression analysis (using SF36-PCS, SF-36 MCS and BASFI as dependent variables). Variables with univariate associations with a p value <0.10 were retested in multivariate models. By default, all multivariate models were adjusted for disease duration, age, BMI and gender.

Separate multivariate models were run using either ASDAS or BASDAI as independent variables (as they represent the same health outcome), and using either mSASSS or BASMI (to avoid collinearity and because we wanted to test if BASMI is an intermediate variable between mSASSS and BASFI). A similar approach (and for the same reasons) was used for BASMI or BASFI as the regressors.

As measures of the strength of the relationship between the models and the dependent variable, we used the R-square (R^2) value (the coefficient of determination), which is the squared value of the multiple correlation coefficient (R) and shows how much variation in the dependent variable is explained by the model. As a further measure of the strength of the model fit, we used the adjusted R-square (adjR^2) value, which compensates for model complexity providing a fairer comparison of multivariate model performance.

Non-normally distributed variables (mSASSS, ASspiMRI-a score, CRP and disease duration) underwent a normalisation procedure based on rank order using the van der Waerden technique before being entered into the linear regression analysis. All tests were two-sided and p values <0.05 were considered statistically significant. Analyses were performed using SPSS Version 16.

RESULTS

Baseline characteristics of the study population

Supplementary table 1 shows the baseline characteristics of the study population. The study population was typical of patients with moderate to severe AS, with poor physical function (median BASFI 5.7), high disease activity (median BASDAI 6.5 and median ASDAS 4.0) and substantial impairment of spinal mobility (median BASMI 4.6). The median SF-36 PCS score (29.5) was well below that of the general population of the USA and Europe (range 49.7–52.7).[23] However, the median SF-36 MCS score (47.1) was in the lower range of that of the general population of the USA and Europe (range 47.6–54.0).[23]

Correlation matrix for health outcomes

Table 1 presents a correlation matrix for all health outcomes in our population. SF-36 MCS correlated weakly with BASFI (r=−0.28), BASDAI (r=−0.25) and ASDAS (r=−0.13). SF-36 PCS correlated moderately well with BASFI (r=−0.58), BASDAI (r=−0.47), ASDAS (r=−0.40) and weakly with BASMI (r=−0.20). BASFI correlated moderately well with BASDAI (r=0.45), ASDAS (r=0.38), BASMI (r=0.42) and weakly with mSASSS (r=0.18). BASMI correlated moderately well with mSASSS (r=0.59) and weakly with ASspiMRI-a (r=0.30).

Table 1. Correlation matrix between health outcomes in ankylosing spondylitis

		SF-36 MCS	SF-36 PCS	BASFI	BASDAI	ASDAS	BASMI	mSASSS	ASspiMRI-a
SF-36 MCS	r	1	−0.01	−0.28	−0.25	−0.13	−0.07	0.04	0.08
	p Value	NA	0.88	**<0.001**	**<0.001**	0.051	0.279	0.596	0.255
SF-36 PCS	r		1	−0.58	−0.47	−0.40	−0.20	−0.10	0.13
	p Value		NA	**<0.001**	**<0.001**	**<0.001**	**0.004**	0.154	0.051
BASFI	r			1	0.45	0.38	0.42	0.18	0.04
	p Value			NA	**<0.001**	**<0.001**	**<0.001**	**0.008**	0.535
BASDAI	r				1	0.68	−0.03	−0.13	−0.12
	p Value				NA	**<0.001**	0.631	0.064	0.079
ASDAS	r					1	0.11	0.11	0.14
	p Value					NA	0.103	0.127	0.045
BASMI	r						1	0.59	0.30
	p Value						NA	**<0.001**	**<0.001**
mSASSS	r							1	0.38
	p Value							NA	**<0.001**
ASspiMRI-a	r								1
	p Value								NA

p Values <0.05 are highlighted in bold. ASDAS, Ankylosing Spondylitis Disease Activity Score; ASspiMRI-a, Ankylosing Spondylitis spinal MRI activity; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, linear definition of the Bath Ankylosing Spondylitis Metrology Index; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; SF-36 PCS, SF-36 Physical Component Summary Score; SF-36 MCS, SF-36 Mental Component Summary Score.

Univariate associations between BASFI, SF-36 PCS, SF-36 MCS and other outcome measures and clinical-demographic variables

Table 2 shows the results of univariate linear regression analysis using physical function and HRQoL (physical and mental components) as dependent variables:

1. BASFI was positively associated with ASDAS (R^2=0.15), BASDAI (R^2=0.20), BASMI (R^2=0.18), mSASSS (R^2=0.040), age (R^2=0.038) and BMI (R^2=0.064).
2. SF-36 PCS was negatively associated with BASFI (R^2=0.33), ASDAS (R^2=0.16), BASDAI (R^2=0.22), BASMI (R^2=0.038) and age (R^2=0.037), and positively associated with male gender (R^2=0.034).
3. SF-36 MCS was negatively associated with BASFI (R^2=0.076), ASDAS (R^2=0.018), BASDAI (R^2=0.064) and BMI (R^2=0.039).

Multivariate linear regression analysis for BASFI, SF-36 PCS and SF-36 MCS

Independent associations with BASFI, SF-36 PCS and SF-36 MCS were explored using multivariate linear regression analysis. By default, all models were adjusted for disease duration, age, BMI and gender. The results are presented in tables 3–5 and summarised below:

1. BASFI was independently associated with BASMI and with measures of clinical disease activity (ASDAS or BASDAI) (table 3, models 1 and 2). If BASMI and mSASSS were forced into the same model as regressors simultaneously, the mSASSS contribution did not reach statistical significance owing to collinearity (data not shown).
2. When BASMI was replaced by mSASSS in the BASFI models (table 3, models 3 and 4), both ASDAS/BASDAI and mSASSS were independently associated with BASFI, suggesting that BASMI is hierarchically an intermediate variable between mSASSS and BASFI. This is supported by the improved fit in the model with BASFI when BASMI (adjR^2=0.39–0.45) is used instead of mSASSS (adjR^2=0.26–0.31) in otherwise similar multivariate models (table 3).
3. SF-36 PCS was independently determined by BASFI and by measures of clinical disease activity (ASDAS or BASDAI) (table 4, models 1 and 2). If BASFI and BASMI were forced into the same model as regressors simultaneously, the contribution of BASMI was not statistically significant (collinearity, data not shown).
4. When BASFI was replaced by BASMI in the SF-36 PCS models (table 4, models 3 and 4), both ASDAS/BASDAI and BASMI were independently associated with SF-36 PCS, suggesting that BASFI is hierarchically an intermediate variable between BASMI and SF-36 PCS. This is supported by the improved fit in the model with SF-36 PCS when BASFI (adjR^2=0.39–0.40)

Table 2. Associations between BASFI, SF-36 PCS and SF-36 MCS (dependent variables) and other outcome measures and clinical-demographic variables (univariate linear regression analyses)

	B (95% CI)	β	R^2	p Value	B (95% CI)	β	R^2	p Value	B (95% CI)	β	R^2	p Value
BASFI	NA	NA	NA	NA	−2.198 (−2.620 to −1.776)	−0.576	0.332	**<0.001**	−1.565 (−2.303 to −0.828)	−0.276	0.076	**<0.001**
ASDAS	0.861 (0.581 to 1.141)	0.384	0.148	**<0.001**	−3.383 (−4.445 to −2.321)	−0.396	0.157	**<0.001**	−1.695 (-3.397 to 0.007)	−0.134	0.018	0.051
BASDAI	0.562 (0.411 to 0.713)	0.450	0.203	**<0.001**	−2.249 (−2.817 to −1.680)	−0.472	0.223	**<0.001**	−1.796 (−2.723 to −0.869)	−0.254	0.064	**<0.001**
CRP	0.194 (−0.076 to 0.464)	0.097	0.009	0.158	−0.857 (−1.884 to 0.170)	−0.112	0.013	0.101	0.346 (−1.188 to 1.880)	0.031	0.001	0.657
BASMI	0.518 (0.368 to 0.668)	0.423	0.179	**<0.001**	−0.915 (−1.535 to −0.295)	−0.196	0.038	**0.004**	−0.515 (−1.452 to 0.421)	−0.074	0.006	0.279
mSASSS	0.387 (0.129 to 0.645)	0.199	0.040	**0.003**	−0.826 (−1.825 to 0.172)	−0.111	0.012	0.104	0.594 (−0.896 to 2.084)	0.054	0.003	0.433
ASspiMRI-a	0.120 (−0.153 to 0.393)	0.059	0.004	0.387	0.791 (−0.248 to 1.830)	0.102	0.011	0.135	0.769 (−0.779 to 2.317)	0.067	0.005	0.328
Disease duration	−0.043 (−0.347 to 0.178)	−0.084	0.002	0.528	0.050 (−0.953 to 1.052)	0.007	0.001	0.922	0.226 (−1.262 to 1.715)	0.021	0.000	0.765
Age	0.037 (0.012 to 0.063)	0.196	0.038	**0.004**	−0.140 (−0.237 to −0.043)	−0.192	0.037	**0.005**	−0.106 (−0.253 to 0.040)	−0.098	0.010	0.152
Gender (male)	−0.343 (−0.965 to 0.279)	−0.074	0.006	0.279	3.220 (0.880 to 5.559)	0.183	0.034	**0.007**	0.528 (−3.005 to 4.061)	0.020	0.000	0.769
BMI	0.119 (0.057 to 0.181)	0.253	0.064	**<0.001**	−0.191 (−0.433 to 0.050)	−0.107	0.011	0.120	−0.527 (−0.881 to −0.173)	−0.198	0.039	**0.004**
HLA-B27	0.238 (−0.607 to 1.083)	0.038	0.001	0.580	−0.172 (−3.397 to 3.053)	−0.007	0.001	0.916	−1.976 (−6.756 to 2.805)	−0.056	0.003	0.416

p Values <0.05 are highlighted in bold. ASDAS, Ankylosing Spondylitis Disease Activity Score; ASspiMRI-a, Ankylosing Spondylitis spinal MRI activity; B, regression coefficient; β, standardised coefficient; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, linear definition of the Bath Ankylosing Spondylitis Metrology Index; BMI, Body Mass Index; CRP, C-reactive protein; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; R^2, an estimate of the proportion of variance in the dependent variable accounted for by the regression; SF-36 PCS, SF-36 Physical Component Summary Score; SF-36 MCS, SF-36 Mental Component Summary Score; NA, not applicable.

Table 3. Multivariate linear regression models exploring the independent association between BASFI (dependent variable) and other clinical and demographic variables

	BASFI (model 1)			BASFI (model 2)			BASFI (model 3)			BASFI (model 4)		
	B (95% CI)	**β**	**p Value**	**B (95% CI)**	**β**	**p Value**	**B (95% CI)**	**β**	**p Value**	**B (95% CI)**	**β**	**p Value**
ASDAS	0.812 (0.573 to 1.051)	0.363	**<0.001**				0.884 (0.621 to 1.147)	0.395	**<0.001**			
BASDAI				0.545 (0.418 to 0.671)	0.436	**<0.001**				0.570 (0.427 to 0.712)	0.456	**<0.001**
BASMI	0.489 (0.352 to 0.626)	0.399	**<0.001**	0.542 (0.413 to 0.671)	0.443	**<0.001**						
mSASSS							0.270 (0.002 to 0.538)	0.139	**0.048**	0.464 (0.206 to 0.723)	0.239	**<0.001**
Disease duration	–0.472 (–0.700 to –0.243)	–0.243	**<0.001**	–0.360 (–0.578 to –0.141)	–0.185	**0.001**	–0.354 (–0.604 to –0.104)	–0.183	**0.006**	–0.244 (–0.487 to –0.002)	–0.126	**0.048**
Age	0.031 (0.007 to 0.054)	0.160	**0.011**	0.026 (0.004 to 0.048)	0.134	**0.023**	0.032 (0.005 to 0.060)	0.168	**0.022**	0.021 (–0.006 to 0.047)	0.109	0.121
BMI	0.093 (0.040 to 0.144)	0.197	**0.001**	0.080 (0.030 to 0.129)	0.170	**0.002**	0.097 (0.040 to 0.154)	0.206	**0.001**	0.082 (0.027 to 0.137)	0.174	**0.004**
Gender (male)	–0.535 (–1.031 to –0.144)	–0.116	**0.034**	–0.283 (–0.756 to 0.189)	–0.062	0.239	–0.537 (–1.111 to 0.037)	–0.117	0.067	–0.385 (–0.940 to 0.171)	–0.083	0.174
	R^2=0.40			R^2=0.47			R^2=0.28			R^2=0.33		
	adjR^2=0.39			adjR^2=0.45			adjR^2=0.26			adjR^2=0.31		

p Values <0.05 are highlighted in bold. adjR^2, adjusted R^2, a better estimate of the population value of R^2; ASDAS, Ankylosing Spondylitis Disease Activity Score; B, regression coefficient; β, standardised coefficient; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, linear definition of the Bath Ankylosing Spondylitis Metrology Index; BMI, Body Mass Index; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; R^2, an estimate of the proportion of variance in the dependent variable accounted for by the regression.

is used instead of BASMI (adjR^2=0.25–0.30) in otherwise similar multivariate models (table 4).

5. SF-36 MCS was independently determined by BASFI when ASDAS was used as an independent variable (ASDAS lost statistical significance in this model, table 5, model 1), and by disease activity when BASDAI was used as an independent variable (BASFI lost statistical significance in this model, table 5, model 2). When BASFI was excluded from the models, ASDAS was also independently associated with SF-36 MCS (table 5, model 3: r=−1.82, p=0.035), similarly to BASDAI (table 5, model 4: r=−1.74, p<0.001). Overall, the robustness of the models was lower for SF-36 MCS (adjR^2=0.07–0.10) compared with SF-36 PCS and BASFI models.
6. An increase of 1 unit in BASMI leads to an estimated average increase of 0.49 in BASFI independent of the effect of ASDAS; similarly, an increase of 1 unit in ASDAS leads to an increase of 0.81 in BASFI (table 3). An increase of 1 unit in BASFI leads to a decrease of 1.7 in SF-36 PCS (table 4) and to a decrease of 1.2 in SF-36 MCS (table 5), independent of the effect of ASDAS; similarly, an increase of 1 unit in ASDAS leads to a decrease of 2.0 units in SF-36 PCS (table 4).

DISCUSSION

In a large cohort of patients we have studied the relationships between health outcomes in AS. This analysis showed that physical function is independently determined both by the level of clinical disease activity and by the degree of spinal mobility impairment, and that the physical component of HRQoL is independently determined by physical function and by the level of clinical disease activity. This study also supports the view that spinal mobility is hierarchically an intermediate variable between structural damage and physical function, while physical function itself is intermediate between spinal mobility and the physical component of SF-36.

Combined with a previous analysis of the same cohort showing that spinal mobility impairment in AS is independently determined both by irreversible radiographic spinal damage and by reversible MRI spinal inflammation,[24] the results from this study allow us to propose a stratified model for health outcomes in AS (figure 1). This stratified model endorses the ASAS core set choice of relevant domains,[2-4] and suggests that the generic domain HRQoL is highest in hierarchy and that all other domains contribute to some extent and independently to HRQoL.

The results were largely similar using either ASDAS or BASDAI as the measurement tool for clinical disease activity, providing further evidence for the validity of the ASDAS as a

Table 4. Multivariate linear regression models exploring the independent association between SF-36 PCS (dependent variable) and other clinical and demographic variables

	SF-36 PCS (model 1)			SF-36 PCS (model 2)			SF-36 PCS (model 3)			SF-36 PCS (model 4)		
	B (95% CI)	**β**	**p Value**	**B (95% CI)**	**β**	**p Value**	**B (95% CI)**	**β**	**p Value**	**B (95% CI)**	**β**	**p Value**
BASFI	−1.739 (−2.210 to −1.268)	−0.456	**<0.001**	−1.652 (−2.126 to −1.179)	−0.433	**<0.001**						
BASMI							−0.715 (−1.295 to −0.136)	−0.153	**0.016**	−0.945 (−1.502 to −0.388)	−0.202	**0.001**
ASDAS	−2.046 (−3.051 to −1.041)	−0.240	**<0.001**				−3.487 (−4.497 to −2.476)	−0.408	**<0.001**			
BASDAI				−1.309 (−1.877 to −0.741)	−0.275	**<0.001**				−2.209 (−2.755 to −1.663)	−0.464	**<0.001**
Disease duration	0.271 (−0.601 to 1.143)	0.037	0.540	−0.019 (−0.878 to 0.840)	−0.003	0.965	1.049 (0.083 to 2.015)	0.142	**0.033**	0.591 (−0.348 to 1.530)	0.080	0.216
Age	−0.092 (−0.183 to −0.001)	−0.126	**0.049**	−0.085 (−0.175 to 0.004)	−0.117	0.062	−0.148 (−0.247 to −0.049)	−0.203	**0.004**	−0.127 (−0.222 to −0.031)	−0.173	**0.010**
BMI	0.063 (−0.141 to 0.267)	0.035	0.545	0.082 (−0.119 to 0.283)	0.046	0.424	−0.101 (−0.320 to 0.119)	−0.056	0.367	−0.049 (−0.262 to 0.163)	−0.027	0.649
Gender (male)	2.572 (0.679 to 4.464)	0.146	**0.008**	1.926 (0.054 to 3.799)	0.110	**0.044**	3.451 (1.357 to 5.546)	0.196	**0.001**	2.415 (0.381 to 4.448)	0.137	**0.020**
	R^2=0.41			R^2=0.42			R^2=0.27			R^2=0.32		
	adjR^2=0.39			adjR^2=0.40			adjR^2=0.25			adjR^2=0.30		

p Values <0.05 are highlighted in bold. adjR^2, adjusted R^2, a better estimate of the population value of R^2; ASDAS, Ankylosing Spondylitis Disease Activity Score; B, regression coefficient; β, standardised coefficient; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, Body Mass Index; R^2, an estimate of the proportion of variance in the dependent variable accounted for by the regression; SF-36 PCS, SF-36 Physical Component Summary Score; SF-36 MCS, SF-36 Mental Component Summary Score.

Table 5. Multivariate linear regression models exploring the independent association between SF-36 MCS (dependent variable) and other clinical and demographic variables

	SF-36 MCS (model 1)			SF-36 MCS (model 2)			SF-36 MCS (model 3)			SF-36 MCS (model 4)		
	B (95% CI)	**β**	**p Value**	**B (95% CI)**	**β**	**p Value**	**B (95% CI)**	**β**	**p Value**	**B (95% CI)**	**β**	**p Value**
BASFI	−1.181 (−2.042 to −0.319)	−0.208	**0.007**	−0.844 (−1.707 to 0.020)	−0.149	0.056						
ASDAS	−0.736 (−2.574 to 1.101)	−0.058	0.430				−1.817 (−3.501 to −0.132)	−0.143	0.035			
BASDAI				−1.275 (−2.311 to −0.239)	−0.180	**0.016**				−1.736 (−2.664 to −0.809)	−0.245	**<0.001**
Disease duration	0.497 (−1.097 to 2.091)	0.045	0.540	0.336 (−1.230 to 1.902)	0.031	0.673	0.873 (−0.721 to 2.467)	0.079	0.281	0.492 (−1.076 to 2.060)	0.045	0.537
Age	−0.043 (−0.209 to 0.124)	−0.040	0.612	−0.055 (−0.219 to 0.108)	−0.051	0.505	−0.093 (−0.258 to 0.072)	−0.086	0.267	−0.087 (−0.248 to 0.074)	−0.081	0.286
BMI	−0.373 (−0.746 to 0.000)	−0.140	0.050	−0.376 (−0.743 to −0.009)	−0.141	**0.045**	−0.491 (−0.860 to −0.123)	−0.184	**0.009**	−0.451 (−0.813 to −0.090)	−0.169	**0.015**
Gender (male)	0.178 (−3.282 to 3.638)	0.007	0.919	−0.258 (−3.673 to 3.158)	−0.010	0.882	0.590 (−2.909 to 4.088)	0.023	0.740	−0.204 (−3.641 to 3.234)	−0.008	0.907
	R^2=0.10			R^2=0.12			R^2=0.07			R^2=0.10		
	adjR^2=0.07			adjR^2=0.10			adjR^2=0.04			adjR^2=0.08		

p Values <0.05 are highlighted in bold. adjR^2, adjusted R^2, a better estimate of the population value of R^2; ASDAS, Ankylosing Spondylitis Disease Activity Score; B, regression coefficient; β, standardised coefficient; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, Body Mass Index; R^2, an estimate of the proportion of variance in the dependent variable accounted for by the regression; SF-36 PCS, SF-36 Physical Component Summary Score; SF-36 MCS, SF-36 Mental Component Summary Score.

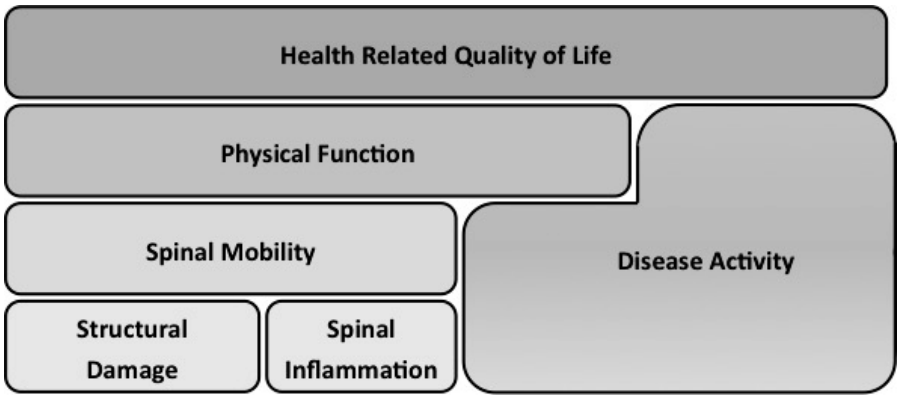

Figure 1. Stratified model for health outcomes in ankylosing spondylitis. The evidence that spinal mobility impairment in ankylosing spondylitis is independently determined both by structural damage and by spinal inflammation is derived from Machado et al.[24]

new measure of disease activity in AS. Some discrepancies were observed for the SF-36 MCS models, where BASFI and BASDAI were associated with SF-36 MCS to a greater extent than ASDAS. However, SF-36 MCS was still independently determined by ASDAS when BASFI was deleted as regressor. Erythrocyte sedimentation rate was not tested because it was not available in ASSERT, and CRP was not included in the multivariate models because its p value was >0.1 in univariate analysis.

We have estimated the numerical contribution of each variable over the other. This helps to interpret the results of the regression models by giving them a practical meaning. However, we acknowledge that this is a simplification of reality and that the relations we have investigated may not be truly linear but rather curvilinear, as previously suggested by the correlation between damage and mobility which seems to increase with the level of damage.[25]

The results from this study are consistent with a previous report[26] showing that physical function in AS is determined by the level of patient-reported disease activity and by the level of radiographic structural damage, in one of the few longitudinal studies addressing health outcomes in AS, with 188 patients included in multivariate analysis. Another longitudinal study[27] looked at 5-year predictors of disability in 212 patients and found that higher age, smoking, less frequent back exercise and worse social support were associated with a poorer functional outcome. However, this study did not adjust for other variables potentially associated with function such as structural damage, spinal mobility and disease activity.

At the cross-sectional level, Wanders et al[25] showed acceptable correlations between measures of spinal mobility and measures of structural damage; we have previously

shown an independent association between spinal mobility, spinal damage and MRI inflammation of the spine[24]; and Almodovar et al[28] described associations between functional capacity and spinal mobility measures. Vesovic-Potic et al[29] reported a negative independent association between the physical functioning domain of SF-36 and BASFI, while Ozdemir[30] showed that all SF-36 domains (except for general health) had significant negative correlations with BASDAI and BASFI scores. However, Turan et al[31] only found a significant negative correlation between the general health domain and BASDAI, and between the role-emotional domain and BASFI.

A limitation of our study is its cross-sectional design. Another limitation is that it is a clinical trial cohort involving patients with severe and active disease. It would be of interest to validate this model in patients with earlier and less severe disease status. However, we analysed a large cohort of patients (n=214) and explored a large number of outcome measures (from MRI inflammation to HRQoL), adjusting for a number of possible contributing and confounding factors. Such a broad and detailed analysis has never been reported to date. Furthermore, the items used for analysis are generally used in daily clinics and clinical studies. We believe that the associations described here are relevant for the management of patients with AS and may serve as the background model for future longitudinal studies where temporal relationships may be tested. An association does not necessarily imply causation, and only longitudinal studies can evaluate if a change in an outcome measure translates into a subsequent change in the associated measure.

In summary, we have studied in detail the relationships between several AS outcome measures and propose a stratified model for health outcomes in AS. According to this model (figure 1), HRQoL is determined by physical function and disease activity, physical function is determined by spinal mobility and disease activity, and spinal mobility is determined by structural damage and inflammation of the spine. This model explains a large percentage of the variation in the dependent variables, but not the entire variation, suggesting that other variables such as psychological, social, cultural, ethnic and educational factors should also be taken into account in future studies. However, the relationships that we describe are indisputable, are consistent with the conceptual 'continuum of outcome measures' proposed by Tennant and McKenna[12] and suggest that, in order to optimise HRQoL, both physical function and disease activity should be considered major goals in the treatment of AS. They also suggest that optimal physical function-preserving therapy should focus on improving disease activity and also on maintaining spinal mobility which, on its own, requires both the elimination of spinal inflammation and the prevention of structural damage. This stratified model explains why optimal treatment of AS should be multimodal, involving non-steroidal anti-inflammatory drugs (NSAIDs) and antitumour necrosis factor (anti-TNF) therapy (drugs that have been shown to improve patient-reported disease activity while, for MRI

inflammation of the spine, the effect is only clear for anti-TNF) as well as therapies more specifically addressing spinal mobility (such as physical therapy) and progression of structural damage (such as NSAIDs which have shown to inhibit structural progression independently of inflammation).[32]

As we learn more about how to measure AS, our knowledge about the disease improves and we can make better decisions on how to assess and treat it. The model we propose is useful both for the design and interpretation of clinical trials and also for daily clinical practice, and may contribute to guide best practice in the assessment and treatment of patients with AS.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Summary of the baseline clinical, imaging and demographic characteristics of the study population (n=214)*

Characteristics	Value
Male (n (%))	168 (78.5)
Age (years)	40 (32, 46)
Disease duration (years)	9 (3, 16)
BMI (kg/m^2)	25.5 (22.6, 27.9)
History of uveitis (n (%))	135 (63.1)
History of psoriasis (n (%))	20 (9.3)
History of IBD (n (%))	15 (7.0)
HLA-B27 positive (n (%))†	191 (89.7)
SF-36 PCS	29.5 (24.5, 34.3)
SF-36 MCS	47.1 (37.0, 53.6)
BASFI	5.7 (4.4, 6.9)
BASMI	4.6 (3.6, 5.8)
ASDAS	4.0 (3.4, 4.6)
BASDAI	6.5 (5.3, 7.0)
CRP level (mg/dl)‡	1.5 (0.7, 2.9)
mSASSS	13.8 (4.5, 29.1)
ASspiMRI-a	4.5 (0.5, 9.8)

*Except were indicated otherwise, values are the median (interquartile range). †One patient was not assessed for HLA-B27 status. ‡Normal range 0-0.5 mg/dl. ASDAS, Ankylosing Spondylitis Disease Activity Score; ASspiMRI-a, Ankylosing Spondylitis spinal Magnetic Resonance Imaging activity; BASDAI, Bath Anklyosing Spondylitis Disease Activity Index; BASMI, linear definition of the Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, Body Mass Index; CRP, C-reactive protein; IBD, Inflammatory Bowel Disease; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; SF-36 PCS, SF-36 Physical Component Summary score; SF-36 MCS, SF-36 Mental Component Summary score.

Chapter 6

MRI inflammation and its relation with measures of clinical disease activity and different treatment responses in patients with ankylosing spondylitis treated with a tumour necrosis factor inhibitor

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ABSTRACT

Objectives

To investigate the relationship between MRI inflammation and measures of clinical disease activity as well as treatment responses in patients with ankylosing spondylitis (AS) treated with a tumour necrosis factor inhibitor.

Methods

MRI at baseline (n=221), 24 (n=158) and 102 weeks (n=179) were scored for inflammation/ activity (MRIa, Berlin scoring system). Treatment responses according to the AS disease activity score (ASDAS), Bath AS disease activity index (BASDAI) and assessment of spondyloarthritis 20 (ASAS20) criteria were calculated. For each treatment response criterion, subgroups of responders and non-responders changes in MRIa scores were compared.

Results

Higher baseline ASDAS and C-reactive protein (CRP) values were associated with higher baseline MRIa scores and with greater decreases in MRIa scores at follow-up. ASDAS and CRP improvements correlated with MRIa improvement. Stronger correlations were observed for CRP. Differences in MRIa change scores between responders and non-responders were greater when subgroups were defined according to ASDAS response than according to BASDAI or ASAS20 response.

Conclusion

MRIa correlates better with CRP than with other measures of disease activity. By including both CRP and patient-reported outcomes in its formula, ASDAS has the advantage of providing combined information on objective and subjective measures. As a status and response measure ASDAS better reflects the spinal inflammatory disease process in AS than other composite measures.

INTRODUCTION

The contribution of MRI to our understanding of spondyloarthritis including ankylosing spondylitis (AS) is indisputable. MRI can be used to detect inflammatory lesions of the spine and sacroiliac joints, and spinal MRI is currently considered a powerful tool to document treatment effects by detecting improvement, persistence or new onset of spinal inflammation in AS.[1]

The relationship between MRI inflammation and measures of clinical disease activity, including the recently developed AS disease activity score (ASDAS),[2–4] is incompletely understood. Our aim was to investigate the relationship between MRI inflammation and measures of clinical disease activity as well as treatment responses in patients with AS treated with a TNF inhibitor.

METHODS

Patients and assessments

A random 80% sample of the AS Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) database was used for this analysis. Details of the ASSERT study have been published previously.[5,6] Briefly, ASSERT was a 24-week randomized controlled trial comparing infliximab monotherapy and placebo in patients with active AS, with an open extension until 102 weeks with all patients on infliximab.

MRI (T1-weighted before and after gadolinium, and short tau inversion recovery) at baseline, week 24 and week 102 were scored by two independent readers using the AS spinal MRI activity (ASspiMRI-a) score[7] that assesses 23 vertebral units of the entire spine (C2 to S1). For this analysis, ASspiMRI-a scores were re-coded using the Berlin modification[8] in order to exclude erosions from the scores. The two-way random model, absolute agreement type and average measures intraclass correlation coefficients for the Berlin re-coded MRI activity (MRIa) scores were 0.90 (baseline), 0.47 (24 weeks), 0.66 (102 weeks), 0.86 (24 weeks change) and 0.88 (102 weeks change).

The Bath AS disease activity index (BASDAI),[9] the C-reactive protein (CRP) version of the ASDAS[2–4] and individual BASDAI and ASDAS questions were used as measures of disease activity. At 24 and 102 weeks, three response criteria were calculated: ASDAS clinically important improvement (ASDAS response),[4] BASDAI 50% improvement and/or absolute change of 2 units on a 0–10 scale (BASDAI response)[1] and the assessment of spondyloarthritis 20 response (ASAS20 response).[1]

Statistical analysis

Analyses were performed for all patients at baseline (n=221), for changes in the infliximab group at 24 weeks (n=158) and for changes in all patients at 102 weeks (n=179). Spearman correlation coefficients were determined to assess the relationships between MRIa scores and disease activity measures, namely ASDAS, BASDAI and individual components of BASDAI and ASDAS (including CRP).

At 24 and 102 weeks, for each treatment response criterion (ASDAS, BASDAI and ASAS20 response), responders and non-responders were identified and changes in MRIa scores over time were compared among these responder subgroups using four statistical approaches:

The standardised mean difference (SMD) - the SMD (difference of the group means divided by the pooled SD of the group means) was used to assess the discriminatory capacity of changes in MRIa with respect to subgroups of patients with and without a clinical response. The SMD is unitless and the higher the absolute value, the greater the discriminatory capacity.

The difference in the standardised response mean (ΔSRM) between responders and non-responders - the SRM for each subgroup was calculated as the change between the mean follow-up and baseline MRIa score divided by the SD of the change score. The SRM is a measure of responsiveness and the ΔSRM was used to compare the performance of different response criteria with regard to changes in MRIa; the higher the absolute value of ΔSRM, the better the performance.

The F-score and p value of a two-sided analysis of variance on van der Waerden normal scores was used as an additional measure of discrimination; the higher the F-score, the greater the discriminatory capacity.

The area under the receiver operating characteristic (AUC) curve and its 95% CI were used to assess the discriminatory ability of changes in MRIa scores on clinical response according to the various criteria; the higher the AUC, the better the discriminatory ability.

RESULTS

Correlation analysis

At baseline, ASDAS (r=0.16, p=0.016) and CRP (r=0.28, p<0.001) correlated weakly with MRIa scores. Similarly, changes in ASDAS (r=0.22, p=0.006 at 24 weeks; r=0.23, p=0.002 at 102 weeks) and changes in CRP (r=0.25, p=0.002 at 24 weeks; r=0.32, p<0.001 at 102 weeks) correlated with changes in MRIa scores. Higher baseline ASDAS

and CRP values were associated with greater decreases in MRIa scores (ASDAS: r=−0.14, p=0.076 at 24 weeks; r=−0.15, p=0.044 at 102 weeks; CRP: r=−0.25, p=0.002 at 24 weeks; r=−0.31, p<0.001 at 102 weeks). None of the associations described for CRP and ASDAS were consistently present for BASDAI, individual BASDAI questions and patient global (table 1).

Performance of the various response criteria with regard to changes in MRIa

Differences in MRIa change scores between responders and non-responders were greater when subgroups were defined according to the ASDAS response criterion than when subgroups were defined according to the BASDAI or ASAS20 response criteria (table 2). All statistical approaches showed consistent results, with higher absolute values (modulus) for SMD, F-scores, ΔSRM and AUC when responders and non-responders were defined according to the ASDAS response criterion, in comparison with the BASDAI or ASAS20 response criteria. Differences between the various response criteria were small, especially comparing the ASDAS and BASDAI response, but more pronounced at 102 weeks than at 24 weeks (table 2).

DISCUSSION

This study shows that MRIa correlates better with CRP than with other measures of disease activity. MRIa also correlates with ASDAS, a discriminatory instrument for assessing AS disease activity that includes patient-reported outcomes and CRP levels.[2-4] Improvement in MRIa correlated with improvements in CRP and ASDAS, and a greater improvement in spinal inflammation was seen for those with higher CRP or ASDAS values at baseline. The other measures of disease activity, namely BASDAI, individual BASDAI questions and patient global, did not correlate with MRIa.

Our data are supported by recent observations from the MRI substudy of the golimumab trial in AS,[10] in which in the combined active group (75 patients) there was a significant correlation between ASDAS and ASspiMRI-a change scores at week 14 (r=0.35), and between baseline ASDAS and changes in ASspiMRI-a at both week 14 (r=−0.30) and week 104 (r=−0.33). Baseline CRP levels also correlated with baseline ASspiMRI-a (r=0.38) and with changes from baseline to weeks 14 and 104 in ASspiMRI-a (r=−0.30 and −0.33, respectively); moreover, changes from baseline to weeks 14 and 104 in CRP levels significantly correlated with changes in ASspiMRI-a (r=0.45 and 0.38, respectively). Regarding response criteria, the golimumab study only investigated the ASAS20 response, which was not significantly associated with ASspiMRI-a change scores. Similarly to our and previous reports,[11-13] in this study there were no consistent correlations between MRIa and other disease activity measures, namely BASDAI, total

Table 1. Spearman correlation coefficients (and p values) between measures of disease activity and MRIa score

	MRIa score		
	Baseline (n=221)	**Change from baseline to week 24 (n=158)***	**Change from baseline to week 102 (n=179)***
CRP			
Baseline	0.28 (<0.001)	−0.25 (0.002)	−0.31 (<0.001)
Change from baseline to week 24/week 102	NA	0.25 (0.002)	0.32 (<0.001)
ASDAS			
Baseline	0.16 (0.016)	−0.14 (0.076)	−0.15 (0.044)
Change from baseline to week 24/week 102	NA	0.22 (0.006)	0.23 (0.002)
BASDAI			
Baseline	−0.09 (0.174)	0.12 (0.132)	0.14 (0.063)
Change from baseline to week 24/week 102	NA	0.14 (0.090)	0.14 (0.057)
Patient global			
Baseline	−0.02 (0.759)	−0.02 (0.816)	0.02 (0.837)
Change from baseline to week 24/week 102	NA	0.10 (0.196)	0.12 (0.116)
BASDAI Q1—fatigue/tiredness			
Baseline	−0.08 (0.216)	0.08 (0.351)	0.08 (0.289)
Change from baseline to week 24/week 102	NA	0.11 (0.179)	0.18 (0.015)
BASDAI Q2—axial pain			
Baseline	−0.01 (0.877)	−0.02 (0.716)	0.01 (0.892)
Change from baseline to week 24/week 102	NA	0.21 (0.009)	0.18 (0.019)
BASDAI Q3—joint pain/swelling			
Baseline	−0.18 (0.008)	0.17 (0.033)	0.21 (0.004)
Change from baseline to week 24/week 102	NA	0.00 (0.976)	−0.05 (0.518)
BASDAI Q4—discomfort to touch			
Baseline	0.00 (0.983)	0.10 (0.237)	0.02 (0.797)
Change from baseline to week 24/week 102	NA	0.06 (0.436)	0.12 (0.098)
BASDAI Q5—intensity of morning stiffness			
Baseline	−0.08 (0.227)	0.11 (0.179)	0.13 (0.078)
Change from baseline to week 24/week 102	NA	0.10 (0.201)	0.12 (0.099)
BASDAI Q6—duration of morning stiffness			
Baseline	−0.05 (0.490)	0.09 (0.264)	0.10 (0.175)
Change from baseline to week 24/week 102	NA	0.07 (0.380)	0.11 (0.135)
BASDAI Q5/6—morning stiffness (inflammation)			
Baseline	−0.08 (0.262)	0.12 (0.121)	0.14 (0.064)
Change from baseline to week 24/week 102	NA	0.11 (0.171)	0.14 (0.063)

*Data are shown for the all patients at baseline, for changes in the infliximab group at 24 weeks (placebo-controlled phase of the ASSERT trial) and for changes in all patients at 102 weeks (open extension phase of the ASSERT trial); the corresponding follow-up change score in each clinical/laboratory variable was used to calculate the correlation coefficient with MRI change scores.

ASDAS, ankylosing spondylitis disease activity score; ASSERT, AS Study for the Evaluation of Recombinant Infliximab Therapy; BASDAI, Bath ankylosing spondylitis disease activity index; CRP, C-reactive protein; MRIa, MRI activity; NA, not applicable; Q, question.

Table 2. Measures of discrimination and responsiveness for changes in MRIa score according to different types of treatment response

	MRIa score													
	Change from baseline to week 24 (n=158)*							Change from baseline to week 102 (n=179)*						
	Mean (SD)	**Median (IQR)**	**SRM**	**ΔSRM**	**SMD**	**F-score (p value)†**	**AUC (95% CI)**	**Mean (SD)**	**Median (IQR)**	**SRM**	**ΔSRM**	**SMD**	**F-score (p value)†**	**AUC (95% CI)**
ASDAS response‡														
No	−2.3 (4.0)	−1 (−4, 0)	−0.56	–	–	–	–	−2.3 (4.1)	−1 (−5, 0)	−0.57	–	–	–	–
Yes (Δ ≥1.1)	−4.3 (4.8)	−3 (−8, 0)	−0.90	−0.34	−0.45	6.4 (0.012)	0.63 (0.54, 0.72)	−5.0 (5.0)	−4 (−8, −1)	−0.99	−0.42	−0.56	13.8 (<0.001)	0.66 (0.58, 0.75)
BASDAI response‡														
No	−2.6 (4.3)	−1 (−4, 0)	−0.60	–	–	–	–	−3.1 (4.7)	−1 (−5, 0)	−0.66	–	–	–	–
Yes (Δ≥50% and/or Δ≥2)	−4.3 (4.7)	−3 (−8, 0)	−0.91	−0.31	−0.37	5.4 (0.022)	0.61 (0.52, 0.70)	−4.7 (4.9)	−4 (−8, −1)	−0.96	−0.30	−0.32	5.2 (0.023)	0.61 (0.52, 0.70)
ASAS20 response‡														
No	−3.1 (4.7)	−2 (−5, 0)	−0.66	–	–	–	–	−3.2 (4.7)	−2 (−6, 0)	−0.68	–	–	–	–
Yes (ASAS20)	−4.0 (4.6)	−2 (−8, 0)	−0.88	−0.22	−0.19	1.5 (0.221)	0.56 (0.47, 0.65)	−4.6 (4.9)	−3 (−8, −1)	−0.93	−0.25	−0.29	4.8 (0.030)	0.59 (0.49, 0.69)

ASAS20 response criterion is based on four independent domains: spinal pain, physical function measured by the Bath ankylosing spondylitis functional index, patient global assessment and inflammation measured as the mean of the last two BASDAI questions (severity and duration of morning stiffness); ASAS20 treatment response is defined as improvement of 20% or greater and 1 unit or greater (range 0–10) in at least three of the four above domains, and no worsening of 20% or greater and 1 unit or greater in the remaining fourth domain. BASDAI response is defined by at least 50% improvement or absolute improvement of at least 2 units on a 0–10 scale. ASDAS response is defined by an improvement of at least 1.1 units in ASDAS.

*Data are shown for the infliximab group at 24 weeks (placebo-controlled phase of the ASSERT trial) and for all patients at 102 weeks (open extension phase of the ASSERT trial). †Results from analysis of variance on van der Waerden normal scores. ‡Percentage of patients achieving a response at 24 weeks: ASDAS response, 69%; BASDAI response, 64%; ASAS20 response, 61%. Percentage of patients achieving a response at 102 weeks: ASDAS response, 73%; BASDAI response, 70%; ASAS20 response, 68%.

ASSERT, AS Study for the Evaluation of Recombinant Infliximab Therapy; ASDAS, ankylosing spondylitis disease activity score; AUC, area under the receiver operating characteristic curve; BASDAI, Bath ankylosing spondylitis disease activity index; SMD, standardised mean difference; SRM, standardised response mean.

back pain and morning stiffness.

Other previous studies provided conflicting or inconsistent results and were limited by the small numbers of patients, short follow-up time (or cross-sectional nature) and frequently only lumbar spine and/or sacroiliac joint MRI assessment.[14-17] We found weak to moderate correlations between CRP/ASDAS and MRIa scores. Therefore, these clinical and laboratory measures cannot be used to replace MRI assessment of spinal inflammation, which has become an important tool in the diagnosis, management, monitoring and prognosis of patients with axial spondyloarthritis. Nevertheless, in this respect, ASDAS performs better than BASDAI because it is more capable of measuring spinal inflammation and changes in spinal inflammation than BASDAI.

A limitation of our study is that it was a clinical trial cohort involving rather severe and active patients. It would be of interest to investigate these relationships in patients with earlier and less severe disease status or in a mixed cohort of patients. However, we have analysed the largest cohort of patients to date (158–221 patients) and explored a large number of disease activity measures and response criteria. Such a broad and detailed analysis has never been reported. Furthermore, and in contrast to the majority of previous studies,[14-16] we included MRIa assessment of the entire spine; importantly, it has been reported that spinal inflammatory lesions are more frequent in the thoracic spine.[17,18]

In summary, in a large population of AS patients treated with infliximab, baseline levels and improvements in spinal inflammation correlated with baseline levels and improvements in ASDAS and CRP, but not with various other subjective measures of disease activity. By including both CRP and patient-reported outcomes in its formula, ASDAS has the advantage of providing combined information on objective and subjective measures. As a status and response measure ASDAS better reflects the spinal inflammatory disease process in AS than BASDAI. This study strengthens the construct validity of ASDAS and provides further evidence that ASDAS may be a useful tool for monitoring patients with axial spondyloarthritis.

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Chapter 7

HLA-B27 positive patients differ from HLA-B27 negative patients in clinical presentation and imaging: results from the DESIR cohort of patients with recent onset axial spondyloarthritis

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ABSTRACT

Objectives

To clarify the influence of human leucocyte antigen B27 (HLA-B27) status on the phenotype of early axial spondyloarthritis (SpA).

Methods

708 patients with inflammatory back pain (IBP) defined by Calin or Berlin criteria were recruited; 654 fulfilled at least one of the SpA criteria (modified New York, European Spondyloarthropathy Study Group, Amor or Assessment of SpondyloArthritis international Society classification criteria for axial SpA) and were included in the analyses. Clinical, demographic and imaging parameters were compared between HLA-B27 positive and negative groups. Significant parameters in univariate differences between HLA-B27 positive and negative groups were retested in multivariate models explaining various outcomes.

Results

Patients had a short duration of axial symptoms (mean 1.5 years) and HLA-B27 was present in 61.5%. In multivariate analysis, HLA-B27 positivity was associated with a younger age at onset of IBP (regression coefficient (B)=(−2.60), $p<0.001$), less delay in diagnosis (B=(−1.02), $p=0.01$), lower frequency of psoriasis (OR 0.59, $p=0.01$) and higher frequency of MRI inflammation of the sacroiliac joints (SIJ) (OR 2.13, $p<0.001$), MRI inflammation of the spine (OR 1.59, $p=0.04$) and radiographic sacroiliitis (OR 1.56, $p=0.03$). MRI inflammation of the SIJ was shown to be an intermediate variable between HLA-B27 positivity and radiographic sacroiliitis.

Conclusion

In early axial SpA, HLA-B27 is associated with earlier onset of IBP, less delay in diagnosis, axial inflammation (spine and SIJ), radiographic damage of the SIJ, decreased disease activity and lower frequency of psoriasis. It is not associated with physical function and MRI structural lesions of the SIJ.

INTRODUCTION

Spondyloarthritis (SpA) describes a spectrum of rheumatic diseases where inflammatory back pain (IBP) is a typical feature. The disease is associated with the human leucocyte antigen B27 (HLA-B27) and has other important clinical features such as asymmetrical peripheral arthritis (lower limb predominance), enthesitis, dactylitis, uveitis, psoriasis and inflammatory bowel disease.

Since HLA-B27 was first reported in 1973, its role in the diagnosis, prognosis and management of SpA has been extensively investigated. It is estimated to be present in 75–95% of cases of ankylosing spondylitis (AS) and 42–75%[1–6] of cases of axial non-radiographic/undifferentiated SpA. Its diagnostic importance is reflected by the inclusion of HLA-B27 in the Amor criteria for spondyloarthropathy in 1990[7] and in the Assessment of SpondyloArthritis international Society (ASAS) classification criteria[8,9] for axial SpA in 2009. HLA-B27 is also known to be associated with earlier age of axial SpA onset,[2,10] increased severity and persistence of MRI-demonstrated inflammation at the sacroiliac joints (SIJ) and lumbar spine in early IBP,[11] and anterior uveitis in SpA patients.[10,12]

However, the exact role of HLA-B27 in early axial SpA is still unknown as previous studies focused mainly on its association with AS. The recent shift in focus to earlier diagnosis has enabled more patients to be classified as axial SpA. It is therefore important to explore the role of HLA-B27 in this early disease phase. Our aim was to clarify the influence of HLA-B27 status on the phenotype of early axial SpA. The results may provide important information about its contribution to disease spectrum manifestations in axial SpA.

METHODS

Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) is a prospective longitudinal cohort in France involving 25 rheumatology centres and 708 patients.[13] The aim of DESIR is to study comprehensively the nature and outcome of SpA from early symptom onset. The data presented here comprise a cross-sectional analysis of baseline data of all patients included in DESIR (inclusion period October 2007 to April 2010).

Inclusion and Exclusion

Consecutive patients aged >18 years and <50 years with IBP involving the thoracic, lumbar spine or buttock area for >3 months but <3 years and symptoms suggestive of SpA according to the rheumatologists' assessment (score ≥5 on a Numerical Rating

Scale (NRS) of 0–10 where 0=not suggestive and 10=very suggestive of SpA) were included in the DESIR cohort. Patients had to fulfil the IBP criteria of Calin et al[14] or Berlin.[15] Patients with a definite diagnosis of non-SpA back pain, conditions which might interfere with the validity of the informed consent and/or prevent an optimal compliance (eg, alcoholism, psychiatric disorders) and a history of anti-tumour necrosis factor usage were excluded. Corticosteroid intake was permitted only in doses of <10 mg prednisone per day and had to be stable for at least 4 weeks before recruitment. Details of the protocol and the case record form are accessible on the website.[16] Patients with non-inflammatory chronic back pain were not included in DESIR, although they may represent up to 20–30% of patients with axial SpA.[17]

The sample size was based on the estimated predictive validity of sacroiliac evaluation.[13,16] The last patient was recruited on 29 April 2010 and the database used in our study was locked on 30 June 2010 (intended follow-up of the cohort 10 years). Patients were classified according to different criteria for AS and SpA: modified New York (MNY) criteria,[18] European Spondyloarthropathy Study Group (ESSG) criteria,[19] Amor criteria[7] and ASAS classification criteria for axial SpA.[8,9] Only patients fulfilling at least one of these criteria were included in our analyses.

Study design

In the DESIR cohort, patients are evaluated every 6 months for the first 2 years and annually thereafter. In the present analysis we only used data collected at the first visit. Patients were interviewed for baseline characteristics which included age, ethnicity, date at onset of IBP and peripheral arthritis, nature of IBP, presence of SpA features, relevant family history, medication including use of non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs and the number of patient-reported missed work days in the previous year. The duration of axial symptoms was defined as the time difference between the first axial symptom and the initial interview. Delay in diagnosis was defined as the time difference between the onset of any SpA feature and SpA diagnosis by the physician. Physical examination was also performed to determine the Ritchie articular index (53 joints) and swollen joint count (28 joints), spinal mobility as measured by the Bath Ankylosing Spondylitis Metrology Index (BASMI)[20] and chest expansion. Extra-articular features were evaluated in those with relevant complaints.

Intensity of axial, nocturnal and peripheral joint pain was measured on a NRS of 0–10. Patients were asked to complete the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[21] and the Bath Ankylosing Spondylitis Functional Index (BASFI).[22]

Blood tests were performed in the regional rheumatology centres. These included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and HLA-B27 antigen.

The Ankylosing Spondylitis Disease Activity Score (ASDAS),[23] recently validated for assessing disease activity in AS,[24] was calculated using either CRP (ASDAS-CRP) or ESR (ASDAS-ESR). An ASDAS value ≥2.1 represents high disease activity.[25]

All imaging modalities (x-rays and MRIs) were evaluated by the local radiologist or rheumatologist; x-rays of the SIJ were graded according to the following grading scale: 0=normal, 1=doubtful, 2=obvious and 3=fusion, and radiographic sacroiliitis was defined as the presence of grade 2 or grade 3 lesions. Lateral x-rays of the cervical and lumbar spine were used to calculate the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).[26]

T1-weighted fast spin echo and short tau inversion recovery 1–1.5 tesla MRIs of the whole spine and the SIJ were performed to assess inflammatory and structural lesions (missing MRI data in 6.0–6.9% of patients). The MRIs were classified as having definite, doubtful or absent inflammatory (bone oedema) or structural lesions (erosions, sclerosis or bone formation) at the spinal and sacroiliac level, according to ASAS recommendations.[27] Doubtful images were considered as being negative images.

Statistical methods

SPSS Version 17.0 was used for data analysis. Differences between HLA-B27 positive and negative patients were investigated using the χ^2 statistic and independent sample t test for categorical and continuous variables, respectively. Variables noted to have differences in the t tests/χ^2 statistic were used as dependent variables in univariate and multivariate linear/logistic regression analysis. Based on previous literature and knowledge about the disease, other factors in addition to HLA-B27 status known or expected to be associated with the dependent variable under study were also tested in univariate analyses - namely, ethnicity, gender, family history of SpA, current use of NSAIDs, MRI inflammation, duration of IBP, acute phase reactants, clinical disease activity and spinal mobility. Significant ($p<0.1$) independent variables in univariate analyses were retested in multivariate regression models. Interactions between HLA-B27 and gender were tested in each model. Separate regression models were built according to gender if such an interaction existed. Variables with a skewed distribution were transformed using natural logarithms (ln) in linear regression models (ESR and CRP). The results were reported as OR in logistic regression models and regression coefficients (B) and standard coefficients (β) in linear regression models. p Values <0.05 were considered statistically significant in multivariate regression models.

RESULTS

Baseline characteristics

Of the 708 patients included in the DESIR cohort, 654 patients (92.4%) fulfilled at least one of the SpA criteria and were included in the analysis (figure 1). Discordant cases differed in HLA-B27 status, with a subgroup of mainly HLA-B27 negative patients fulfilling ESSG and/or Amor criteria but not ASAS criteria for axial SpA, and a subgroup of mainly HLA-B27 positive patients fulfilling ASAS criteria for axial SpA but not ESSG or Amor (figure 1). The analysed cohort included slightly more women (54%) and HLA-B27

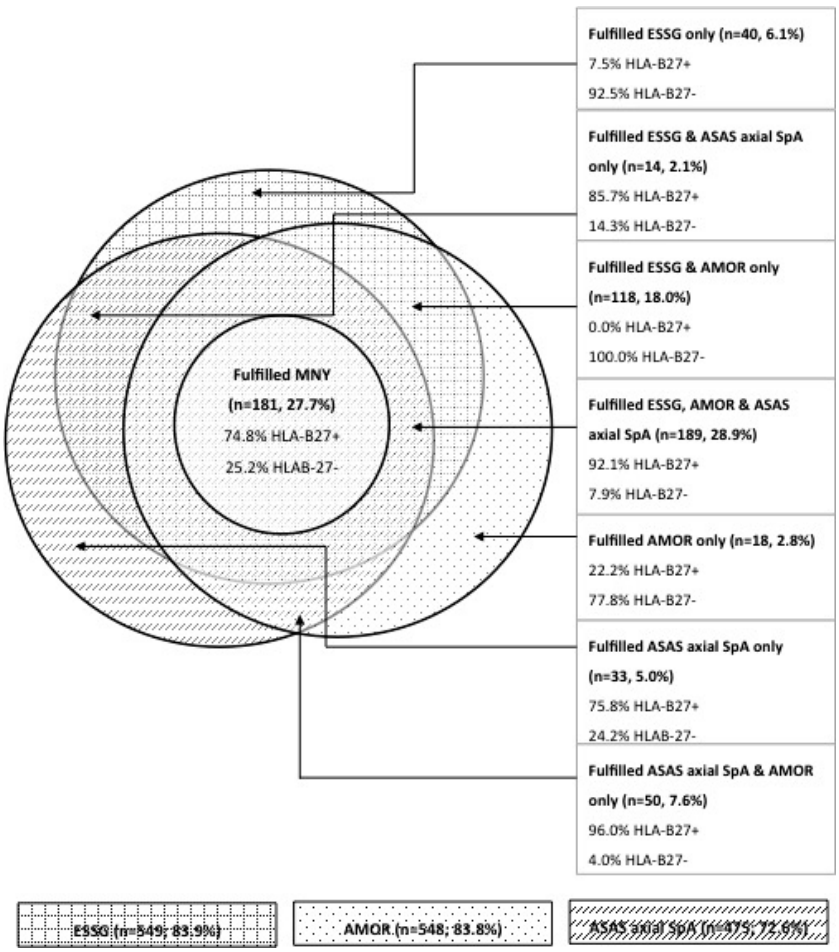

Figure 1. Frequency of HLA-B27 positivity in various subgroups of spondyloarthritis (SpA) classification criteria. AMOR, Amor criteria for spondyloarthropathy; ASAS axial SpA, Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis; ESSG, European Spondyloarthropathy Study Group criteria; MNY, modified New York criteria.

was positive in 61.5% of the patients.

Our cohort was characterised by young age (mean 33.6 years, median 33.0 years) and short duration of axial symptoms (mean 1.5 years, median 1.4 years). Patients had high disease activity (mean BASDAI 4.5, median 4.6), minimal radiographic spinal damage (mean mSASSS 1.1, median 0.0) and moderately affected physical function (mean BASFI 3.1, median 2.6).

Comparisons of baseline characteristics between HLA-B27 positive and negative groups are shown in table 1. The dependent variables selected for regression analysis were: age at onset of IBP, delay in diagnosis, clinical disease activity (ASDAS-CRP and BASDAI), MRI inflammatory lesions of the spine and SIJ, MRI structural lesions of the SIJ, radiographic sacroiliitis, extra articular features and physical function (BASFI).

Regression analysis

A core set of four independent variables were investigated in all univariate analyses: Caucasian race, male gender, HLA-B27 positivity and family history of SpA. Additional independent variables were tested according to the dependent variable under study.

Age at onset of IBP as dependent variable

All the independent variables in the above core set showed a p value of <0.1 in univariate analyses (Caucasian race (B=2.50, p=0.03), male gender (B=(−2.06), p=0.003), HLA-B27 positivity (B=(−2.95), p<0.001) and family history of SpA (B=1.58, p=0.05)) and were therefore retested in multivariate linear regression analysis.

In multivariate analysis, the age at onset of IBP was found to be positively associated with Caucasian race (β=0.12, B=3.54, 95% CI 1.31 to 5.76, p=0.002) and negatively associated with HLA-B27 positivity (β=(−0.15), B=(−2.60), 95% CI −4.02 to −1.19, p<0.001) and male gender (β=(−0.10), B=(−1.77), 95% CI −3.14 to −0.40, p=0.01). The percentage of HLA-B27 positivity in relation to age at onset of IBP is shown in figure 2.

Delay in diagnosis as dependent variable

From the core set of independent variables, only HLA-B27 positivity was significantly associated with delay in diagnosis. This association was negative (β=(−0.11), B=(−1.02), 95% CI −1.75 to −0.28, p=0.01).

Table 1. Comparison of baseline characteristics between HLA-B27 positive and negative patients

	HLA-B27 positive	HLA-B27 negative	p Value
Male gender	206 (51.2%)	92 (37.4%)	0.001
Mean age (years)	32.5±8.4	35.6±8.7	<0.001
Mean age at onset of IBP (years)	31.0±8.5	34.0±8.8	<0.001
Mean duration of axial symptoms (years)	1.5±1.0	1.5±0.8	0.64
Mean delay in diagnosis (years)	2.7±4.2	3.7±5.1	0.01
Caucasian race	368 (91.5%)	212 (86.5%)	0.04
Family history of ankylosing spondylitis	120 (30.2%)	48 (19.7%)	0.003
Presence of peripheral arthritis	216 (53.9%)	165 (67.3%)	0.001
Mean age at onset of peripheral arthritis (years)	31.5±9.6	32.8±8.7	0.02
Presence of enthesitis	186 (46.3%)	158 (64.2%)	<0.001
Using NSAIDs	299 (74.4%)	147 (59.8%)	<0.001
Ever used NSAIDs	386 (96.0%)	217 (88.2%)	<0.001
Using steroids	54 (13.4%)	29 (11.8%)	0.54
Using DMARDs	36 (9.0%)	23 (9.3%)	0.87
Ever used DMARDs	54 (13.5%)	36 (14.6%)	0.68
Using analgesics	249 (61.9%)	164 (66.7%)	0.23
Mean CRP (mg/l)	8.1±14.0	7.6±14.0	0.67
Percentage of patients with elevated CRP	28.6	30.6	0.59
Mean ESR (mm/h)	14.5±16.3	14.0±16.0	0.72
Percentage of patients with elevated ESR	22.0	17.6	0.19
Percentage of patients with elevated CRP or ESR	34.1	37.4	0.40
Dactylitis	54 (13.4%)	38 (15.4%)	0.48
Presence of any extra-articular features	98 (24.4%)	82 (33.3%)	0.01
Psoriasis	57 (14.2%)	52 (21.1%)	0.02
Crohn's disease	7 (1.7%)	11 (4.5%)	0.04
Ulcerative colitis	5 (1.2%)	9 (3.7%)	0.04
Palmoplantar pustulosis	5 (1.2%)	3 (1.2%)	0.98
History of uveitis	38 (9.5%)	18 (7.3%)	0.35
BASDAI	4.2±2.1	4.9±1.8	<0.001
BASDAI ≥4	213 (53.4%)	178 (73.3%)	<0.001
ASDAS-CRP	2.4±1.1	2.7±1.0	0.07
ASDAS-CRP >2.1	233 (60.5%)	159 (68.2%)	0.053
ASDAS-ESR	2.4±1.0	2.7±0.9	0.04
ASDAS-ESR >2.1	226 (59.0%)	159 (70.4%)	0.01
BASFI	2.8±2.2	3.5±2.3	<0.001
BASFI ≥4	120 (30.2%)	99 (41.4%)	0.004
Intensity of axial pain (NRS)	4.6±2.8	5.5±2.5	<0.001
Intensity of nocturnal axial pain (NRS)	4.3±3.1	5.1±2.8	<0.001
Intensity of peripheral joints pain (NRS)	3.0±2.8	3.8±2.7	<0.001
Physician global assessment	4.2±2.2	4.6±2.1	0.01
Tender joint count (53 joint count)	3.4±6.6	6.2±10.8	<0.001
Swollen joint count (28 joint count)	0.1±0.7 8.5	0.2±1.0 7.3	0.28
Percentage of patients with swollen joint(s)	8.5	7.3	0.55
Number of missing work days due to spondyloarthritis	26.6±55.3	46.7±87.9	0.003
BASMI	2.2±0.9	2.4±0.9	0.03
Chest expansion (cm)	5.7±2.0	5.5±2.3	0.33
MRI inflammatory lesions of the SIJ	168 (44.1%)	57 (24.9%)	<0.001
MRI inflammatory lesions of the spine	98 (25.9%)	38 (16.8%)	0.01
MRI structural lesions of the SIJ	119 (31.2%)	49 (21.4%)	0.01
MRI structural lesions of the spine	38 (10.1%)	16 (7.2%)	0.23
Definite radiographic changes in SIJ	131 (32.8%)	49 (19.4%)	0.001
mSASSS	1.2±3.0	0.9±2.9	0.34
mSASSS >0	105 (26.9%)	51 (22.1%)	0.18

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HLA-B27, human leucocyte antigen B27; IBP, inflammatory back pain; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; NSAIDs, non-steroidal anti-inflammatory drugs; NRS, Numerical Rating Scale; SIJ, sacroiliac joints.

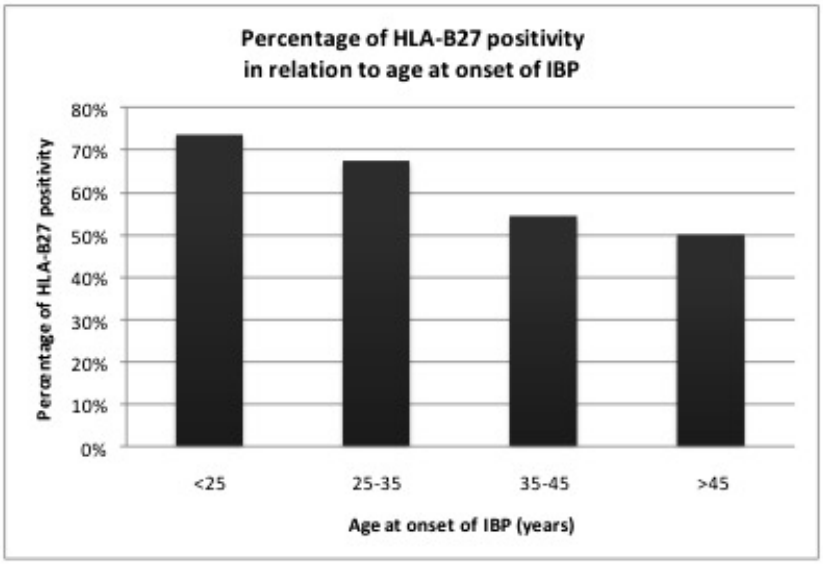

Figure 2. Percentage of HLA-B27 positivity in relation to age at onset of inflammatory back pain (IBP). Spondyloarthritis (SpA) was defined as patients fulfilling at least one of the following criteria: modified New York criteria, European Spondyloarthropathy Study Group criteria, Amor criteria or Assessment of SpondyloArthritis international Society classification criteria for axial SpA.

ASDAS-CRP and BASDAI as dependent variables

In addition to the core set of four independent variables, the following variables were also investigated in univariate regressions: MRI inflammatory lesions of SIJ, MRI inflammatory lesions of the spine and current use of NSAIDs. CRP and ESR were also tested in models with BASDAI as dependent variable.

Significant variables in the ASDAS-CRP univariate linear regression analysis were Caucasian race (B=(−0.57), p<0.001), HLA-B27 positivity (B=(−0.20), p=0.02) and MRI spinal inflammation (B=0.21, p=0.04). For BASDAI analysis, significant variables were Caucasian race (B=(−1.07), p<0.001), male gender (B=(−0.63), p<0.001), HLA-B27 positivity (B=(−0.75), p<0.001), CRP (B=0.25, p<0.001), ESR (B=0.46, p<0.001) and MRI inflammatory lesions of SIJ (B=(−0.60), p<0.001). The results of multivariate linear regression models are shown in table 2. ASDAS-CRP and BASDAI were found to be negatively associated with HLA-B27 positivity.

Imaging outcomes

Independent variables investigated in univariate regressions for all imaging outcomes included the core set of four independent variables and age at onset of IBP, duration of IBP, CRP and current use of NSAIDs.

Table 2. Multivariate linear regression analysis of factors associated with ASDAS-CRP and BASDAI

	ASDAS-CRP			BASDAI		
	Standard coefficient	**Regression coefficient (95% CI)**	**p Value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p Value**
HLA-B27 positivity	−0.11	−0.23 (−0.40 to −0.05)	0.01	−0.13	−0.53 (−0.86 to −0.21)	<0.001
Caucasian race	−0.16	−0.56 (−0.83 to −0.28)	<0.001	−0.17	−0.91 (−1.45 to −0.38)	0.001
Male gender	NS	NS	NS	−0.09	−0.34 (−0.68 to −0.00)	0.048
CRP	NI	NI	NI	0.11	0.18 (0.03 to 0.33)	0.02
ESR	NI	NI	NI	0.13	0.31 (0.10 to 0.52)	0.01
MRI spinal inflammation	0.10	0.24 (0.04 to 0.44)	0.02	NS	NS	NS
MRI SIJ inflammation	NS	NS	NS	−0.16	−0.66 (−1.00 to −0.32)	<0.001

ASDAS, Ankylosing Spondylitis Disease Activity Score (CRP-based); BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leucocyte antigen B27; NI, not included in multivariate analysis; NS, not significant in multivariate analysis; SIJ, sacroiliac joints.

Table 3. Multivariate logistic regression analysis of factors associated with MRI inflammatory lesions and radiographic sacroiliitis

	MRI inflammatory lesions (SIJ or spine)		MRI inflammatory lesions of the SIJ		MRI inflammatory lesions of the spine		Radiographic sacroiliitis	
	OR (95% CI)	**p Value**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
HLA-B27 positivity	2.08 (1.44 to 3.01)	<0.001	2.13 (1.44 to 3.15)	<0.001	1.59 (1.02 to 2.46)	0.04	1.56 (1.04 to 2.33)	0.03
Caucasian race	NS	NS	0.49 (0.27 to 0.86)	0.01	NS	NS	NS	NS
Male gender	1.80 (1.27 to 2.56)	0.001	1.85 (1.28 to 2.66)	0.001	2.07 (1.37 to 3.12)	0.001	1.56 (1.07 to 2.28)	0.02
Age at onset of IBP	0.98 (0.96 to 1.00)	0.045	0.97 (0.95 to 0.99)	0.01	NS	NS	0.97 (0.95 to 0.99)	0.04
Family history of SpA	NS	NS	NS	NS	NS	NS	NS	NS
CRP	1.02 (1.00 to 1.03)	0.01	1.01 (1.00 to 1.03)	0.047	1.02 (1.00 to 1.03)	0.01	1.02 (1.01 to 1.03)	0.03

CRP, C-reactive protein; HLA-B27, human leucocyte antigen B27; IBP, inflammatory back pain; NS, not significant in multivariate analysis; SIJ, sacroiliac joints; SpA, spondyloarthritis.

MRI inflammatory lesions as dependent variable

Significant variables associated with MRI inflammatory lesions in the univariate models were as follows:

1. SIJ: Caucasian race (OR 0.59, p=0.05), male gender (OR 2.37, p<0.001), HLA-B27 positivity (OR 2.38, p<0.001), age at onset of IBP (OR 0.96, p<0.001) and CRP (OR 1.02, p=0.002).
2. Spine: male gender (OR 2.47, p<0.001), HLA-B27 positivity (OR 1.73, p=0.01), family history of SpA (OR 1.68, p=0.03) and CRP (OR 1.02, p=0.03).
3. SIJ or spine: male gender (OR 2.32, p<0.001), HLA-B27 positivity (OR 2.33, p<0.001), age at onset of IBP (OR 0.97, p=0.001) and CRP (OR 1.02, p=0.001).

Table 3 shows the multivariate logistic regression models for MRI inflammatory lesions of the SIJ and/or the spine: male gender and HLA-B27 positivity were positively associated with MRI inflammatory lesions of the SIJ and/or the spine. An interaction between male gender and HLA-B27 positivity was found in the regression model for SIJ: more men had MRI SIJ inflammatory lesions (47.5% of men; 27.9% of women), and a stronger association was observed between HLA-B27 positivity and MRI inflammatory lesions of the SIJ in the men (OR 2.80, 95% CI 1.56 to 5.05, p=0.001). This association was lost in the women.

MRI structural lesions of the SIJ and radiographic sacroiliitis as dependent variables

Significant variables associated with MRI structural lesions of the SIJ in univariate analysis were HLA-B27 positivity (OR 1.67, p=0.01), age at onset of IBP (OR 0.97, p=0.002) and CRP (OR 1.01, p=0.04). For radiographic sacroiliitis, associated variables were male gender (OR 1.96, p<0.001), HLA-B27 positivity (OR 1.91, p=0.001), age at onset of IBP (OR 0.96, p<0.001) and CRP (OR 1.02, p<0.001). In multivariate analysis, HLA-B27 positivity was found to be positively associated with radiographic sacroiliitis (table 3) while the association with MRI structural lesions of the SIJ was lost.

When included as one of the regressors in the multivariate models, MRI inflammation of the SIJ was found to be associated with MRI inflammation of the spine (OR 3.87, 95% CI 2.52 to 5.94, p<0.001) and radiographic sacroiliitis (OR 9.75, 95% CI 6.26 to 15.18, p<0.001). The independent associations with HLA-B27 were lost in these models.

Extra-articular features as dependent variables (uveitis, psoriasis, Crohn's disease, ulcerative colitis and palmoplantar pustulosis)

Independent variables investigated in univariate regressions included the core set of four independent variables and age at onset of IBP, duration of IBP, CRP, ESR and current use of NSAIDs. In univariate regression, Crohn's disease, ulcerative colitis and psoriasis were negatively associated with HLA-B27 (OR 0.38, p=0.048; OR 0.33, p=0.05; and OR 0.62, p=0.02, respectively). However, in multivariate analyses, only psoriasis was found to be associated negatively with HLA-B27 (OR 0.59, 95% CI 0.39 to 0.90, p=0.01).

BASFI as dependent variable

Independent variables investigated in univariate regressions included the core set of four independent variables and MRI inflammatory lesions of the SIJ, MRI inflammatory lesions of the spine, current use of NSAID, ASDAS-CRP and BASMI. Significant variables associated with BASFI in the univariate models included Caucasian race (B=(−0.68), p<0.001), male gender (B=(−0.57), p=0.002), HLA-B27 positivity (B=(−0.66), p<0.001), MRI inflammatory lesions of SIJ (B=(−0.39), p=0.04), MRI inflammatory lesions of the spine (B=0.46, p=0.04), ASDASCRP (B=1.30, p<0.001) and BASMI (B=0.85, p<0.001). In multivariate analysis, BASFI was not associated with HLA-B27 positivity (β=(−0.05), B=(−0.25), 95% CI −0.56 to 0.05, p=0.11).

DISCUSSION

The analyses of the large DESIR cohort resulted in important new insights into the phenotypic associations in patients with early axial SpA. HLA-B27 was independently associated with earlier age at onset of IBP, less delay in diagnosis, MRI spinal and SIJ inflammation, radiographic sacroiliitis and lower frequency of psoriasis. In addition, MRI SIJ inflammation was associated with MRI spinal inflammation and with radiographic damage of the SIJ.

The effects of HLA-B27 status on age at disease onset have been reported in previous studies but not in patients with such a short duration of symptoms. Feldtkeller et al[10] reported an earlier age at disease onset in HLA-B27 positive patients with AS. Recently, the German Spondyloarthritis Inception Cohort also reported such an association in patients with expert-diagnosed axial SpA (radiographic and non-radiographic) with mean symptom duration of 5.2 years.[2] We report the presence of such an association even in the very early stage of the disease, further supporting the concept of axial SpA as a continuous spectrum.

The regression models for MRI lesions and radiographic sacroiliitis yielded new and relevant findings. Our models showed that HLA-B27 positivity was independently associated with MRI inflammation of the SIJ and the spine, while MRI inflammation of the SIJ was independently associated with radiographic sacroiliitis. Interestingly, when MRI inflammation of the SIJ was removed from the models, HLA-B27 positivity was also found to be associated with MRI spinal inflammation and radiographic sacroiliitis. HLA-B27 therefore seems to be contributing to SIJ inflammation which may lead to subsequent structural damage, inflammation being an intermediate variable between HLA-B27 and SIJ structural damage. The association between radiographic sacroiliitis and HLA-B27 positivity also suggests that the HLA-B27 group may have more rapid progression of new bone formation, a phenomenon where inflammation may play an intermediate role. These findings are consistent with previous findings of HLA-B27 association with radiographic sacroiliitis as well as with the severity and persistence of MRI-demonstrated inflammatory changes in the SIJ and lumbar spine in early IBP.[11]

The association between MRI SIJ and spinal inflammation is expected as inflammation at both sites shares similar mechanisms. The association between MRI SIJ inflammation and structural damage is also consistent with a recent follow-up study showing that MRI SIJ activity is related to the diagnosis of AS (according to MNY criteria) at follow-up.[28] Our model for radiographic sacroiliitis also echoes previous findings showing that MRI sacroiliitis in HLA-B27 positive patients with IBP has high specificity for development of MNY-defined AS.[29]

Apart from HLA-B27 positivity, we found male gender to be independently associated with MRI inflammation. Although in previous studies male gender had been associated with more severe spinal radiographic damage,[30] we did not find a similar association, possibly due to the early disease phase of our cohort, with very low mSASSS values. Further follow-up of the DESIR cohort may reveal this association.

The analyses of extra-articular features showed a negative association between HLA-B27 positivity and psoriasis. This is probably due to the selection bias of HLA-B27 negative patients (by the Amor criteria) because they require more extra-articular features in order to be classified as having SpA.

Finally, the negative association between HLA-B27 positivity and clinical disease activity (ASDAS-CRP and BASDAI) was a rather unexpected finding. This could be explained by increased use of NSAIDs in HLA-B27 positive patients during the survey (table 1). Furthermore, a decreased delay in diagnosis was also found in the HLA-B27 positive group. We therefore hypothesise that HLA-B27 positive patients may have lower disease activity because they were diagnosed earlier and were more adequately treated than HLA-B27 negative patients. These findings highlight the importance of early diagnosis and treatment.

It is noteworthy that ASDAS-CRP was positively associated with MRI inflammation of the spine while BASDAI was negatively associated with MRI inflammation of the SIJ. These results support the validity of ASDAS-CRP as a measurement instrument for clinical disease activity in early axial SpA and suggest that ASDAS-CRP performs better than BASDAI.

Our study has several limitations. First, there is no international consensus about the assessment of chronic MRI lesions which limits their interpretation. Second, images were not anonymised, which may have biased some of the imaging results. However, the technique used to acquire the images was standardized and centres were selected based on the experience of investigators in conducting multicentre controlled trials, longitudinal epidemiological studies and had to fulfil predefined quality standards. The use of such quality standards is likely to have reduced the potential of bias and increased the quality of the imaging evaluation. A third limitation of our study relates to the potential exclusion of affected joints using the Richie articular index and 28-joint count instead of a more extensive joint count (eg, 66/68 joint count).

The DESIR cohort enabled us to study the HLA-B27 phenotype in a very large (n=654) and unique population of patients with early axial SpA and IBP duration of <3 years. In the early disease stage of axial SpA, we have shown an association between HLA-B27 and earlier age of IBP onset, less delay in diagnosis. We have also shown that HLA-B27 and male gender are associated with axial inflammation and that HLA-B27 is associated with skeletal damage of the SIJ. Moreover, inflammation seems to act as an intermediate variable between HLA-B27 and radiographic sacroiliitis. These findings may have prognostic importance and HLA-B27 status, gender and inflammation should all be investigated as potential prognostic factors contributing to structural damage in SpA.

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7

Chapter 8

Smokers in early axial spondyloarthritis have earlier disease onset, more disease activity, inflammation and damage, and poorer function and health-related quality of life: results from the DESIR cohort

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ABSTRACT

Objectives

To investigate the association of smoking with various clinical, functional and imaging outcomes in patients with early axial spondyloarthritis (SpA).

Methods

647 patients with early inflammatory back pain (IBP) fulfilling at least one of the internationally accepted SpA criteria and with available smoking data were included in the analyses. Clinical, demographic and imaging parameters were compared between smokers and non-smokers at a cross-sectional level. Variables with significant differences in univariate analyses were used as dependent variables in multivariate linear and logistic regression models adjusted for potential confounding/contributing factors.

Results

Multivariate analysis showed that smoking was associated with an earlier onset of IBP (regression coefficient (B)=(−1.46), p=0.04), higher disease activity (ankylosing spondylitis disease activity score B=0.20, p=0.03; Bath ankylosing spondylitis disease activity index B=0.50, p=0.003), worse functional status (Bath ankylosing spondylitis functional index B=0.38, p=0.02), more frequent MRI inflammation of the sacroiliac joints (OR 1.57, p=0.02) and the spine (OR 2.33, p<0.001), more frequent MRI structural lesions of the sacroiliac joints (OR 1.54, p=0.03) and the spine (OR 2.02, p=0.01), and higher modified Stoke ankylosing spondylitis spine score (B=0.54, p=0.03) reflecting radiographic structural damage of the spine. Smoking was also associated with poorer quality of life (Euroquality of life questionnaire B=1.38, p<0.001, short form 36 physical B=(−4.89), p<0.001, and mental component score B=(−5.90), p<0.001).

Conclusion

In early axial SpA patients, smoking was independently associated with earlier onset of IBP, higher disease activity, increased axial inflammation on MRI, increased axial structural damage on MRI and radiographs, poorer functional status and poorer quality of life.

INTRODUCTION

The interaction between genetic and environmental factors is important in rheumatic diseases, with rheumatoid arthritis (RA) being the classic example of this gene–environment interaction model. Smoking is the best established and most extensively studied environmental risk factor in RA since an association was first reported in the 80's.[1] Smoking in men,[2] in the presence of anticitrullinated protein antibodies,[3] and with the human leucocyte antigen (HLA)-DR shared epitope gene[4] were each individually found to be risk factors for developing RA. Recent research has also shown additive and multiplicative interactions between PTPN22 and heavy smoking in RA.[5]

Fewer studies have been performed in ankylosing spondylitis (AS), and none in early axial spondyloarthritis (SpA). Smoking was found to be associated with increased disease activity,[6] worse physical functioning[6–10] and poorer quality of life,[11] but inconsistently associated with radiographic severity[7,12] in established AS.

The newly developed Assessment of SpondyloArthritis International Society classification criteria for axial SpA[13,14] are more inclusive of patients at an early disease stage. As smoking is a well-established risk factor for developing RA[15–17] and other inflammatory diseases, such as systemic lupus erythematosus[18] and inflammatory bowel disease,[19] and has also been associated with phenotypic variations in AS,[6–10,12] it would be worthwhile to clarify the impact of smoking in the axial SpA spectrum, particularly in early stage SpA. The aim of our study was to determine the prevalence of smoking and its association with various clinical, functional and imaging outcomes in early axial SpA.

METHODS

This is a cross-sectional analysis involving data collected during the first visit of the Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort,[20] a large multicentre sample consisting of 708 patients in France. Only patients fulfilling at least one of the following classification criteria for axial SpA or AS were included in the analyses: the modified New York criteria,[21] European Spondyloarthropathy Study Group criteria,[22] Amor criteria,[23] or Assessment of SpondyloArthritis International Society classification criteria for axial SpA. Details about the cohort design and data collection were described in previous publications.[20,24] In this study, we investigated the influence of smoking on the outcome measures described below. In DESIR, smoking status was obtained through interview by the physician, without a standardised questionnaire. It was collected as past history or concomitant smoking, without any reference to the quantity (eg, pack-years). The drinking status was captured in a similar way as the smoking status.

Disease activity, function, mobility and quality of life

Disease activity was assessed using both the Bath ankylosing spondylitis disease activity index (BASDAI)[25] and the ankylosing spondylitis disease activity score (ASDAS).[26] The ASDAS was calculated using C-reactive protein (ASDAS–CRP). The Ritchie articular index (53 joints) and swollen joint count (28 joints) were performed to evaluate the peripheral joints, and those with relevant symptoms were assessed for extra-articular features.

Patients also completed the Bath ankylosing spondylitis functional index (BASFI)[27] and the health assessment questionnaire for ankylosing spondylitis (HAQ–AS),[28] to assess functional status. Higher scores represent increased disease activity (ASDAS and BASDAI) and poorer functional status (BASFI and HAQ–AS).

Mobility was measured by the degree of chest expansion and by the Bath ankylosing spondylitis metrology index (BASMI).[29] A higher BASMI score represents worse spinal mobility.

Patients completed the Euro-quality of life questionnaire (Euro-QoL),[30] and the short form 36 (SF-36)[31] to assess healthrelated quality of life (HRQoL). A higher Euro-QoL score represents worse HRQoL, while a higher SF-36 score represents better HRQoL.

Radiographs of the sacroiliac joints and the spine

Radiographs of the cervical spine, lumbar spine and sacroiliac joints were performed. Sacroiliac joint radiographs were graded according to the following grading scale: 0, normal; 1, doubtful; 2, obvious; 3, fusion. Radiographic sacroiliitis was defined by at least a unilateral 'obvious' grading scale. The modified Stoke ankylosing spondylitis spine score (mSASSS)[32] was calculated from the radiographs of the cervical and lumbar spine. All radiographs were graded by regional radiologists or rheumatologists.

Inflammation and structural lesions in MRI

MRI were performed to look for inflammatory and structural lesions. Similar to radiographs, they were evaluated by regional radiologists or rheumatologists. The MRI were classified as having definite, doubtful or absent inflammatory and/or structural lesions at the spinal and sacroiliac joint levels according to short τ inversion recovery and T1-weighted fast spin echo images, respectively (1–1.5 Tesla). Positive images in our analyses were defined as MRI with definite lesions.

Statistical analyses

The χ^2 statistic and independent samples t test were used to compare categorical and continuous variables between smokers and non-smokers. Variables noted to have

differences (with a p value <0.1) in the previous analyses were used as dependent variables in univariate and multivariate linear/logistic regression models.

In addition to smoking status, factors known or expected to be associated with the investigated dependent variables were also tested as regressors in linear/logistic univariate regression analyses. These included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, age of inflammatory back pain (IBP) onset, duration of IBP, drinking status, CRP, erythrocyte sedimentation rate (ESR), MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions, non-steroidal anti-inflammatory drug (NSAID) use, ASDAS–CRP and BASMI. Independent variables with a p value less than 0.1 in univariate linear/logistic regression analyses were re-tested in multivariate regression models. Interactions between smoking status and gender/HLAB27 were tested in each model. Separate regression models were built according to gender/HLA B27 status if such an interaction existed. Variables with a skewed distribution were transformed using natural logarithms in linear regression models (ESR and CRP). The results were reported as OR in logistic regression models, and regression coefficients (B) and standard coefficients (β) in linear regression models. The 95% CI were calculated and p values less than 0.05 were considered statistically significant. All statistical analyses were performed using the statistical product and service solutions package 18.0.

RESULTS

Six hundred and fifty-four patients (92.4% of recruited patients) fulfilled at least one of the internationally accepted SpA criteria. Smoking data were missing in seven of 654 patients (1.1%), resulting in 647 patients included in our analyses. Detailed characteristics of this study population have previously been reported.[24] The number of smokers (past history or concomitant smoking) in the analysed sample was 241 (37.2%).

Table 1 compares the baseline characteristics between smoking and non-smoking early SpA patients. Smokers were more likely to be men, had an earlier onset of IBP and higher disease activity (higher BASDAI and ASDAS–CRP). Functionally, smokers had poorer functional status (increased BASFI and HAQ–AS) and also had poorer HRQoL (increased Euro-QoL and decreased SF-36) and more missing workdays as a result of SpA. On imaging examinations, smokers were more likely to have MRI inflammation and structural damage as well as radiographic lesions in the spine and sacroiliac joints.

Table 1. Baseline characteristics of the study population, according to smoking status

	Smoker	Non-smoker	p Value
Male sex (N=647)	123 (51.0%)	174 (42.9%)	0.04
Mean age at onset of IBP (years) (N=628)	31.1±8.3	32.6±9.0	0.04
Mean duration of axial symptoms (years) (N=628)	1.6±1.0	1.5±0.9	0.44
Mean age at onset of peripheral arthritis (years) (N=359)	31.3±8.8	33.1±9.7	0.08
Mean age at onset of enthesitis (years) (N=324)	31.6±8.5	33.4±9.0	0.08
Caucasian race (N=646)	220 (91.7%)	360 (88.7%)	0.22
Drinker (N=644)	55 (23.1%)	40 (9.9%)	<0.001
Family history of ankylosing spondyloarthritis (N=640)	63 (26.4%)	106 (26.4%)	0.98
HLA-B27 positive (N=641)	157 (65.7%)	244 (60.7%)	0.21
History of peripheral arthritis (N=645)	137 (57.3%)	241 (59.4%)	0.61
Signs of peripheral arthritis (N=386)	46 (32.9%)	99 (40.2%)	0.15
History of enthesitis (N=647)	125 (51.9%)	218 (53.7%)	0.65
NSAID user (N=647)	271 (66.7%)	173 (71.8%)	0.18
Steroid user (N=647)	53 (13.1%)	29 (12.0%)	0.71
DMARD user (N=648)	40 (9.9%)	19 (7.9%)	0.40
Analgesics user (N=647)	258 (63.5%)	152 (63.1%)	0.90
Mean CRP (mg/l) (N=626)	8.0±13.7	7.7±14.0	0.78
Patients with elevated CRP (N=626)	106 (27.0%)	80 (34.3%)	0.051
Mean ESR (mm/h) (621)	12.9±14.7	14.8±16.6	0.14
Patients with elevated ESR (N=618)	79 (20.5%)	45 (19.4%)	0.75
Patients with elevated CRP or ESR	131 (34.4%)	89 (38.9%)	0.26
Patients with extra-articular features (N=647)	116 (28.6%)	63 (26.1%)	0.50
BASDAI (N=641)	4.6±1.9	4.3±2.1	0.06
BASDAI ≥4 (N=641)	150 (63.3%)	238 (58.9%)	0.27
ASDAS–CRP (N=618)	2.6±1.0	2.4±1.1	0.051
BASFI (N=634)	3.4±2.2	2.8±2.3	0.001
BASFI ≥4 (N=634)	96 (40.5%)	121 (30.5%)	0.01
Intensity of axial pain in last 2 days (NRS) (N=644)	5.2±2.8	4.7±2.7	0.03
Intensity of peripheral joints pain in last 2 days (NRS) (N=643)	3.3±2.8	3.2±2.8	0.76
Tender joint count (out of 53 joints) (N=647)	5.0±9.5	4.1±7.9	0.22
Swollen joint count (out of 28 joints) (N=645)	0.2±1.0	0.2±0.8	0.56
BASMI (N=616)	1.6±1.2	1.5±1.1	0.12
Chest expansion (cm) (N=645)	5.7±2.0	5.7±2.2	0.99
Euro-quality of life questionnaire (N=645)	10.4±4.8	8.7±5.0	<0.001
HAQ–AS – disability index (N=644)	1.0±0.7	0.9±0.7	0.06
SF-36 mental health component score (N=642)	46.2±20.2	52.7±20.5	<0.001
SF-36 physical health component score (N=642)	35.6±15.8	40.5±16.9	<0.001
Patients with MRI inflammatory lesions in sacroiliac joints (N=610)	104 (46.8%)	123 (31.7%)	<0.001
Patients with MRI inflammatory lesions in spine (N=605)	72 (32.9%)	64 (16.6%)	<0.001
Patients with MRI structural lesions in sacroiliac joints (N=610)	78 (35.1%)	92 (23.7%)	0.002
Patients with MRI structural lesions in spine (N=601)	28 (12.8%)	26 (6.8%)	0.01
Patients with MRI inflammation, spine or sacroiliac joints (N=608)	125 (56.6%)	149 (38.5%)	<0.001
Patients with MRI structural lesions, spine or sacroiliac joints (N=604)	88 (40.2%)	108 (28.1%)	0.002
mSASSS (N=623)	1.4±3.3	0.9±2.6	0.09
Patients with mSASSS >0 (N=623)	66 (28.6%)	92 (23.5%)	0.16
Patients with radiographic sacroiliitis (N=625)	78 (33.8%)	103 (26.1%)	0.04
Missing workdays (N=555)	45.6±79.6	27.3±61.4	0.003

ASDAS–CRP, ankylosing spondylitis disease activity score, C-reactive protein based; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis metrology index; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ–AS, health assessment questionnaire for ankylosing spondylitis; HLA, human leucocyte antigen; IBP, inflammatory back pain; mSASSS, modified Stoke ankylosing spondylitis spine score; NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drug; SF-36, short form 36.

Regression analyses

Age of IBP onset as dependent variable

Independent variables tested in univariate analyses included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, and smoking and drinking status. Significant variables associated with the age of onset of IBP ($p<0.1$) were: Caucasian race (B=2.5, p=0.03), male sex (B=(−2.06), p=0.003), HLA-B27 positivity (B=(−2.95), $p<0.001$), family history of SpA (B=1.58, p=0.05) and smoking (B=(−1.46), p=0.04).

Multivariate analysis showed that Caucasian race (β=0.13, B=3.79, 95% CI 1.55 to 6.04, p=0.001) was independently associated with later age of IBP onset while HLA-B27 positivity (β=(−0.44), B=(−2.60), 95% CI −4.03 to −1.18, p=0.02), smoking (β=(−0.08), B=(−1.46), 95% CI −2.87 to −0.06, p=0.04) and male sex (β=(−0.10), B=(−1.67), 95% CI −3.06 to −0.29, p=0.02) were independently associated with earlier age of IBP onset.

ASDAS–CRP and BASDAI as dependent variables

Independent variables tested in univariate models of ASDAS–CRP included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, smoking, drinking, MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions and NSAID use. Independent variables with a p value less than 0.1 were: Caucasian race (B=(−0.57), $p<0.001$), HLA-B27 positivity (B=(−0.2), p=0.02), smoking (B=0.17, p=0.051), drinking (B=(−0.25), p=0.04) and MRI spine inflammatory lesions (B=0.21, p=0.04).

Independent variables tested in univariate models of BASDAI included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, smoking, drinking, CRP, ESR, MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions and NSAID use. Independent variables with a p value less than 0.1 were: Caucasian race (B=(−1.07), $p<0.001$), male sex (B=(−0.63), $p<0.001$), HLA-B27 positivity (B=(−0.75), $p<0.001$), smoking (B=0.31, p=0.06), drinking (B=(−0.59), p=0.01), CRP (B=0.25, $p<0.001$), ESR (B=0.46, $p<0.001$) and MRI sacroiliac joint inflammatory lesions (B=(−0.60), $p<0.001$).

The multivariate analyses for ASDAS–CRP and BASDAI are shown in table 2. Smoking was independently associated with higher ASDAS–CRP and BASDAI scores.

BASFI and HAQ–AS as dependent variables

Independent variables tested in univariate models of BASFI and HAQ–AS included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, duration of IBP, smoking, drinking, MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions, NSAID use, ASDAS–CRP and BASMI.

Independent variables with a p value less than 0.1 in the BASFI model were: Caucasian

Table 2. Multivariate linear regressions analyses of factors associated with ASDAS–CRP, BASDAI, BASFI and HAQ–AS

	ASDAS–CRP			BASDAI			BASFI			HAQ–AS		
	Standard coefficient	**Regression coefficient (95% CI)**	**p Value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p Value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p Value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p Value**
Smoker	0.09	0.20 (0.02 to 0.38)	0.03	0.12	0.50 (0.17 to 0.83)	0.003	0.08	0.38 (0.07 to 0.69)	0.02	NS	NS	–
Caucasian race	−0.16	−0.55 (−0.83 to −0.27)	<0.001	−0.14	−0.94 (−1.48 to −0.41)	0.001	NS	NS	–	NS	NS	–
Male sex	NI	NI	–	NS	NS	–	−0.08	−0.35 (−0.65 to −0.05)	0.02	−0.23	−0.32 (−0.43 to −0.22)	<0.001
HLA-B27 positivity	−0.10	−0.22 (−0.39 to −0.04)	0.02	−0.13	−0.52 (−0.85 to −0.19)	0.002	NS	NS	–	NS	NS	–
Drinker	−0.09	−0.25 (−0.49 to −0.02)	0.04	NS	NS	–	NS	NS	–	NS	NS	–
CRP	NI	NI	–	0.10	0.16 (0.02 to 0.31)	0.03	NI	NI	–	NI	NI	–
ESR	NI	NI	–	0.16	0.34 (0.13 to 0.55)	0.002	NI	NI	–	NI	NI	–
MRI spine inflammatory lesions	NS	NS	–	NI	NI	–	NS	NS	–	NI	NI	–
MRI sacroiliac joint inflammatory lesions	NI	NI	–	−0.17	−0.70 (−1.04 to −0.36)	<0.001	−0.10	−0.48 (−0.80 to −0.16)	0.04	−0.08	−0.11 (−0.22 to 0.00)	0.04
ASDAS–CRP	NI	NI	–	NI	NI	–	0.54	1.16 (1.02 to 1.30)	<0.001	0.43	0.29 (0.24 to 0.34)	<0.001
BASMI	NI	NI	–	NI	NI	–	0.20	0.51 (0.34 to 0.68)	<0.001	0.14	0.09 (0.04 to 0.13)	<0.001

ASDAS–CRP, ankylosing spondylitis disease activity score, C-reactive protein based; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis metrology index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ–AS, health assessment questionnaire for ankylosing spondylitis; HLA, human leucocyte antigen; NI, not included in the multivariate model; NS, non-significant in multivariate analysis.

race (B=(–0.68), p<0.001), male sex (B=(–0.57), p=0.002), HLA-B27 positivity (B=(–0.66), p<0.001), smoking (B=0.61, p=0.001), drinking (B=(–0.63), p=0.01), MRI sacroiliac joint inflammatory lesions (B=(–0.39), p=0.04), MRI spine inflammatory lesions (B=0.46, p=0.04), ASDAS–CRP (B=1.30, p<0.001) and BASMI (B=0.64, p<0.001).

Independent variables with a p value less than 0.1 in the HAQ–AS model were: Caucasian race (B=(–0.27), p=0.003), male sex (B=(–0.37), p<0.001), HLA-B27 positivity (B=(–0.23), p<0.001), smoking (B=0.11, p=0.06), drinking (B=(–0.16), p=0.06), ASDAS–CRP (B=0.33, p<0.001), MRI sacroiliac joint inflammatory lesions (B=(–0.15), p=0.02) and BASMI (B=0.16, p<0.001).

The multivariate analyses of BASFI and HAQ–AS are shown in table 2. Smoking was independently associated with higher BASFI scores. The univariate association between smoking and HAQ–AS was lost in multivariate analysis.

Euro-QoL and SF-36 as dependent variables

Independent variables tested in univariate models of Euro-QoL and SF-36 physical/mental component scores included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, duration of IBP, smoking, drinking, ASDAS–CRP, MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions and BASMI.

Independent variables in the Euro-QoL univariate models with a p value less than 0.1 were: Caucasian race (B=(–2.44), p<0.001), male sex (B=(–2.02), p<0.001), HLA-B27 positivity (B=(–1.67), p<0.001), smoking (B=1.67, p<0.001), drinking (B=(–1.27), p=0.02), ASDAS–CRP (B=2.75, p<0.001), MRI sacroiliac joint inflammatory lesions (B=(–1.39), p=0.001) and BASMI (B=1.10, p<0.001).

Independent variables in the SF-36 physical component univariate models with a p value less than 0.1 were: Caucasian race (B=9.79, p<0.001), male sex (B=5.65, p<0.001), HLA-B27 positivity (B=5.18, p<0.001), smoking (B=(–4.93), p<0.001), drinking (B=4.02, p=0.03), ASDAS–CRP (B=(–9.19), p<0.001), MRI sacroiliac joint inflammatory lesions (B=4.81, p=0.001) and BASMI (B=(–3.57), p<0.001).

Independent variables in the SF-36 mental component univariate models with a p value less than 0.1 were: Caucasian race (B=12.2, p<0.001), male sex (B=5.68, p<0.001), HLA-B27 positivity (B=5.02, p=0.03), smoking (B=(–6.51), p<0.001), drinking (B=5.29, p=0.02), ASDAS–CRP (B=(–10.14), p<0.001), MRI sacroiliac joint inflammatory lesions (B=4.89, p=0.01) and BASMI (B=3.13, p<0.001).

Table 3 shows the multivariate analyses for Euro-QoL and SF-36. Smoking was independently and positively associated with the Euro-QoL score and negatively associated with the SF-36 physical and mental component scores.

Table 3. Multivariate linear regressions analyses of factors associated with Euro-QoL and SF-36

	Euro-QoL			SF-36 (physical health score)			SF-36 (mental health score)		
	Standard coefficient	**Regression coefficient (95% CI)**	**p Value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p Value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p Value**
Smoker	0.13	1.38 (0.69 to 2.07)	<0.001	−0.14	−4.89 (−7.24 to −2.54)	<0.001	−0.14	−5.90 (−8.99 to −2.81)	<0.001
Caucasian race	NS	NS	–	0.11	6.09 (2.21 to 9.98)	0.002	0.12	8.17 (3.01 to 13.31)	0.002
Male sex	−0.18	−1.73 (−2.40 to −1.06)	<0.001	0.13	4.37 (2.08 to 6.66)	<0.001	0.11	4.38 (1.37 to 7.39)	0.004
HLA-B27 positivity	NS	NS	–	NS	NS	–	NS	NS	–
Drinker	NS	NS	–	NS	NS	–	NS	NS	–
ASDAS–CRP	0.52	2.47 (2.15 to 2.80)	<0.001	−0.52	−8.32 (−9.41 to −7.21)	<0.001	−0.46	−9.08 (−10.52 to −7.63)	<0.001
MRI sacroiliac joint inflammation	−0.12	−1.26 (−1.96 to −0.56)	<0.001	0.14	4.94 (2.56 to 7.32)	<0.001	0.13	5.33 (2.20 to 8.46)	0.001
BASMI	0.12	0.56 (0.26 to 0.86)	<0.001	−0.09	−1.42 (−2.45 to −0.39)	0.01	NS	NS	–

ASDAS–CRP, ankylosing spondylitis disease activity score, C-reactive protein based; BASMI, Bath ankylosing spondylitis metrology index; Euro-QoL, Euro-quality of life questionnaire; HLA, human leucocyte antigen; NI, not included in the multivariate model; NS, non-significant in multivariate analysis; SF-36, short form 36.

MRI spine and/or sacroiliac joint inflammation, MRI spine inflammation and MRI sacroiliac joint inflammation as dependent variables

Independent variables tested in univariate models of the above three dependent variables included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, age at onset of IBP, duration of IBP, CRP, smoking, drinking and NSAID use.

Independent variables in MRI spine and/or sacroiliac joint inflammation models with p value less than 0.1 were: male sex (OR 2.32, p<0.001), HLA-B27 positivity (OR 2.33, p<0.001), age at onset of IBP (OR 0.97, p=0.001), CRP (OR 1.02, p=0.001) and smoking (OR 2.08, p<0.001).

Independent variables in MRI spine inflammation models with a p value less than 0.1 were: male sex (OR 2.47, p<0.001), HLA-B27 positivity (OR 1.73, p=0.01), family history of SpA (OR 1.68, p=0.03), CRP (OR 1.02, p=0.03) and smoking (OR 2.46, p<0.001).

Independent variables in MRI sacroiliac joint inflammation models with a p value less than 0.1 were: Caucasian race (OR 0.59, p=0.05), male sex (OR 2.37, p<0.001), HLA-B27 positivity (OR 2.38, p<0.001), age at onset of IBP (OR 0.96, p<0.001), CRP (OR 1.02, p=0.002), smoking (OR 1.90, p<0.001) and drinking (OR 1.52, p=0.07).

In multivariate analyses, smoking was independently and positively associated with the presence of both sacroiliac joint and spine MRI inflammation (table 4).

MRI spine and/or sacroiliac joint structural lesions, MRI spine structural lesions and MRI sacroiliac joint structural lesions as dependent variables

Independent variables included in univariate models of the above three dependent variables included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, age at onset of IBP, disease duration, CRP, smoking, drinking and NSAID use.

Independent variables in MRI structural lesion models (spine and/or sacroiliac joints) with a p value less than 0.1 were: HLA-B27 positivity (OR 1.47, p=0.04), duration of IBP (OR 1.19, p=0.06), CRP (OR 1.01, p=0.06) and smoking (OR 1.72, p=0.02).

Independent variables in MRI sacroiliac joint structural lesion models with a p value less than 0.1 were: HLA-B27 positivity (OR 1.67, p=0.01), age at onset of IBP (OR 0.97, p=0.002), CRP (OR 1.01, p=0.04) and smoking (OR 1.74, p=0.003).

The only independent variable with a p value less than 0.1 in MRI spine structural lesion models was smoking (OR 2.02, p=0.01).

The multivariate analyses of the above three dependent variables are shown in table 5.

Table 4. Multivariate logistic regressions analyses of factors associated with MRI inflammation

	MRI inflammation (spine or sacroiliac joints)		MRI sacroiliac joint inflammation		MRI spine inflammation	
	OR (95% CI)	**p Value**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
Smoker	1.91 (1.34 to 2.72)	<0.001	1.57 (1.08 to 2.30)	0.02	2.33 (1.55 to 3.51)	<0.001
Caucasian race	NI	–	0.49 (0.27 to 0.87)	0.02	NI	–
Male sex	1.87 (1.31 to 2.64)	<0.001	1.80 (1.24 to 2.62)	0.002	1.98 (1.30 to 3.01)	0.001
HLA-B27 positivity	2.06 (1.43 to 2.97)	<0.001	2.08 (1.40 to 3.10)	<0.001	NS	–
Drinker	NI	–	NS	–	NI	–
Family history of SpA	NI	–	NI	–	NS	–
Age at onset of IBP	NS	–	0.97 (0.95 to 0.99)	0.01	NI	–
CRP	1.02 (1.01 to 1.03)	0.01	NS	–	1.02 (1.00 to 1.03)	0.02

CRP, C-reactive protein; HLA, human leucocyte antigen; IBP, inflammatory back pain; NI, not included in the multivariate model; NS, non-significant in multivariate analysis; SpA, spondyloarthritis.

Table 5. Multivariate logistic regressions analyses of factors associated with MRI structural lesions

	MRI structural lesions (sacroiliac joints or spine)		MRI sacroiliac joint structural lesions		MRI spine structural lesions	
	OR (95% CI)	**p Value**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
Smoker	1.56 (1.08 to 2.26)	0.02	1.54 (1.05 to 2.26)	0.03	2.02 (1.15 to 3.55)	0.01
HLA-B27 positivity	NS		NS		NI	
Age at onset of IBP	NI	–	0.97 (0.95 to 1.00)	0.02	NI	–
CRP	NS		NS		NI	
IBP duration	1.26 (0.03 to 1.54)	0.02	NI	–	NI	–

CRP, C-reactive protein; HLA, human leucocyte antigen; IBP, inflammatory back pain; NI, not included in the multivariate model; NS, non-significant in multivariate analysis.

Smoking was found to be positively associated with the presence of both sacroiliac joint and spine MRI structural lesions.

Smoking was found to interact with male sex regarding MRI sacroiliac joint structural lesions. Therefore, separate univariate and multivariate logistic regression models were performed according to gender. Variables with a p value less than 0.1 in the male population were: HLA-B27 positivity (OR 2.41, p=0.01), age at onset of IBP (OR 0.97, p=0.09) and smoking (OR 2.99, p<0.001). Multivariate analysis showed that smoking (OR 2.78, p<0.001) was positively associated with MRI sacroiliac joint structural lesions, while HLA-B27 positivity (OR 1.85, p=0.07) and age at onset of IBP (OR 0.98, p=0.23) were not significantly associated. Variables with a p value less than 0.1 in the female population were: Caucasian race (OR 0.63, p=0.03) and age at onset of IBP (OR 0.97, p=0.02); multivariate analysis showed that both Caucasian race (OR 0.48, p=0.046) and age at onset of IBP (OR 0.97, p=0.03) were associated with MRI sacroiliac joint structural lesions.

Radiographic sacroiliitis and mSASSS as dependent variables

Independent variables included in univariate models of the above two dependent variables included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, age at onset of IBP, duration of IBP, CRP, smoking, drinking and NSAID use.

Independent variables in radiographic sacroiliitis models with a p value less than 0.1 were: male sex (OR 1.96, p<0.001), HLA-B27 positivity (OR 1.91, p=0.001), age at onset of IBP (OR 0.96, p<0.001), CRP (OR 1.02, p<0.001), smoking (OR 1.44, p=0.04) and drinking (OR 1.77, p=0.02).

Independent variables in mSASSS models with a p value less than 0.1 were: male sex (B=0.54, p=0.02), family history of SpA (B=(–0.58), p=0.03), age at onset of IBP (B=0.06, p<0.001), CRP (B=0.25, p=0.01) and smoking (B=0.44, p=0.07).

Multivariate models of radiographic sacroiliitis and mSASSS are shown in table 6. Smoking was found to be independently and positively associated with mSASSS but not with radiographic sacroiliitis.

Interaction between smoking and HLA-B27 positivity

There was no interaction between smoking and HLA-B27 positivity for any of the studied outcomes.

Subgroup analysis

Sacroiliac joint radiographic data were missing in 22/647 patients (3.4%). Subgroup analyses were performed for patients fulfilling (n=181) and not fulfilling (n=444) the

Table 6. Multivariate linear/logistic regressions analyses of factors associated with radiographic sacroiliitis and mSASSS

	Radiographic sacroiliitis		mSASSS		
	OR (95% CI)	**p Value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p Value**
Smoker	NS	–	0.09	0.54 (0.05 to 1.03)	0.03
HLA-B27 positivity	NS	–	NI	NI	–
Male sex	1.48 (1.00 to 2.18)	0.049	0.11	0.64 (0.17 to 1.12)	0.01
Family history of SpA	NI	–	−0.13	−0.91 (−1.45 to −0.37)	0.001
Age at onset of IBP	0.97 (0.95 to 0.99)	0.004	0.23	0.08 (0.05 to 0.11)	<0.001
CRP	1.02 (1.01 to 1.03)	0.02	0.14	0.32 (0.13 to 0.51)	0.001
Drinker	NS	–	NI	NI	–

CRP, C-reactive protein; HLA, human leucocyte antigen; IBP, inflammatory back pain; mSASSS, modified Stoke ankylosing spondylitis spine score; NI, not included in the multivariate model; NS, non-significant in multivariate analysis; SpA, spondyloarthritis.

modified New York criteria (see supplementary tables 1 and 2). In the subgroup of patients with radiographic axial SpA smoking was independently and positively associated with BASFI, Euro-QoL, MRI spinal inflammation, MRI spine or sacroiliac joint inflammation and radiographic damage of the spine. Smoking was also negatively associated with SF-36 (physical and mental component scores). In the subgroup of patients with non-radiographic axial SpA smoking was independently and positively associated with BASDAI, Euro-QoL and MRI spinal inflammation. It was negatively associated with age at onset of IBP and SF-36 (physical and mental component scores). Subgroup differences are likely due to loss of statistical power.

DISCUSSION

The negative impact of smoking on AS disease parameters has been reported in previous studies, and confirmed more robustly in our study. Importantly, we confirmed these associations in an early disease stage population with IBP of less than 3 years.

In addition to the negative impact of smoking on radiographic severity, clinical disease activity, functional status and quality of life, we have shown new associations: for the first time, smoking was found to be associated with the presence of MRI inflammation and structural damage. Radiographically, smoking was only associated with spinal, but not sacroiliac joint, damage (non-significant in multivariate analysis).

In the general population, smokers were found to have poorer HRQoL, increased alcohol consumption and increased frequency of reported pain.[33] We studied drinking as a potential confounder in all our models and the effect of smoking was independent of drinking (and independent of other important variables such as NSAID intake). Drinking was only independently associated with ASDAS–CRP in multivariate analyses (negative association).

Previous studies have proposed that the negative impact of smoking on functional status and quality of life may be related to poor health behaviour, increased osteoporotic fractures and impaired cardiorespiratory functions in smokers.[6,9,10] However, this negative impact might also be mediated by a direct toxic effect of smoking. Notably, cigarette smoke is well known to possess pro-inflammatory effects, via various proposed mechanisms: smokers have increased pro-inflammatory reactants such as tumour necrosis factor α, interleukin (IL) 1, IL-6, IL-8 and granulocyte– macrophage colony-stimulating factor;[34,35] increased concentration of free radicals;[36] and augmentation of autoreactive B cells.[37] Cigarette smoke triggers the nuclear factor κB pathway and promotes pro-inflammatory cytokine gene expression.[38] Moreover, smokers were also found to have increased circulating polymorphonuclear neutrophil counts[39,40] and T lymphocytes.[41]

The DESIR cohort is characterised by SpA patients with short disease duration, in contrast with previous studies on AS patients with a longer course of disease. In this early SpA population (average duration of IBP only 1.5 years), smokers had an earlier age of IBP onset, which was not found in smaller studies.[8] This demonstrates the enhanced power inherent in the large sample size of the DESIR cohort, allowing us to detect more subtle differences.

The cumulative effects of smoking in RA meta-analyses have established that male smokers are at increased risk but as the quantity of smoking increases, risk between male and female smokers becomes more equal.[42] We found an interaction between male sex and smokers regarding MRI sacroiliac joint structural lesions. Given that the quantification of smoking affects the gender interaction in RA, it would be of interest to quantify the cumulative effect of cigarette smoking in future studies with SpA patients. Unfortunately, the number of pack-years of smoking is not known in the DESIR cohort. Furthermore, it would have been useful to analyse ‘current smokers’ and patients with a ‘past history of smoking’ separately - however, these data are also not known in DESIR.

The lack of international consensus about the assessment of MRI structural lesions poses another potential limitation to our study. However, in DESIR, the imaging techniques were standardized and the centres involved had to fulfil predefined quality criteria in order to be able to participate in the study, namely regarding previous experience with multicentre, longitudinal epidemiological studies.[20] Therefore, the required high quality standards are expected to have reduced potential bias during the imaging evaluation.

Another concern is whether the physician interview-captured smoking status might have led to an under-reporting of smoking. However, the prevalence of smoking in DESIR is in line with the prevalence of smoking in the French[43] population (37.2% current smokers and ex-smokers in DESIR vs 26.2% current smokers in the French population). Furthermore, a previous study has shown that obtaining a history of tobacco use is an accurate method of detecting smokers in epidemiological studies.[44]

Our study found that, in young axial SpA patients with short disease duration, smoking was independently associated with earlier onset of IBP, higher disease activity, increased axial inflammation and structural damage, poorer functional status and poorer quality of life. This also translated into increased missing workdays as a result of disease (table 1), which may lead to a higher socioeconomic burden and costs, especially taking into account the relatively young age of onset and long expected disease survival of these patients. Taking into account that smoking is a potentially modifiable lifestyle factor, axial SpA patients who smoke should be strongly advised to quit this habit, as there seem to be disease-specific benefits that go beyond those described for the general population.

The DESIR cohort allowed us to establish the negative impact of smoking in axial SpA; continued follow-up of the cohort may allow detailed quantification of the deleterious impact of smoking at the individual and societal levels. The true magnitude and implications of this effect is yet to be unravelled.

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Supplementary table 1.1. Baseline comparisons among patients fulfilling MNY criteria

	Smoker	Non-smoker	p-value
Mean age (years) (N=181)	31.1±8.5	31.4±9.5	0.85
Mean age at onset of IBP (years) (N=174)	29.7±8.7	29.9±9.5	0.86
Mean duration of axial symptoms (years) (N=174)	1.7±0.9	1.5±0.8	0.19
Drinker (N=179)	23 (30.3%)	14 (13.6%)	0.01
Male sex (N=181)	51 (65.4%)	55 (53.4%)	0.11
HLA-B27 positive (N=181)	51 (65.4%)	55 (53.4%)	0.11
NSAIDs score (N=178)	117.7±90.7	129.3±121.3	0.48
Mean CRP (mg/l) (N=173)	10.8±12.8	11.8±17.0	0.68
Mean ESR (mm) (171)	15.9±15.9	20.7±22.6	0.10
BASDAI (N=180)	4.2±1.9	3.9±2.2	0.31
ASDAS-CRP (N=181)	2.7±1.0	2.5±1.1	0.37
ASDAS-ESR (N=180)	2.5±1.0	2.5±1.2	0.88
BASFI (N=177)	3.3±2.2	2.5±2.2	0.02
BASMI (N=181)	2.3±0.9	2.4±0.9	0.50
Euro-quality of life questionnaire (N=180)	9.7±4.6	7.9±5.2	0.02
Health assessment questionnaire - disability index (N=181)	0.9±0.7	0.8±0.7	0.58
SF-36 Mental health score (N=179)	49.2±20.5	58.0±21.5	0.01
SF-36 Physical health score (N=180)	38.2±15.6	44.5±18.0	0.01
Inflammatory lesions in SI joints (N=173)	61 (82.4%)	68 (68.7%)	0.04
Inflammatory lesions in spine (N=171)	40 (54.8%)	22 (22.4%)	<0.001
Structural lesions in SI joints (N=173)	55 (74.3%)	59 (59.6%)	0.04
Structural lesions in spine (N=171)	14(19.2%)	11 (11.2%)	0.15
MRI inflammation, spine or SI joints (N=173)	67 (90.5%)	71 (71.7%)	0.002
MRI structural lesions, spine or SI joints (N=172)	55 (75.3%)	62 (62.6%)	0.08
mSASSS (N=179)	2.6±4.4	1.7±4.0	0.15
mSASSS>0 (N=179)	38 (49.4%)	37 (36.3%)	0.08

NSAID, non-steroidal anti-inflammatory drug; DMARD, disease modifying anti-rheumatic drug; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score (CRP based); BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; MRI, magnetic resonance imaging; SI, sacroiliac; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; IBP, inflammatory back pain.

Supplementary table 1.2. Multivariate linear regressions analyses of factors associated with BASFI

	BASFI		
	Standard coefficient	**Regression coefficient (95% CI)**	**p-value**
Smoker	0.19	0.87 (0.28, 1.46)	0.004
HLA-B27 positivity	-0.21	-1.06 (-1.70, -0.43)	0.001
Drinker	-0.15	-0.77 (-1.44, -0.11)	0.02
MRI spine inflammatory lesions	NS	NS	--
ASDAS-CRP	0.50	1.02 (0.76, 1.27)	<0.001
BASMI	NS	NS	--

ASDAS-CRP, Anklosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; HAQ-AS, health assessment questionnaire for ankylosing spondylitis; HLA, Human Leukocyte Antigen; CRP, C-reactive protein; MRI, magnetic resonance imaging; SI, sacroiliac; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, confidence interval; NS, Non-significant in multivariate analysis; NI, Not included in the multivariate model.

Supplementary table 1.3. Multivariate linear regressions analyses of factors associated with Euro-QoL and SF-36

	Euro-QoL			SF-36 (physical health score)			SF-36 (mental health score)		
	Standard coefficient	**Regression coefficient (95% CI)**	**p-value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p-value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p-value**
Smoker	0.18	1.82 (0.64; 3.00)	0.003	-0.23	-7.95 (-12.11; -3.78)	<0.001	-0.20	-8.49 (-14.00; -2.98)	0.003
Caucasian race	NS	NS	--	0.17	8.46 (2.39; 14.53)	0.01	0.16	10.54 (2.67; 18.41)	0.01
Male sex	-0.20	-2.09 (-3.30; -0.88)	0.001	0.18	6.54 (2.27; 10.80)	0.003	0.24	10.76 (5.30; 16.22)	<0.001
HLA-B27 positivity	-0.19	-2.14 (-3.54; -0.74)	0.003	0.13	5.28 (0.30; 10.25)	0.04	0.16	7.71 (1.47; 13.95)	0.02
MRI SI joints inflammation	NS	NS	--	NS	NS	--	NS	NS	--
ASDAS-CRP	0.49	2.28 (1.73; 2.83)	<0.001	-0.48	-7.77 (-9.69; -5.85)	<0.001	-0.47	-9.44 (-11.93; -6.96)	<0.001
BASMI	0.15	0.84 (0.14; 1.53)	0.02	NS	NS	--	NS	NS	--

Euro-QoL, Euro- quality of life questionnaire; SF-36, short form 36; ASDAS-CRP, Anklosing Spondylitis Disease Activity Score, C-reactive protein based; MRI, magnetic resonance imaging; SI, sacroiliac; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, confidence interval; NS, Non-significant in multivariate analysis.

Supplementary table 1.4. Multivariate logistic regressions analyses of factors associated with MRI inflammation

	MRI inflammation (spine or SI joints)		MRI SI joints inflammation		MRI spine inflammation	
	Odds ratio (95% CI)	**p-value**	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Smoker	3.03 (1.20; 7.67)	0.02	NS	--	3.92 (1.96; 7.83)	<0.001
Male sex	NS	--	NS	--	2.23 (1.08; 4.60)	0.03
HLA-B27 positivity	NS	--	NS	--	NI	--
Age at onset of IBP	NS	--	NS	--	NI	--
Disease duration	NI	--	NI	--	NS	--

MRI, magnetic resonance imaging; SI, sacroiliac; CI, confidence interval; HLA, Human Leukocyte Antigen; IBP, inflammatory back pain; NS, Non-significant in multivariate analysis; NI, Not included in the multivariate model.

Supplementary table 1.5. Multivariate logistic regressions analyses of factors associated with MRI structural lesions and spinal radiographic damage

	MRI structural lesions (SI joints or spine)		MRI SI joints structural lesions		mSASSS>0	
	Odds ratio (95% CI)	**p-value**	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Smoker	NS	--	NS	--	2.11 (1.08; 4.12)	0.03
Caucasian race	NI	--	0.28 (0.09; 0.89)	0.03	0.28 (0.09; 0.89)	0.03
HLA-B27 positivity	NS	--	NS	--	1.26 (0.03; 1.54)	0.02
Age at onset of IBP	NI	--	NI	--	1.07 (1.03; 1.11)	0.001
Family history of AS	NS	--	NI	--	NI	--
Disease duration	NI	--	NS	--	NI	--
CRP	NI	--	NI	--	1.03 (1.01; 1.05)	0.01

MRI, magnetic resonance imaging; HLA, Human Leukocyte Antigen; SI, sacroiliac; NS, Non-significant in multivariate analysis; NI, Not included in the multivariate model.

SUPPLEMENTARY TABLES 2

Supplementary table 2.1. Baseline comparisons among patients not-fulfilling MNY criteria

	Smoker	Non-smoker	p-value
Mean age (years) (N=442)	33.3±8.0	35.1±8.4	0.03
Mean age at onset of IBP(years) (N=432)	31.8±8.1	33.5±8.5	0.04
Mean duration of axial symptoms (years) (N=432)	1.5±0.9	1.5±0.9	0.66
Drinker (N=443)	31 (20.4%)	26 (8.9%)	0.001
Male sex (N=444)	67 (43.8%)	117 (40.2%)	0.47
HLA-B27 positive (N=439)	89 (58.6%)	170 (59.2%)	0.89
NSAIDs score (N=401)	95.6±84.5	91.5±188.8	0.81
Mean CRP (mg/l) (N=432)	6.4±14.0	6.3±12.8	0.94
Mean ESR (mm) (426)	11.4±14.2	12.5±13.2	0.42
BASDAI (N=439)	4.9±1.9	4.5±2.0	0.04
ASDAS-CRP (N=426)	2.6±1.0	2.4±1.0	0.12
ASDAS-ESR (N=420)	2.2±0.8	2.1±0.8	0.30
BASFI (N=436)	3.5±2.3	2.9±2.3	0.01
BASMI (N=441)	2.3±0.9	2.1±0.9	0.11
AS quality of life questionnaire (N=443)	10.7±4.9	9.0±4.9	<0.001
Health assessment questionnaire - disability index (N=441)	1.0±0.7	0.9±0.7	0.06
SF-36 Mental health score (N=441)	44.9±20.0	50.9±20.0	0.003
SF-36 Physical health score (N=440)	34.3±16.1	39.1±16.3	0.003
Inflammatory lesions in SI joints (N=427)	42 (28.8%)	53 (18.9%)	0.02
Inflammatory lesions in spine (N=424)	31 (21.5%)	39 (13.9%)	0.046
Structural lesions in SI joints (N=427)	22 (15.1%)	31 (11.0%)	0.23
Structural lesions in spine (N=421)	13(9.1%)	14 (5.0%)	0.11
MRI inflammation, spine or SI joints (N=425)	57 (39.3%)	74 (26.4%)	0.01
MRI structural lesions, spine or SI joints (N=423)	32 (22.2%)	43 (15.4%)	0.08
mSASSS (N=440)	0.8±2.5	0.7±1.8	0.64
mSASSS>0 (N=440)	27 (17.9%)	54 (18.7%)	0.84

NSAID, non-steroidal anti-inflammatory drug; DMARD, disease modifying anti-rheumatic drug; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score (CRP based); BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; MRI, magnetic resonance imaging; SI, sacroiliac; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; IBP, inflammatory back pain.

Supplementary table 2.2. Multivariate linear regressions analyses of factors associated with age at onset of IBP

	Standard coefficient	Regression coefficient (95% CI)	p-value
Smoker	-0.12	-2.06 (-3.72; -0.40)	0.02
Caucasian race	0.13	3.80 (1.03; 6.58)	0.01
HLA-B27 positivity	NS	NS	--
Family history of SpA	-0.10	-1.88 (-3.72; 0.04)	0.045

IBP, inflammatory back pain; HLA, Human leukocyte antigen; SpA, spondyloarthritis; CI, confidence interval; NS, not significant in multivariate model.

Supplementary table 2.3. Multivariate linear regressions analyses of factors associated with BASDAI and BASFI

	BASDAI			BASFI		
	Standard coefficient	**Regression coefficient (95% CI)**	**p-value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p-value**
Smoker	0.12	0.48 (0.10, 0.86)	0.02	NS	NS	--
Caucasian race	-0.11	-0.78 (-1.44, -0.12)	0.02	NS	NS	--
Male sex	NS	NS	--	-0.07	-0.34 (-0.68, 0.00)	0.047
HLA-B27 positivity	-0.11	-0.42 (-0.79, -0.05)	0.03	NS	NS	--
Drinker	NS	NS	--	NI	NI	--
CRP	0.13	0.20 (0.04, 0.36)	0.02	NI	NI	--
ESR	0.21	0.47 (0.22, 0.72)	<0.001	NI	NI	--
MRI SI joints inflammatory lesions	-0.15	-0.71 (-1.16, -0.25)	0.002	NI	NI	--
ASDAS-CRP	NI	NI	--	0.55	1.23 (1.06, 1.39)	<0.001
BASMI	NI	NI	--	0.27	0.69 (0.51, 0.88)	<0.001

ASDAS-CRP, Anklosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; HAQ-AS, health assessment questionnaire for ankylosing spondylitis; HLA, Human Leukocyte Antigen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; SI, sacroiliac; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, confidence interval; NS, Non-significant in multivariate analysis; NI, Not included in the multivariate model.

Supplementary table 2.4. Multivariate linear regressions analyses of factors associated with Euro-QoL and SF-36

	Euro-QoL			SF-36 (physical health score)			SF-36 (mental health score)		
	Standard coefficient	**Regression coefficient (95% CI)**	**p-value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p-value**	**Standard coefficient**	**Regression coefficient (95% CI)**	**p-value**
Smoker	0.12	1.29 (049; 2.09)	0.002	-0.12	-4.02 (-6.74; -1.30)	0.004	-0.12	-5.01 (-8.61; -1.41)	0.01
Caucasian race	NS	NS	--	0.10	5.78 (1.20; 10.37)	0.01	0.11	7.87 (1.80; 13.93)	0.01
Male sex	-0.13	-1.33 (-2.10; -0.55)	0.001	NS	NS	--	NS	NS	--
HLA-B27 positivity	NS	NS	--	NS	NS	--	NI	NI	--
Drinker	NS	NS	--	NS	NS	--	NS	NS	--
MRI SI joints inflammation	-0.13	-1.55 (-2.49; -0.62)	0.001	0.11	4.45 (1.21; 7.63)	0.01	0.13	6.17 (2.02; 10.31)	0.004
ASDAS-CRP	0.53	2.55 (2.17; 2.92)	<0.001	-0.53	-8.45 (-9.72; -7.18)	<0.001	-0.45	-8.72 (-10.39; -7.04)	<0.001
BASMI	0.17	0.98 (0.54; 1.42)	<0.001	-0.16	-3.07 (-4.58; -1.56)	<0.001	-0.09	-2.17 (-4.15; -0.20)	0.03

Euro-QoL, Euro- quality of life questionnaire; SF-36, short form 36; ASDAS-CRP, Anklosing Spondylitis Disease Activity Score, C-reactive protein based; MRI, magnetic resonance imaging; SI, sacroiliac; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, confidence interval; NS, Non-significant in multivariate analysis; NI, Not included in the multivariate model.

Supplementary table 2.5. Multivariate linear regressions analyses of factors associated with HAQ (disability index)

	Standard coefficient	Regression coefficient (95% CI)	p-value
Smoker	NS	NS	--
Caucasian race	NS	NS	--
Male sex	-0.20	-0.30 (-0.41; -0.18)	<0.001
HLA-B27 positivity	NS	NS	--
ASDAS-CRP	0.43	0.30 (0.25; 0.36)	<0.001
BASMI	0.23	0.19 (0.12; 0.26)	<0.001

HAQ, health assessment questionnaire; HLA, human leukocyte antigen; ASDAS, ankylosing spondylitis disease activity score; BASMI, Bath Ankylosing Spondylitis Metrology Index; NS, not significant in multivariate analysis; CI, confidence interval.

Supplementary table 2.6. Multivariate logistic regressions analyses of factors associated with MRI inflammation

	MRI spine inflammation		MRI SI joints inflammation		MRI inflammation (spine or SI joints)	
	Odds ratio (95% CI)	**p-value**	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Smoker	NS	--	NS	--	1.65 (1.05; 2.59)	0.03
Caucasian race	1.74 (1.01; 3.00)	0.045	NI	--	NI	--
Male sex	1.95 (1.09; 3.49)	0.03	1.70 (1.04; 2.76)	0.03	1.61 (1.04; 2.50)	0.04
HLA-B27 positivity	NI	--	1.81 (1.08; 3.05)	0.03	1.84 (1.16; 2.93)	0.01
Age at onset of IBP	NI	--	NS	--	NI	--
Family history of AS	0.34 (0.15; 0.74)	0.01	NI	--	NS	--
CRP	NS	--	NI	--	1.02 (1.00; 1.04)	0.03

MRI, magnetic resonance imaging; SI, sacroiliac; CI, confidence interval; HLA, Human Leukocyte Antigen; IBP, inflammatory back pain; NS, Non-significant in multivariate analysis; NI, Not included in the multivariate model.

Supplementary table 2.7. Multivariate logistic regressions analyses of factors associated with MRI structural lesions

	MRI structural lesions (SI joints or spine)		MRI SI joints structural lesions	
	Odds ratio (95% CI)	**p-value**	**Odds ratio (95% CI)**	**p-value**
Smoker	NS	--	NS	--
Caucasian race	NI	--	0.28 (0.09; 0.89)	0.03
HLA-B27 positivity	NS	--	1.26 (0.03; 1.54)	0.02
Family history of AS	NS	--	NI	--
Disease duration	NI	--	NS	--

MRI, magnetic resonance imaging; HLA, Human Leukocyte Antigen; SI, sacroiliac; NS, Non-significant in multivariate analysis; NI, Not included in the multivariate model.

Chapter 9

Ankylosing spondylitis patients with and without psoriasis do not differ in disease phenotype

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Psoriasis is an important clinical feature in ankylosing spondylitis (AS) and spondyloarthritis (SpA) in general,[1] with inflammatory spinal disease developing in 5% 25% of psoriasis cases.[2,3] However, there have been few studies assessing the differences between AS patients with and without concomitant psoriasis.[4–9] Our aim was to compare the demographic, clinical and imaging characteristics between AS patients with and without psoriasis. Baseline data from an 80% random sample of the AS Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) database were used for this analysis. Details of the ASSERT trial and study population have been previously published.[10] Briefly, patients with active AS (fulfilling modified New York criteria) for at least 3 months, a Bath AS disease activity index score of at least 4 (range 0–10) and a spinal pain assessment score of at least 4 (range 0–10) were eligible for the study. AS patients with psoriasis (n=20) were similar to AS patients without psoriasis (n=191–201) (table 1), namely, regarding baseline demographic characteristics (age, disease duration, body mass index and sex), genetic features (human leukocyte antigen-B27 positivity), presence of extra-articular manifestations (uveitis and inflammatory bowel disease), disease activity measures (AS disease activity score, Bath AS disease activity index, patient global assessment and C-reactive protein), severity of enthesitis (Mander enthesitis index), measures of spinal mobility (individual measures and the Bath AS metrology index), physical function (Bath AS functional index), health related quality of life (36-item short form health survey), spinal radiographic damage (modified Stoke AS spine score), location of damage in cervical versus lumbar spine and MRI inflammation of the spine (AS spine MRI score for activity). The only difference that we found was regarding the number of swollen joints. However, this difference did not seem clinically relevant (average 2.4±3.9 swollen joints in patients with psoriasis vs 1.6±3.5 in patients without psoriasis) and the swollen joint count was not independently associated with the presence of psoriasis in the logistic regression analysis (table 1). Probability plots for several outcome measurements were created and stratified for AS patients with and without psoriasis, confirming the similarity between groups at the individual level (figure 1). In this study, we found that demographic characteristics, disease activity, spinal mobility, physical function, structural damage and quality of life are comparable between AS patients with and without psoriasis. Previous studies, performed in heterogeneous populations (early inflammatory back pain, axial psoriatic arthritis and AS patients) have shown conflicting results.[4–9] One of the advantages of our study is the large number of disease variables that were studied. One of the limitations of our study is the low number of patients with psoriasis (20 patients, 10% of the study population), increasing the risk of type II error (ie, the failure to reject a false null hypothesis). Furthermore, this is a clinical trial cohort of patients with severe and active disease fulfilling modified New York criteria for AS; therefore, results are not generalisable to other axial SpA subgroups. Importantly, futures studies should focus on the whole spectrum of axial SpA patients, including patients with radiographic and non-radiographic axial SpA.[1] The application of the axial SpA paradigm can be a particularly useful and unifying concept, given

the long-standing debate on the question of whether patients with inflammatory back disease and psoriasis represent AS with psoriasis or psoriatic spondylitis.[1,3]

Table 1. Comparison of baseline demographic, genetic, clinical and imaging characteristics of patients with and without psoriasis in the study cohort

Variable	No psoriasis (N=191–201)*		Psoriasis (N=20)				
	Mean (SD) or number (%)	**Median (IQR)**	**Mean (SD) or number (%)**	**Median (IQR)**	**p Value† (psoriasis vs no psoriasis)**	**OR (95% CI)‡**	**Adjusted OR (95% CI)§**
Age (years)	39.3 (10.4)	40 (32–46)	40 (7.4)	40.5 (36–47)	0.629	–	–
Disease duration (years)	10.5 (8.6)	8.6 (3.1–16.1)	13.2 (9.7)	13.4 (3.6–20)	0.217	–	–
BMI (Kg/m^2)	25.6 (4.1)	25.6 (22.5–28)	27.0 (4.9)	26.8 (23.3–29.2)	0.259	–	–
Sex (male)	158 (79%)	–	17 (85%)	–	0.773	–	–
HLA-B27*	181 (90.5%)	–	16 (80%)	–	0.140	–	–
Uveitis†	70 (35.5%)	–	6 (30%)	–	0.806	–	–
IBD‡	13 (6.6%)	–	2 (10%)	–	0.634	–	–
ASDAS-CRP	4.0 (0.8)	4.0 (3.4–4.6)	4.2 (1.1)	4.2 (3.2–4.8)	0.516	1.37 (0.80 to 2.32)	1.42 (0.81 to 2.49)
BASDAI	6.4 (1.5)	6.6 (5.3–7.4)	6.6 (1.5)	6.6 (5.7–7.8)	0.545	1.10 (0.81 to 1.49)	1.12 (0.81 to 1.55)
Patient global (0–10 scale)	6.7 (1.7)	6.8 (5.7–7.9)	6.6 (2.5)	7.4 (5–8.2)	0.792	0.97 (0.75 to 1.25)	0.97 (0.76 to 1.25)
CRP (mg/l)	22.4 (24.5)	15 (7–30)	33.1 (45.2)	20 (8.3–34.5)	0.330	1.01 (1.00 to 1.02)	1.01 (1.00 to 1.03)
SJC	1.6 (3.5)	0 (0–1)	2.4 (3.9)	1 (0–3.5)	0.025	1.05 (0.95 to 1.17)	1.06 (0.95 to 1.19)
Mander enthesitis index	11.9 (13.4)	8 (2–15)	8.8 (6.5)	8.5 (4–14.3)	0.883	0.98 (0.93 to 1.02)	0.98 (0.93 to 1.02)
BASFI	5.7 (1.9)	5.7 (4.4–7)	6.1 (1.9)	6.1 (4.9–8)	0.384	1.11 (0.87 to 1.41)	1.12 (0.86 to 1.46)
SF-36 Physical	29.8 (7.1)	29.1 (24.6–34.2)	28 (8.3)	30.6 (19.6–34.6)	0.486	0.96 (0.90 to 1.03)	0.96 (0.89 to 1.03)
SF-36 Mental	45.4 (10.9)	46.7 (36.9–53.6)	44.4 (10.3)	45.8 (34.3–52.9)	0.645	0.99 (0.95 to 1.04)	0.99 (0.95 to 1.04)
Chest expansion (cm)	3.4 (2)	3 (2–4)	4 (2.3)	4 (1.6–5.9)	0.228	1.16 (0.95 to 1.42)	1.22 (0.98 to 1.53)
Tragus to wall (cm)	17.2 (6.6)	15.5 (12–20.4)	16.6 (5.8)	15.3 (11.6–19.9)	0.743	0.99 (0.91 to 1.06)	0.96 (0.88 to 1.04)
Modified schober (cm)	2.5 (1.5)	2.5 (1–3.5)	2.5 (1.4)	2.1 (1–4)	0.868	1.02 (0.74 to 1.39)	1.01 (0.73 to 1.40)
Cervical rotation (cm)	45.9 (21.9)	45 (30–60)	47.6 (23.9)	51.5 (27.8–67.5)	0.762	1.00 (0.98 to 1.03)	1.01 (0.98 to 1.03)
Lateral spinal flexion (cm)	9.2 (5.2)	8.5 (5.5–12.5)	9.1 (6.5)	9.3 (3.25–13)	0.829	1.00 (0.92 to 1.09)	1.01 (0.92 to 1.11)
Intermalleolar distance (cm)	97.2 (27)	100 (78.3–114)	104.1 (26.4)	107 (96.3–122.3)	0.238	1.01 (0.99 to 1.03)	1.01 (1.00 to 1.03)
BASMI-2	4.3 (2.1)	4 (3–6)	4.1 (2.2)	4 (2–6.8)	0.736	0.96 (0.77 to 1.19)	0.90 (0.71 to 1.15)
BASMI-10	4.7 (1.6)	4.6 (3.4–5.8)	4.5 (1.6)	4.5 (3–6.2)	0.620	0.92 (0.69 to 1.23)	0.86 (0.63 to 1.18)
BASMI-linear	4.8 (1.6)	4.7 (3.6–5.9)	4.6 (1.6)	4.5 (3–6.1)	0.616	0.93 (0.69 to 1.24)	0.86 (0.62 to 1.18)
mSASSS total	18.6 (17.4)	13.5 (5–29)	24.2 (25)	14.3 (2.6–43.4)	0.785	1.02 (0.99 to 1.04)	1.01 (0.99 to 1.04)
mSASSS cervical	11.7 (10.9)	7.7 (3–19)	14.1 (14.5)	6.1 (2.1–31)	0.934	1.02 (0.98 to 1.06)	1.02 (0.97 to 1.06)

Variable	No psoriasis (N=191–201)*		Psoriasis (N=20)				
	Mean (SD) or number (%)	**Median (IQR)**	**Mean (SD) or number (%)**	**Median (IQR)**	**p Value† (psoriasis vs no psoriasis)**	**OR (95% CI)‡**	**Adjusted OR (95% CI)§**
mSASSS lumbar	6.9 (9.7)	2.5 (0.5–8.5)	10.1 (12.6)	3.3 (0.1–16)	0.586	1.03 (0.99 to 1.07)	1.02 (0.98 to 1.07)
ASspiMRI-a	6.1 (6.7)	4.5 (0.5–9.5)	7.8 (6.7)	5.6 (2.3–14.1)	0.188	1.03 (0.97 to 1.10)	1.02 (0.96 to 1.09)

*N=201 for all demographic variables, 200 for HLA-B27, 197 for uveitis, 198 for IBD, 200 for all other clinical and laboratory variables, 191 for mSASSS, 198 for ASspiMRI-a and 196 for ASspiMRI-c.
†Mann–Whitney U test for continuous variables and Fisher's exact test for nominal variables.
‡OR of the variable of interest (first column) for the presence of psoriasis (vs no psoriasis) in univariable logistic regression analysis.
§OR of the variable of interest (first column) for the presence of psoriasis (vs no psoriasis) in multivariable logistic regression analysis adjusted for age, gender, BMI, disease duration and HLA-B27 status.
ASDAS, ankylosing spondylitis disease activity score; ASspiMRI-a, ankylosing spondylitis spine MRI score for activity; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis metrology index; BMI, body mass index; CRP, C-reactive protein; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; mSASSS, modified Stoke ankylosing spondylitis spine score; SF-36, 36-item short for health survey; SJC, swollen joint count.

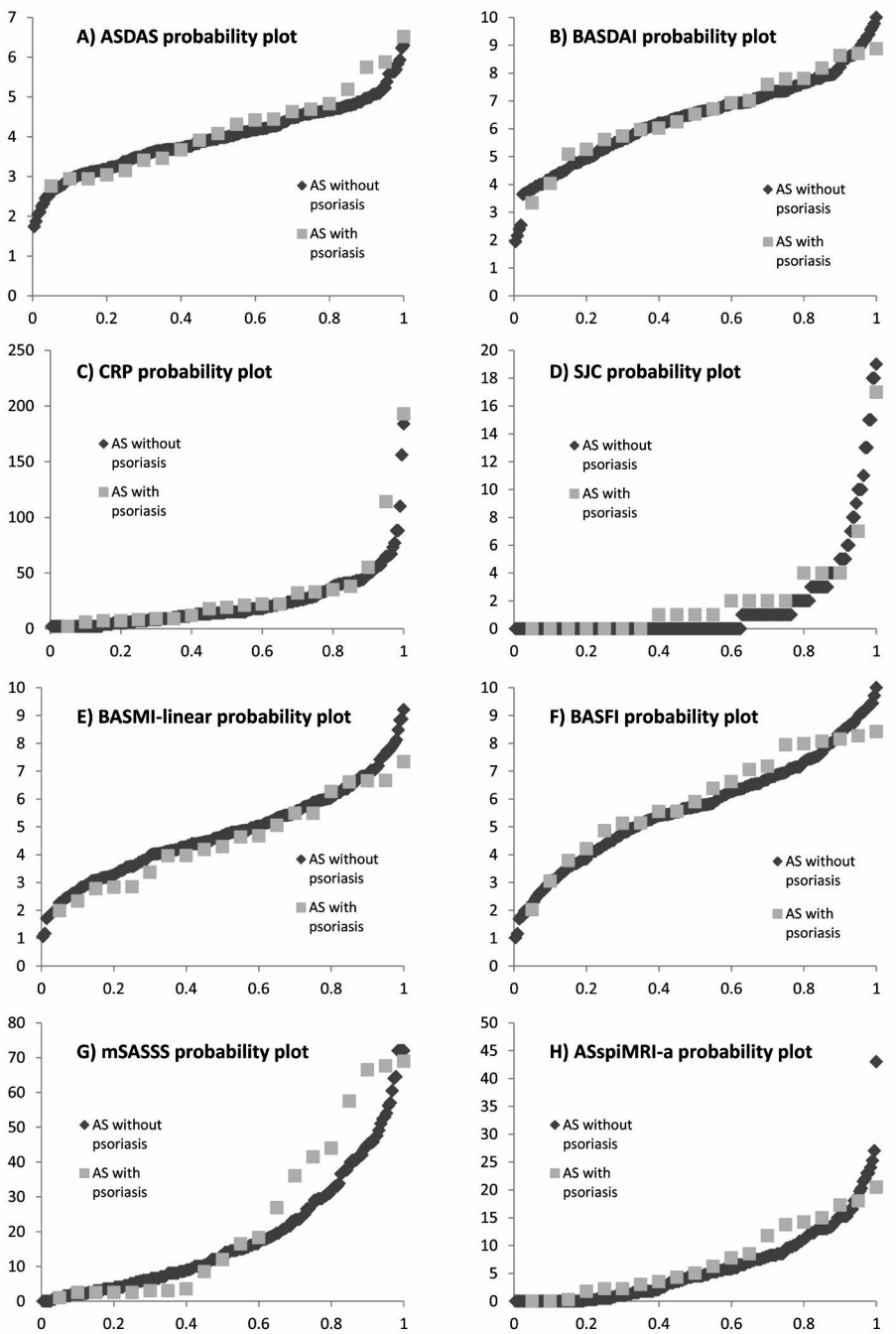

Figure 1. Probability plots for (A) ASDAS, (B) BASDAI, (C) CRP, (D) SJC, (E) BASMI-linear, (F) BASFI, (G) mSASSS and (H) ASspiMRI-a, stratified for AS patients with and without psoriasis. The y-axis represents the score of the outcome measure and the x-axis represents the cumulative probability. AS, ankylosing spondylitis; ASDAS, ankylosing spondylitis disease activity score; ASspiMRI-a, ankylosing spondylitis spine MRI score for activity; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis metrology index; CRP, C-reactive protein; mSASSS, modified Stoke ankylosing spondylitis spine score; SJC, swollen joint count.

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Chapter 10

MRI inflammation at the vertebral unit only marginally predicts new syndesmophyte formation: a multilevel analysis in patients with ankylosing spondylitis

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ABSTRACT

Objective

To investigate the relationship between MRI inflammation at the vertebral unit and the formation and growth of syndesmophytes at the same vertebral unit.

Methods

An 80% random sample of the ASSERT database was analysed. MRI were scored using the ankylosing spondylitis (AS) spinal MRI activity score (at baseline, 24 and 102 weeks) and spinal x-rays were scored using the modified Stoke AS spine score (at baseline and 102 weeks). Data were analysed at the patient level and the vertebral unit level using a multilevel approach to adjust for within-patient correlation.

Results

There was a slightly increased probability of developing syndesmophytes in vertebral units with MRI activity, which was maintained after adjustment for within-patient correlation (per vertebral unit level) and treatment, and after further adjustment for potential confounders, resulting in significant OR ranging from 1.51 to 2.26. Growth of existing syndesmophytes at the vertebral unit level was not associated with MRI activity. At the patient level only a trend for an association was observed.

Conclusion

MRI inflammation in a vertebral unit slightly increases the propensity to form a new syndesmophyte in the same vertebral unit, but does not predict the growth of already existing syndesmophytes. Despite this association, the large majority of new syndesmophytes developed in vertebral units without inflammation. The subtle association at the vertebral unit level did not translate into an association at the patient level.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterised by reversible inflammation and irreversible structural damage of the spine.[1] MRI has emerged in recent years as a useful assessment tool because of its ability to detect active inflammatory lesions in the spine.[2–5]

Structural damage in AS is characterised by excessive bone formation, with syndesmophytes as the typical lesion. x-Rays are still considered the gold standard for the assessment of syndesmophytes in AS.[1]

The processes underlying syndesmophyte formation are insufficiently understood. Bone proliferation may reflect a pathologically enhanced repair response of bone[1,6] and a causal relationship between MRI inflammation and syndesmophyte formation is hypothesised. However, tumour necrosis factor (TNF) blockers that dramatically reduce inflammation as measured on MRI[7,8] do not inhibit syndesmophyte formation and growth.[9–11]

Our aim was to investigate the relationship between inflammation on MRI and the formation/growth of syndesmophytes, both at the level of the vertebral unit and the patient. In this analysis we carefully adjusted for other factors potentially being associated with syndesmophyte formation. Furthermore, and in contrast to analyses in previous reports,[12,13] we considered within-patient correlation as a spurious source of positive correlations, and we undertook detailed multilevel analysis to adjust for such effects.

METHODS

AS patient population

A random 80% sample of the AS Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) cohort was used for this analysis.[14] ASSERT was a 24-week randomised controlled trial comparing infliximab and placebo in patients with active AS, with an open extension until 102 weeks with all patients treated with infliximab. The details of the ASSERT study have been reported elsewhere.[14] Data from 1827 to 2070 vertebral units, belonging to 177–182 patients were available for paired analysis (the total number of available vertebral units/patients in each analysis depends on the case definition and reader used per analysis; an additional source of variation in numbers is because sometimes one of the two readers scored a vertebral unit as not evaluable).

MRI assessment

Images were scored according to the AS spinal MRI activity (ASspiMRI-a) score.[15] A vertebral unit is defined as the region between two virtual lines through the middle of each vertebra, and all 23 vertebral units of the spine (C2–S1) are scored for enhancement (T1 postgadolinium images) and bone marrow oedema (short-tau inversion recovery images), with a grading system from 0 to 3, with three more grades (4–6) if, in addition to inflammation, erosions are also visualised (maximum total score 138).

Radiographic assessment

Lateral views of the cervical and lumbar spine were scored according to the modified Stoke AS spine score (mSASSS).[16] The mSASSS scores anterior vertebral corners of the cervical and lumbar spine at 24 levels (C2–T1 and T12–S1, corresponding to 12 vertebral units). It includes squaring, erosions, sclerosis (score 1 for one or more of these features present), syndesmophyte (score 2) and bridging (score 3). Therefore, the total mSASSS ranges from 0 (completely normal) to 72 (complete bridging).

Reading of radiographs and MRI images

MRI and spinal radiographs were scored by four qualified and well-trained readers (two for the radiographs and two for the MRI images), who were blinded to the patient's identity, time order and treatment. The two-way random model, absolute agreement type and average measures intraclass correlation coefficients for the MRI scores were 0.84 (baseline), 0.64 (24 weeks), 0.57 (102 weeks), 0.78 (24 weeks change) and 0.83 (102 weeks change). The intraclass correlation coefficients for the x-ray scores were 0.96 (baseline), 0.97 (102 weeks) and 0.86 (102 weeks change).

Case definition

Five case definitions were used for MRI inflammation (activity) at the vertebral unit:

1. Active vertebral unit at baseline, irrespective of inflammation status at other time points;
2. Active vertebral unit at baseline only;
3. Active vertebral unit at baseline and another time point;
4. Active vertebral unit at any time point;
5. Active vertebral unit at all time points.

The presence of activity/inflammation in a vertebral unit was defined as an MRI score greater than 0 in that vertebral unit. Two case definitions were used for syndesmophyte formation/ growth:

1. A definition based on sensitivity: a case was defined as positive if at least one

of the readers reported progression;
2. A definition based on specificity: a case was defined as positive only if both readers reported progression (absolute agreement).

Syndesmophyte formation at a vertebral unit was defined as an increase of a score of 0 or 1 to a score of 2 or 3 at any of the two vertebral corners of the same vertebral unit. Syndesmophyte growth at a vertebral unit was defined as an increase of a score of 2 to 3 at the vertebral corners of the vertebral unit. The various case definitions for MRI and syndesmophyte formation/growth resulted in 20 scenarios for each MRI reader (table 1).

For the total mSASSS and ASspiMRI-a score, the mean of both readers' scores was used in the analysis.

Statistical analysis

Statistical analyses were performed using SPSS 18. Data were analysed at the vertebral unit level in the 12 vertebral units that are assessed by both scoring systems and at the patient level using total ASspiMRI-a and mSASSS scores of these 12 vertebral units.

Cross-tabulation statistics and measures of association (OR and 95% CI) were first computed using two-way tables to test the association between MRI vertebral unit inflammation and syndesmophyte formation/growth according to all the above-specified definitions.

Statistically significant associations and associations where a trend was observed were re-tested using generalised estimating equation (GEE) analysis, adjusting for within-patient correlation (by vertebral unit level and MRI reader, ie, adjusting for the dependence of observations arising from multiple measurements in different vertebral units of the same patient and adjusting for the MRI reader as another source of dependency of results), treatment and other factors known or expected to be associated with syndesmophyte formation/growth, namely clinical disease activity (assessed by the Bath ankylosing spondylitis disease activity index),[17] C-reactive protein, gender, age, disease duration, human leucocyte antigen (HLA)-B27 status and presence of syndesmophytes/bridging at baseline.

RESULTS

Relationship between MRI activity at the vertebral unit level and formation/growth of syndesmophytes

Excluding the 'always active' case definition, there was a preference to develop syndesmophytes in vertebral units with compared with vertebral units without MRI

Table 1. Two-way analysis to test the association between MRI vertebral unit activity and syndesmophyte formation/growth after 2 years' follow-up*

	New syndesmophytes (R1 or R2)		New syndesmophytes (R1 and R2)		Growth of syndesmophytes (R1 or R2)		Growth of syndesmophytes (R1 and R2)	
	Yes, N (%)	**No, N (%)**	**Yes, N (%)**	**No, N (%)**	**Yes, N (%)**	**No, N (%)**	**Yes, N (%)**	**No, N (%)**
MRI reader 1:								
Active vertebral unit at BL	36 (10.9/*24.2*)	295 (89.1/*16.1*)	12 (3.6/*27.9*)	323 (96.4/*16.2*)	4 (1.2/*15.4*)	327 (98.8/*16.7*)	1 (0.3/*14.3*)	334 (99.7/*16.4*)
Inactive vertebral unit at BL	113 (6.8/*75.8*)	1537 (93.2/*83.9*)	31 (1.8/*72.1*)	1677 (98.2/*83.9*)	22 (1.3/*84.6*)	1627 (98.7/*83.3*)	6 (0.4/*85.7*)	1703 (99.6/*83.6*)
OR (95% CI)	**1.66 (1.12 to 2.47)**		**2.01 (1.02 to 3.96)**		0.91 (0.31 to 2.64)		0.85 (0.10 to 7.08)	
MRI reader 2:								
Active vertebral unit at BL	36 (12.1/*23.8*)	261 (87.9/*14.1*)	10 (3.3/*22.7*)	294 (96.7/*14.5*)	6 (2.0/*22.2*)	291 (98.0/*14.7*)	2 (0.7/*28.6*)	302 (99.3/*14.6*)
Inactive vertebral unit at BL	115 (6.7/*76.2*)	1592 (93.3/*85.9*)	34 (1.9/*77.3*)	1731 (98.1/*85.5*)	21 (1.2/*77.8*)	1685 (98.8/*85.3*)	5 (0.3/*71.4*)	1761 (99.7/*85.4*)
OR (95% CI)	**1.91 (1.28 to 2.84)**		1.73 (0.85 to 3.54)		1.65 (0.66 to 4.13)		2.33 (0.45 to 12.08)	
MRI reader 1:								
Active vertebral unit at BL only	27 (11.4/*18.1*)	209 (88.6/*11.4*)	9 (3.8/*20.9*)	229 (96.2/*11.5*)	2 (0.8/*7.7*)	234 (99.2/*12.0*)	1 (0.4/*14.3*)	237 (99.6/*11.6*)
Inactive vertebral unit at BL, or active at BL and other TP	122 (7.0/*81.9*)	1623 (93.0/*88.6*)	34 (1.9/*79.1*)	1771 (98.1/*88.6*)	24 (1.4/*92.3*)	1720 (98.6/*88.0*)	6 (0.3/*85.7*)	1800 (99.7/*88.4*)
OR (95% CI)	**1.72 (1.11 to 2.67)**		2.05 (0.97 to 4.32)		0.61 (0.14 to 2.61)		1.27 (0.15 to 10.6)	
MRI reader 2:								
Active vertebral unit at BL only	22 (11.3/*14.6*)	173 (88.7/*9.3*)	7 (3.5/*15.9*)	191 (96.5/*9.4*)	4 (2.1/*14.8*)	191 (97.9/*9.7*)	2 (1.0/*28.6*)	196 (99.0/*9.5*)
Inactive vertebral unit at BL, or active at BL and other TP	129 (7.1/*85.4*)	1680 (92.9/*90.7*)	37 (2.0/*84.1*)	1834 (98.0/*90.6*)	23 (1.3/*85.2*)	1785 (98.7/*90.3*)	5 (0.3/*71.4*)	1867 (99.7/*90.5*)
OR (95% CI)	**1.66 (1.03 to 2.67)**		1.82 (0.80 to 4.13)		1.63 (0.56 to 4.75)		3.81 (0.73 to 19.8)	
MRI reader 1:								
Active vertebral unit at BL and another TP	9 (10.8/*6.0*)	74 (89.2/*4.1*)	3 (3.5/*7.0*)	82 (96.5/*4.1*)	2 (2.4/*7.7*)	81 (97.6/*4.2*)	0 (0.0/*0.0*)	85 (100/*4.2*)
Inactive vertebral unit at BL, or active at BL but not at other TP	140 (7.4/*94.0*)	1746 (92.6/*95.9*)	40 (2.1/*93.0*)	1906 (97.9/*95.9*)	24 (1.3/*92.3*)	1861 (98.7/*95.8*)	7 (0.4/*100*)	1940 (99.6/*95.8*)
OR (95% CI)	1.52 (0.74 to 3.09)		1.74 (0.53 to 5.75)		1.92 (0.45 to 8.24)		NA (p=0.580)	

	New syndesmophytes (R1 or R2)		New syndesmophytes (R1 and R2)		Growth of syndesmophytes (R1 or R2)		Growth of syndesmophytes (R1 and R2)	
	Yes, N (%)	**No, N (%)**	**Yes, N (%)**	**No, N (%)**	**Yes, N (%)**	**No, N (%)**	**Yes, N (%)**	**No, N (%)**
MRI reader 2:								
Active vertebral unit at BL and another TP	14 (14.3/*9.3*)	84 (85.7/*4.5*)	3 (2.9/*6.8*)	99 (97.1/*4.9*)	2 (2.0/*7.4*)	96 (98.0/*4.9*)	0 (0.0/*0.0*)	102 (100/*5.0*)
Inactive vertebral unit at BL, or active at BL but not at other TP	137 (7.2/*90.7*)	1765 (92.8/*95.5*)	41 (2.1/*93.2*)	1922 (97.9/*95.1*)	25 (1.3/*92.6*)	1876 (98.7/*95.1*)	7 (0.4/*100*)	1957 (99.6/*95.0*)
OR (95% CI)	**2.15 (1.19 to 3.89)**		1.42 (0.43 to 4.67)		1.56 (0.37 to 6.70)		NA (p=0.546)	
MRI reader 1:								
Active vertebral unit at any TP	40 (11.2/*28.6*)	318 (88.8/*18.7*)	12 (3.3/*31.6*)	349 (96.7/*18.8*)	5 (1.4/*21.7*)	352 (98.6/*19.4*)	1 (0.3/*16.7*)	361 (99.7/*19.1*)
Always inactive vertebral unit	100 (6.7/*71.4*)	1385 (93.3/*81.3*)	26 (1.7/*68.4*)	1511 (98.3/*81.2*)	18 (1.2/*78.3*)	1467 (98.8/*80.6*)	5 (0.3/*83.3*)	1532 (99.7/*80.9*)
OR (95% CI)	**1.74 (1.18 to 2.56)**		2.00 (1.00 to 4.00)		1.16 (0.43 to 3.14)		0.85 (0.10 to 7.29)	
MRI reader 2:								
Active vertebral unit at any TP	40 (11.9/*26.8*)	297 (88.1/*16.7*)	10 (2.9/*23.3*)	334 (97.1/*17.2*)	8 (2.4/*29.6*)	329 (97.6/*17.4*)	2 (0.6/*28.6*)	342 (99.4/*17.3*)
Always inactive vertebral unit	109 (6.9/*73.2*)	1477 (6.9/*73.2*)	33 (2.0/*76.7*)	1607 (98.0/*82.8*)	19 (1.2/*70.4*)	1566 (98.8/*82.6*)	5 (0.3/*71.4*)	1636 (99.7/*82.7*)
OR (95% CI)	**1.83 (1.24 to 2.68)**		1.46 (0.71 to 2.99)		2.00 (0.87 to 4.62)		1.91 (0.37 to 9.90)	
MRI reader 1:								
Always active vertebral unit	0 (0.0/*0.0*)	8 (100/*0.5*)	0 (0.0/*0.0*)	8 (100/*0.4*)	0 (0.0/*0.0*)	8 (100/*0.4*)	0 (0.0/*0.0*)	8 (100/*0.4*)
Not-always active vertebral unit	140 (7.7/*100*)	1679 (92.3/99.5)	38 (2.0/*100*)	1836 (98.0/*99.6*)	23 (1.3/*100*)	1795 (98.7/*99.6*)	6 (0.3/*100*)	1869 (99.7/*99.6*)
OR (95% CI)	NA (p=0.414)		NA (p=0.684)		NA (p=0.749)		NA (p=0.873)	
MRI reader 2:								
Always active vertebral unit	0 (0.0/*0.0*)	6 (100/*0.3*)	0 (0.0/*0.0*)	6 (100/*0.3*)	0 (0.0/*0.0*)	6 (100/*0.3*)	0 (0.0/*0.0*)	6 (100/*0.3*)
Not-always active vertebral unit	149 (7.8/*100*)	1763 (92.2/*99.7*)	43 (2.2/*100*)	1930 (97.8/*99.7*)	27 (1.4/*100*)	1884 (98.6/*99.7*)	7 (0.4/*100*)	1967 (99.6/*99.7*)
OR (95% CI)	NA (p=0.476)		NA (p=0.715)		NA (p= 0.769)		NA (p=0.884)	

*In the table cells, the first percentage uses MRI activity as denominator, while the second percentage (in *italic*) uses syndesmophyte formation/growth as denominator. Statistically significant OR at the 5% level are highlighted in **bold**. For cases in which the cell count is 0, the OR could not be calculated and the p value of the Pearson χ^2 result is provided. BL, baseline; NA, not applicable; R1/R2, reader 1/reader 2; TP, time point.

activity for both syndesmophyte definitions and for both MRI readers (table 1, OR ranging from 1.42 to 2.15, statistically significant in the majority of case definitions). The growth of existing syndesmophytes at the vertebral unit level was not associated with MRI activity (table 1, OR ranging from 0.61 to 3.81, always non-significant). Vertebral units with inflammation at all time points ('always active') did not develop syndesmophytes and did not show growth of existing syndesmophytes (table 1).

From the syndesmophyte perspective, depending on the syndesmophyte case definition, the MRI reader and the MRI case definition (and excluding the 'always active' case definition), 6–32% of new syndesmophytes developed in vertebral units with active inflammation and 68–94% of new syndesmophytes developed in vertebral units without active inflammation. Similarly, 0–30% of the syndesmophytes that showed growth did so in active vertebral units and 70–100% of the syndesmophytes that showed growth did so in vertebral units without inflammation (table 1).

GEE analysis at the vertebral unit level and at the patient level

The increased probability of developing new syndesmophytes in active vertebral units was confirmed by GEE analysis, and maintained after adjustment for within-patient correlation (by vertebral unit level and MRI reader), treatment and further adjustment for potential confounders: OR 1.43–1.57, for syndesmophyte formation according to readers 1 or 2 (table 2), and OR 1.22–2.26 for syndesmophyte formation according to readers 1 and 2 (table 3). However, results were not always statistically significant, and for some case definitions only a trend was observed (tables 2 and 3).

Gender, disease activity, baseline total mSASSS (>5 units), the presence of syndesmophytes or bridging at baseline and HLAB27 were shown to be independent contributors to syndesmophyte formation (tables 2 and 3).

At the patient level, in GEE analysis (by MRI reader and with adjustment for treatment), an increase in the mSASSS from baseline to 2 years was not associated with a higher baseline MRI activity score (regression coefficient (B) 0.109; 95% CI –0.132 to 0.350; p=0.375) or time-integrated MRI activity score (B 0.002; 95% CI –0.02 to 0.05; p=0.337). When variables were dichotomised at the patient level syndesmophyte formation (yes/no) used as dependent variable, and baseline MRI activity or time-integrated MRI activity score (positive/negative) used as independent variable - there was still no association; however, a trend was observed:

1. Syndesmophyte formation according to readers 1 or 2: OR 1.66; 95% CI 0.97 to 2.85; p=0.067 (for positive MRI activity at baseline) and OR 1.43; 95% CI 0.82 to 2.51; p=0.210 (for positive time-integrated MRI activity).

Table 2. GEE results (OR; 95% CI; p values) for the outcome syndesmophyte formation according to reader 1 or reader 2, with MRI vertebral unit inflammation as determinant, and with adjustment for within-patient correlation by vertebral unit level and MRI reader (first line), for individual potential confounders (second to 11th line) and for all significant confounders (last two lines)*

Adjustment factor	Active vertebral unit at baseline	Adjustment factor	Active vertebral unit at baseline only	Adjustment factor	Active vertebral unit at baseline and another time point	Adjustment factor	Active vertebral unit at any time point	Adjustment factor
Within-patient correlation	**1.64 (1.12 to 2.41) p=0.012**	NA	1.50 (0.95 to 2.35) p=0.079	NA	1.69 (0.90 to 3.17) p=0.105	NA	**1.72 (1.20 to 2.44) p=0.003**	NA
Gender	1.57 (1.08 to 2.28) p=0.018	2.79 (1.45 to 5.40) p=0.002	1.44 (0.94 to 2.22) p=0.098	2.81 (1.45 to 5.44) p=0.002	1.66 (0.89 to 3.09) p=0.109	2.89 (1.48 to 5.67) p=0.002	1.64 (1.16 to 2.33) p=0.005	2.73 (1.41 to 5.28) p=0.003
HLA-B27	1.64 (1.12 to 2.41) p=0.011	NS	1.50 (0.95 to 2.36) p=0.079	NS	1.69 (0.90 to 3.17) p=0.103	NS	1.72 (1.21 to 2.46) p=0.003	NS
Age	1.65 (1.12 to 2.43) p=0.011	NS	1.50 (0.95 to 2.37) p=0.083	NS	1.70 (0.90 to 3.20) p=0.101	NS	1.73 (1.21 to 2.46) p=0.003	NS
Disease duration	1.64 (1.11 to 2.40) p=0.012	NS	1.49 (0.95 to 2.35) p=0.083	NS	1.68 (0.90 to 3.15) p=0.106	NS	1.71 (1.20 to 2.44) p=0.003	NS
BASDAI at baseline	1.67 (1.13 to 2.47) p=0.010	NS	1.56 (0.98 to 2.46) p=0.059	NS	1.66 (0.89 to 3.09) p=0.111	NS	1.74 (1.21 to 2.49) p=0.003	NS
BASDAI AUC	1.68 (1.14 to 2.48) p=0.009	0.999 (0.998 to 1.000) p=0.046	1.56 (0.98 to 2.47) p=0.061	0.999 (0.998 to 1.000) p=0.049	1.67 (0.89 to 3.13) p=0.109	NS	1.73 (1.21 to 2.47) p=0.003	0.999 (0.998 to 1.000) p=0.021
CRP at baseline	1.58 (1.06 to 2.34) p=0.024	NS	1.41 (0.89 to 2.25) p=0.145	NS	1.73 (0.91 to 3.30) p=0.096	NS	1.65 (1.15 to 2.38) p=0.007	NS
CRP AUC	1.57 (1.06 to 2.32) p=0.025	NS	1.41 (0.89 to 2.25) p=0.144	NS	1.70 (0.90 to 3.23) p=0.105	NS	1.64 (1.14 to 2.35) p=0.008	NS
Total mSASSS at baseline >5	1.55 (1.06 to 2.25) p=0.023	2.59 (1.29 to 5.20) p=0.007	1.43 (0.92 to 2.22) p=0.115	2.63 (1.31 to 5.29) p=0.007	1.60 (0.86 to 2.97) p=0.136	2.63 (1.30 to 5.29) p=0.007	1.63 (1.15 to 2.31) p=0.006	2.40 (1.20 to 4.80) p=0.014
Syndesmophytes or bridging at baseline	1.57 (1.07 to 2.30) p=0.021	2.58 (1.36 to 4.87) p=0.004	1.44 (0.92 to 2.24) p=0.109	2.64 (1.40 to 4.98) p=0.003	1.64 (0.87 to 3.08) p=0.124	2.67 (1.41 to 5.05) p=0.003	1.62 (1.14 to 2.32) p=0.008	2.39 (1.27 to 4.50) p=0.007
Adjustment for all significant variables†	**1.51(1.05 to 2.19) p=0.028**	NA	1.43 (0.92 to 2.20) p=0.109	NA	1.57 (0.85 to 2.89) p=0.150	NA	**1.55 (1.01 to 2.19) p=0.012**	NA
Adjustment for all significant variables‡	**1.56 (1.07 to 2.27) p=0.020**	NA	1.46 (0.95 to 2.26) p=0.088	NA	1.62 (0.87 to 3.02) p=0.130	NA	**1.57 (1.10 to 2.24) p=0.012**	NA

Statistically significant OR after adjustment for within-patient correlation (first line) and after adjustment for all significant confounders (last two line) are highlighted in **bold**. *All models adjusted for treatment effect (non-significant) and for within-patient correlation (by vertebral unit level and MRI reader). †Adjusted for 'total mSASSS at baseline >5'. ‡Adjusted for presence of 'syndesmophytes or bridging at baseline' (at the patient level, according to both readers). AUC, area under the curve; BASDAI, Bath ankylosing spondylitis disease activity index; CRP, C-reactive protein; GEE, generalised estimating equation; HLA, human leucocyte antigen; mSASSS, modified Stoke AS spine score; NA, not applicable; NS, non-significant.

Table 3. GEE results (OR; 95% CI; p values) for the outcome syndesmophyte formation according to reader 1 and reader 2, with MRI vertebral unit inflammation as determinant, and with adjustment for within-patient correlation by vertebral unit level and MRI reader (first line), for individual potential confounders (second to 11th line) and for all significant confounders (last line)*

Adjustment factor	Active vertebral unit at baseline	Adjustment factor	Active vertebral unit at baseline only	Adjustment factor	Active vertebral unit at baseline and another time point	Adjustment factor	Active vertebral unit at any time point	Adjustment factor
Within-patient correlation	**1.85 (1.01 to 3.41) p=0.048**	NA	**2.06 (1.04 to 4.05) p=0.037**	NA	1.11 (0.46 to 2.67) p=0.813	NA	1.77 (0.95 to 3.27) p=0.070	NA
Gender	1.75 (0.96 to 3.20) p=0.067	3.70 (1.01 to 13.48) p=0.048	1.93 (0.99 to 3.75) p=0.053	NS	1.14 (0.48 to 2.70) p=0.771	4.00 (1.18 to 13.61) p=0.026	1.67 (0.91 to 3.08) p=0.098	NS
HLA-B27	1.91 (1.05 to 3.47) p=0.034	3.38 (1.14 to 9.99) p=0.028	2.11 (1.07 to 4.14) p=0.031	3.46 (1.16 to 10.27) p=0.026	1.16 (0.51 to 2.66) p=0.726	3.18 (1.08 to 9.42) p=0.036	1.85 (1.01 to 3.38) p=0.046	3.77 (1.27 to 11.18) p=0.017
Age	1.85 (0.98 to 3.52) p=0.060	NS	2.08 (1.02 to 4.23) p=0.044	NS	1.11 (0.43 to 2.90) p=0.829	NS	1.76 (0.92 to 3.34) p=0.086	NS
Disease duration	1.85 (0.99 to 3.43) p=0.052	NS	2.06 (1.04 to 4.10) p=0.040	NS	1.10 (0.45 to 2.68) p=0.836	NS	1.77 (0.95 to 3.28) p=0.073	NS
BASDAI at baseline	1.90 (0.96 to 3.76) p=0.065	0.63 (0.44 to 0.89) p=0.010	2.22 (1.06 to 4.64) p=0.034	0.63 (0.45 to 0.88) p=0.007	1.09 (0.40 to 2.95) p=0.866	0.64 (0.45 to 0.90) p=0.010	1.74 j(0.88 to 3.45) p=0.114	0.60 (0.41 to 0.86) p=0.006
BASDAI AUC	1.91 (0.99 to 3.65) p=0.052	NS	2.20 (1.06 to 4.58) p=0.034	0.998 (0.997 to 1.000) p=0.046	1.07 (0.43 to 2.67) p=0.879	NS	1.76 (0.93 to 3.35) p=0.083	NS
CRP at baseline	1.73 (0.91 to 3.33) p=0.097	NS	1.82 (0.90 to 3.69) p=0.097	NS	1.27 (0.55 to 2.91) p=0.573	NS	1.62 (0.84 to 3.13) p=0.147	NS
CRP AUC	1.76 (0.95 to 3.27) p=0.072	NS	1.83 (0.93 to 3.58) p=0.079	NS	1.30 (0.63 to 2.70) p=0.475	NS	1.69 (0.91 to 3.13) p=0.097	NS
Total mSASSS at baseline >5	1.72 (0.91 to 3.24) p=0.094	NS	1.95 (0.95 to 4.01) p=0.068	NS	1.02 (0.41 to 2.57) p=0.963	NS	1.66 (0.87 to 3.14) p=0.121	NS
Syndesmophytes or bridging at baseline	1.67 (0.88 to 3.18) p=0.116	NS	1.91 (0.92 to 3.96) p=0.084	NS	1.00 (0.38 to 2.63) p=0.995	NS	1.62 (0.84 to 3.10) p=0.147	NS
Adjustment for all significant variables	1.89 (0.98 to 3.65) p=0.056	NA	**2.26 (1.08 to 4.74) p=0.031**	NA	1.22 (0.47 to 3.15) p=0.678	NA	1.43 (0.59 to 3.49) p=0.426	NA

Statistically significant OR after adjustment for within-patient correlation (first line) and after adjustment for all significant confounders (last line) are highlighted in **bold**. *All models adjusted for treatment effect (non-significant) and for within-patient correlation (by vertebral unit level and MRI reader). AUC, area under the curve; BASDAI, Bath ankylosing spondylitis disease activity index; CRP, C-reactive protein; GEE, generalised estimating equation; HLA, human leucocyte antigen; mSASSS, modified Stoke AS spine score; NA, not applicable; NS, non-significant.

2. Syndesmophyte formation according to readers 1 and 2: OR 1.63; 95% CI 0.82 to 3.22; p=0.163 (for positive MRI activity at baseline) and OR 1.64; 95% CI 0.83 to 3.25; p=0.154 (for positive time-integrated MRI activity).

DISCUSSION

MRI inflammation in a vertebral unit slightly increases the likelihood of finding a new syndesmophyte in the same vertebral unit 2 years later, but does not predict the growth of already existing syndesmophytes. The majority of syndesmophytes developed in vertebral units without any sign of inflammation on MRI, suggesting that the relationship between MRI inflammation and syndesmophyte formation is not straightforward. For some of the case definitions, this association did not reach statistical significance. The subtle association between MRI activity and new syndesmophytes at the vertebral unit level did not translate into an association at the patient level; however, a trend was also observed.

Two other studies have shown a statistical association between inflammation on MRI of individual vertebral units and the subsequent development of a new syndesmophyte at the same level 2 years later.[12 13] The strength of association was slightly higher in those studies (OR≈3 and OR≈5, respectively) as compared to our study (OR≈1.5–2), but also in those studies there were far more new syndesmophytes in non-inflamed vertebral units compared with inflamed vertebral units. Apart from that, the numbers of patients were far lower (n=39,[12] n=29 and n=41,[13] respectively) and none of them adjusted for within-patient correlation or for potential confounders. Furthermore, we looked at the entire vertebral unit, while the other studies[12,13] focused on the vertebral edge, but the consequence of this is not known. While Baraliakos et al[12] only used one MRI reader and Maksymowych et al[13] only looked at MRI concordant data, our study looked at data from both MRI readers independently.

The subtle association between MRI activity and new syndesmophytes is in conflict with the absence of an effect of TNF blockers on structural damage.[9–11] One possible explanation to reconcile these two discrepant observations is that syndesmophyte formation is a post-inflammatory repair reaction that may only be inhibited if a TNF blocker is started early, before inflammation gives way to repair. This theory implies a switch from inflammation to repair, which is poorly understood. It has been proposed that persisting inflammation in the context of synovitis (with rheumatoid arthritis as the prototype disease) is dominated by destructive bone-erosive processes (mediated by RANKL, Dkk-1 and sclerostin) and suppression of repair. If inflammation is not chronic but fluctuating (as postulated in AS), repair processes may be switched on, resulting in an anabolic response driven by prostaglandins, Wnt and bone morphogenetic proteins.[6,18] In

such a scenario early treatment initiation (before the switch) may prevent the anabolic response that eventually leads to syndesmophyte formation. It is hypothesised that focal fat infiltration at the vertebral corner, which occurs after inflammation of that site, is one of the early signs of repair. In a recent study, the presence of focal fat lesions at a vertebral corner was associated with the development of a syndesmophyte at the same site 2 years later.[19] Recent studies in rat arthritis models suggest that bony spur formation is a response to injury mechanism of the joint, which is turned on rapidly during initial joint damage,[20] an observation that also favours the concept that rapid control of inflammation in the early phase of disease could prevent structural damage. However, other authors have suggested that the triggering of new tissue formation may be completely or partly independent of inflammation.[21]

It was recently postulated that syndesmophytes were more likely to develop at those corners in which inflammation resolved than at those where inflammation persisted.[13,22] None of the vertebral units with persistent inflammation ('active at all time points') in our study developed new syndesmophytes, but the numbers were small and inconclusive. The fact that this is a population treated with anti-TNF, a very effective drug in reducing MRI inflammation, explains the low number of vertebral units without persistent inflammation. It would be of interest to expand our analyses to daily practice cohorts with broader profiles of MRI inflammation over time. It would also be of interest to study an early disease population, in which the interplay between inflammatory and bone formation pathways may be different. Furthermore, as syndesmophytes grow slowly, longer study periods would help to clarify the magnitude of the effect of inflammation in predicting bone formation. In summary, we have shown that MRI inflammation at the vertebral unit only marginally predicts new syndesmophyte formation in that unit. If inflammation is indeed the principal trigger of repair responses, a strong case can be made for early and aggressive anti-inflammatory treatment. Conversely, if inflammation and repair are independent pathways triggered by common factors, new therapies targeting the pathologically enhanced repair response need to be developed.

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Chapter 11

MRI vertebral corner inflammation followed by fat deposition is the strongest contributor to the development of new bone at the same vertebral corner: a multi-level longitudinal analysis in patients with ankylosing spondylitis

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ABSTRACT

Objectives

To study the sequential relationship between MRI vertebral corner inflammation (VCI), vertebral corner fat deposition (VCFD) and the development/growth of radiographic syndesmophytes at the same vertebral corner (VC).

Methods

Baseline, 24 and 102 weeks spinal MRIs were assessed for the presence/absence of VCI and VCFD. Anterior VCs of lateral radiographs of the cervical and lumbar spine (baseline and 102 weeks) were assessed for the development of new bone (syndesmophyte formation or syndesmophyte formation/growth combined). Data from 161 to 177 patients were analysed at the VC level using two-way and multilevel analyses adjusting for within-patient correlation and MRI reader (generalised estimating equations for binomial outcomes).

Results

The presence of VCI (adjusted (adj) OR 1.75 to 1.98) as well as the presence of VCFD (adjOR 1.60 to 2.32) at any time point (TP) were significantly associated with the development of new bone. The combination of VCI and VCFD at the same VC increased the strength of the association, both for the sequential or simultaneous presence of VCI and VCFD across the three TPs (adjOR 2.12 to 2.73), as well as for the development of new VCFD preceded by VCI at a previous TP (adjOR 2.12 to 3.01). The complete absence of both VCI and VCFD across the three TPs 'protected' against new bone formation (adjOR 0.45 to 0.62). However, 40–66% of new bone still developed in VCs without MRI inflammation or fat degeneration at any of the three TPs.

Conclusion

Both VCI and VCFD contribute to new bone formation in ankylosing spondylitis (AS), especially if VCI precedes VCFD. However, VCI, VCFD and this particular sequence of events only partially explain the development of new bone in AS.

INTRODUCTION

Structural damage in ankylosing spondylitis (AS) is characterised by the formation of new bone in the spine. Syndesmophytes and bridging syndesmophytes are the typical lesions,[1,2] with erosions, sclerosis and squaring being additional lesions that also reflect structural damage in AS. Syndesmophytes can lead to decreased spinal mobility, reduced physical function and loss of quality of life.[3–5] Therefore, understanding the mechanisms underlying new bone formation is of importance in AS.

The processes that drive the formation of new bone in AS are not completely understood, and there is debate about whether inflammation and osteoproliferation are related or uncoupled phenomena.[6–8] This is a challenging topic to investigate because the progression of structural damage is typically slow, it is problematic to perform serial histopathological examinations of spinal tissue and reliable biomarkers of new bone formation in AS are lacking.

MRI provides an indirect and non-invasive method of investigating elements of the pathophysiology of new bone formation in AS. Fat deposition can be seen on T1-weighted sequences and bone marrow oedema (reflecting inflammation) can be seen on T2-weighted sequences with fat suppression, such as the short tau inversion recovery (STIR) sequence.[9–12] However, conventional radiography is still the gold standard method to assess syndesmophyte formation/bridging[13] because tissues with low proton density such as cortical bone and paravertebral ligaments exhibit low or no signal intensity in all pulse sequences and are difficult to differentiate on MRI scans.[14]

It has been shown by us in the same cohort[15] and by others in independent cohorts[16–18] that vertebral corners (VCs)/units/edges with inflammation are more likely to develop new syndesmophytes than VCs/units/edges without inflammation. It has also been proposed that syndesmophytes are more likely to develop at VCs in which inflammation resolves compared with those where inflammation persists.[17,18] Resolving inflammation has also been associated with fat deposition.[19] In turn, fat deposition, with or without concomitant inflammation, has been associated with the formation of new syndesmophytes.[20–22]

Our aim was to expand our analytical studies about the association between inflammation and bone formation by investigating the relationship between MRI inflammation and fat deposition at a VC and the subsequent development of new bone at the same site. In this analysis, the focus was on a sequence analysis, addressing the hypothesis that vertebral corner inflammation (VCI) 'leads to' fat deposition, which in turn 'leads to' bone formation.

METHODS

Study population

For this study, we have made use of the same 80% random sample of the AS Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) that we used in our previous analysis.[15] Details of the ASSERT study design and population have been previously reported.[23] In brief, ASSERT was a 24-week double-blind placebo-controlled clinical trial with infliximab that included patients with AS (according to the modified New York criteria), with a Bath AS Disease Activity Index[24] (BASDAI) ≥4 (range 0–10) and a spinal pain score ≥4 (range 0–10), with an open extension until 102 weeks with all patients treated with infliximab.

Imaging assessments

Radiographs were scored by two readers at baseline and 102 weeks according to the modified Stoke AS Spine Score (mSASSS).[25] In this study, we used the mSASSS scores from the original ASSERT trial.[23] Lateral views of the cervical and lumbar spine were assessed and anterior VCs from C2-T1 and from T12-S1 (total 24 VCs) were scored for the presence of an erosion, sclerosis or squaring (score 1), syndesmophyte (score 2) or bridging syndesmophyte (score 3). Change from a score of 0 or 1 to 2 or 3 was defined as syndesmophyte formation. Change from a score of 2 to 3 was defined as syndesmophyte growth. The thoracic spine and posterior corners of the cervical and lumbar spine were not assessed because abnormalities at these sites cannot be reliably detected on radiographs.

MRIs were scored by two readers at baseline, 24 and 102 weeks using a VC approach.[9–11] T1-weighted and STIR sequences were assessed and the same 24 VCs scored with the mSASSS were also scored for the presence/absence of VCI and vertebral corner fat deposition (VCFD). The level of agreement between MRI readers regarding the presence/absence of VCI and VCFD was assessed using the kappa statistic. The two MRI readers were different readers than the two X-ray readers and all readers were unaware of the patients' identity, their treatment, the scores of the other imaging modality and the true time-order of the images (fully unbiased scores). This MRI evaluation was a completely new reading, never used in previous ASSERT publications.[15,21,26] Such detailed MRI description of lesions was neither available in the original infliximab efficacy study[26] nor in our previous publication looking at inflammation only (but not fat deposition) at the vertebral unit level (rather than VC level).[15] This new MRI reading was also different from a previous single-reader publication that included the smaller subset of ASSERT patients that were followed up in an investigator-initiated extension study - the European AS Infliximab Cohort.[21]

Imaging longitudinal case definitions

Five case definitions were used to combine the information about the presence/absence of VCI at the three available time points (TPs): (1) VCI at baseline, irrespective of inflammation status at other TPs; (2) VCI at baseline only; (3) VCI at baseline and another TP; (4) VCI at any TP; and (5) VCI at all three TPs. Similar case definitions were applied to the presence/absence of VCFD at the three available TPs (figure 1A).

Six subsequent case definitions (figure 1B) were used to integrate the information about the presence/absence of both VCI and VCFD at the three available TPs: (1) sequential or simultaneous presence of VCI and VCFD across the three TPs (ie, presence of VCI and VCFD at the same or different TPs), (2) presence of VCI but not VCFD across the three TPs, (3) presence of VCFD but not VCI across the three TPs, (4) absence of

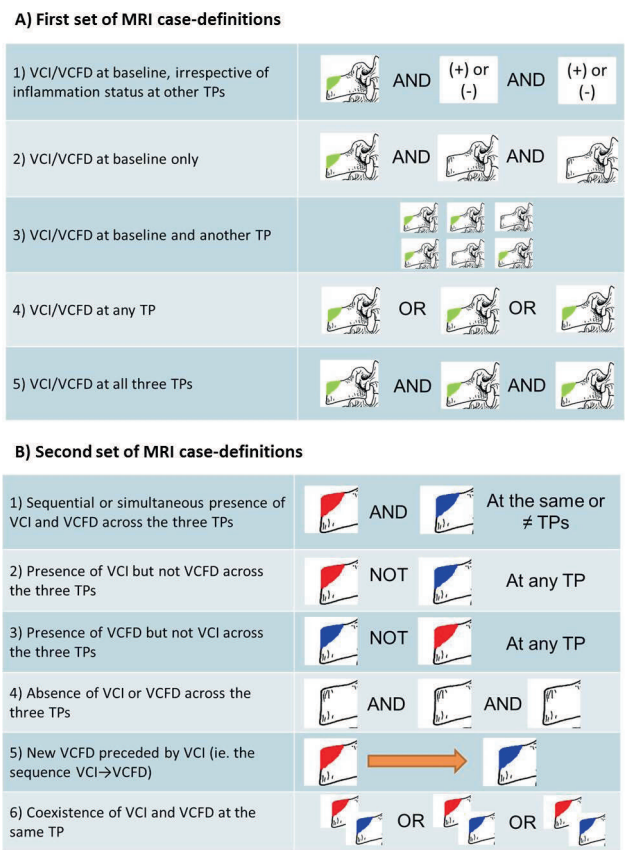

Figure 1. MRI case definitions. (A) MRI case definitions used to combine the information about the presence/absence of vertebral corner inflammation (VCI)/vertebral corner fat deposition (VCFD) at the three available time points (TPs); the green triangle represents VCI or VCFD. (B) MRI case definitions used to integrate the information about the presence/absence of both VCI and VCFD at the three available TPs; the red triangle represents VCI, and the blue triangle represents VCFD.

VCI or VCFD across the three TPs, (5) new VCFD preceded by VCI (ie, the sequence VCI→VCFD) and (6) coexistence of VCI and VCFD at the same TP.

Radiographic data were analysed regarding syndesmophyte formation and regarding syndesmophyte formation/growth combined. Two radiographic case definitions were used in the multilevel approach: (1) one definition aiming at sensitivity: a case was defined as positive if at least one of the readers reported progression of structural damage; and (2) a definition aiming at specificity: a case was defined as positive only if both readers reported progression of structural damage (absolute agreement).

Statistical analysis

Cross-tabulation statistics and measures of association (OR and 95% CI) were first computed using two-way tables to test the association between the various MRI case definitions and radiographic progression after 102 weeks of follow-up. Cross-tabulation statistics were done for every possible pair of imaging readers. The total number of cases in each analysis depended on the imaging case definition and pair of imaging readers used in the analysis (eg, different readers sometimes scored different VCs as not evaluable). Furthermore, VCs with syndesmophytes/ankyloses at baseline (for the outcome syndesmophyte formation) or with ankylosis at baseline (for the outcome syndesmophyte formation/growth) were excluded from the analyses, resulting in another source of variation between readers.

Associations were retested using a multilevel approach to adjust for within-patient correlation and MRI reader (generalised estimating equations (GEEs) for binomial outcomes).[27] The following variables were considered covariates and adjusted for when statistically significant in univariate analysis: gender, age, human leucocyte antigen-B27 status, body mass index, disease duration, presence of syndesmophytes/ankylosis at baseline (at the patient level) and baseline and time-averaged C-reactive protein, BASDAI[24] and AS Disease Activity Score.[28] The treatment variable was forced into all models.

Statistical analyses were performed with IBM SPSS Statistics V.22. Graphics were plotted using GraphPad Prism V.6.

RESULTS

Images belonging to 182 patients with baseline and 102-week radiographic assessments (total of 8736 VCs) and 191 patients with at least one baseline, 24 or 102 weeks MRI assessment (6 patients with one TP, 35 patients with two TPs and 150 patients with three TPs; total of 12624 VCs) were evaluated by the imaging readers. The kappa score

for MRI VCI was 0.46, and the kappa score for MRI VCFD was 0.49. After applying the predefined imaging case definitions and excluding non-evaluable VCs and VCs with syndesmophytes/ankylosis at baseline, data from 3070 to 3389 paired (MRI and radiographic) case definitions belonging to 161–177 patients were analysed. The baseline characteristics of the study population are presented in table 1.

Table 1. Baseline characteristics of the study population (n=177)

Male, no. (%)	141 (79.7)
Age, years	39.0 (32.0, 46.0)
Disease duration, years	9.0 (3.2, 16.1)
BMI, kg/m^2	25.4 (22.6, 27.9)
HLA-B27 positive, no. (%)	160 (90.4)
ASDAS	3.9 (3.3, 4.6)
Time-averaged ASDAS	2.0 (1.4, 2.8)
BASDAI (0–10)	6.5 (5.3, 7.3)
Time-averaged BASDAI (0–10)	3.0 (1.8, 4.9)
CRP, mg/L	15.0 (7.0, 31.0)
Time-averaged CRP, mg/L	3.7 (2.4, 8.1)
mSASSS	13.1 (4.8, 29.5)

Time-averaged values were calculated taking all available time points into account. Except if indicated otherwise, values are the median (IQR). ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C-reactive protein; HLA, human leucocyte antigen; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.

Relationship between VCI and new bone formation

Overall, results showed that the presence of VCI increased the probability of developing new bone at the same VC after 102 weeks of follow-up, irrespective of the MRI case definition, reader pair and radiographic outcome (syndesmophyte formation alone or syndesmophyte formation/growth combined) (supplementary table 1). OR ranged from 1.33 to 3.87 for VCI at baseline, irrespective of inflammation status at other TPs (statistically significant in 7/8 scenarios), 1.46 to 3.86 for VCI at baseline only (statistically significant in 6/8 scenarios), 0.79 to 3.15 for VCI at baseline and another TP (statistically significant in 5/8 scenarios) and 1.19 to 4.10 for VCI at any TP (statistically significant in 7/8 scenarios, figure 2A, B). The analyses for VCI at all TPs were uninterpretable due to the very low number of VCs with persistent inflammation in this tumour necrosis factor (TNF)-blocker treated population.

Relationship between VCFD and new bone formation

Overall, results showed that the presence of VCFD also increased the probability of developing new bone at the same VC after 102 weeks of follow-up. Data were consistent for all reader pairs and for the two definitions of new bone formation (supplementary table 2). The only exception was for the presence of VCFD at baseline only where this trend was not observed. However, the very low number of VCs with VCFD at baseline only,

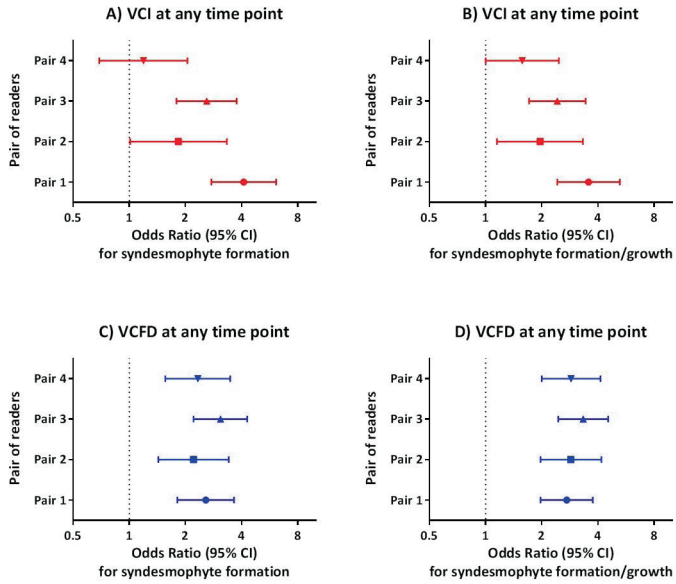

Figure 2. OR (95% CI) of selected vertebral corner inflammation (VCI) or vertebral corner fat deposition (VCFD) MRI case definitions for the outcome syndesmophyte formation (left panel) or syndesmophyte formation/growth (right panel) according to all possible pairs of readers in the two-way analysis. (A) MRI case definition: VCI at any time point, outcome: syndesmophyte formation. (B) MRI case definition: VCI at any time point, outcome: syndesmophyte formation/growth. (C) MRI case definition: VCFD at any time point, outcome: syndesmophyte formation. (D) MRI case definition: VCFD at any time point, outcome: syndesmophyte formation/growth.

makes the interpretation of results difficult. Regarding the other VCFD case definitions, OR ranged from 2.43 to 3.27 for VCFD at baseline, irrespective of fat deposition status at other TPs, 2.62 to 3.37 for VCFD at baseline and another TP, 2.21 to 3.33 for VCFD at any TP (figure 2C, D), and 2.05 to 3.36 for VCFD at all TPs. These associations were statistically significant in all studied scenarios.

Relationship between the various combinations of MRI VCI/VCFD and new bone formation

Supplementary table 3 shows the results for the possible combinations of VCI and VCFD across the three available TPs. The first four MRI case definitions listed in the table are mutually exclusive. The sequential or simultaneous presence of VCI and VCFD across the three TPs was consistently associated with new bone formation (OR 1.77 to 5.80, statistically significant in 7/8 scenarios, figure 3A, B). Associations were weaker for the presence of VCFD but not VCI across the three TPs (OR 1.20 to 2.34, statistically significant in 7/8 scenarios) and even weaker for the presence of VCI but not VCFD across the three TPs (OR 0.40 to 2.32, statistically significant in 2/8 scenarios). The

Table 2. Multivariable GEE results (adjOR; 95% CI) for the outcome syndesmophyte formation or syndesmophyte formation/growth according to X-ray reader 1 or/and reader 2*

Variables	Syndesmophyte formation according to X-ray reader 1 or reader 2					Syndesmophyte formation or growth according to X-ray reader 1 or reader 2				
VCI at any time point	1.98 (1.49, 2.62)	-	-	-	-	1.84 (1.41, 2.41)	-	-	-	-
VCFD at any time point	-	2.32 (1.85, 2.91)	-	-	-	-	2.27 (1.83, 2.81)	-	-	-
Sequential or simultaneous presence of VCI and VCFD across the 3 time points	-	-	2.73 (2.00, 3.74)	-	-	-	-	2.58 (1.91, 3.48)	-	-
New VCFD preceded by VCI	-	-	-	2.45 (1.66, 3.60)	-	-	-	-	2.12 (1.46, 3.08)	-
Absence of VCI or VCFD across the 3 time points	-	-	-	-	0.45 (0.36, 0.56)	-	-	-	-	0.47 (0.38, 0.58)
Treatment (infliximab)	1.03 (0.75, 1.41)	1.09 (0.80, 1.49)	1.02 (0.74, 1.40)	1.05 (0.77, 1.44)	1.04 (0.76, 1.44)	1.15 (0.85, 1.56)	1.23 (0.92, 1.67)	1.18 (0.87, 1.59)	1.14 (0.84, 1.55)	1.18 (0.87, 1.60)
Gender (male)	3.30 (1.94, 5.60)	3.02 (1.79, 5.10)	3.39 (2.01, 5.74)	3.36 (1.98, 5.70)	3.00 (1.77, 5.08)	3.31 (1.96, 5.62)	2.94 (1.75, 4.91)	3.31 (1.96, 5.59)	3.34 (1.98, 5.61)	3.01 (1.79, 5.06)
Syndesmophyte/ankylosis at baseline	2.91 (2.00, 4.25)	2.82 (1.92, 4.13)	2.95 (2.02, 4.29)	2.89 (1.98, 4.21)	2.81 (1.91, 4.11)	3.43 (2.32, 5.08)	3.27 (2.20, 4.85)	3.39 (2.29, 5.01)	3.48 (2.35, 5.14)	3.27 (2.20, 4.85)
Variables	**Syndesmophyte formation according to X-ray reader 1 and reader 2**					**Syndesmophyte formation or growth according to X-ray reader 1 and reader 2**				
VCI at any time point	1.93 (1.22, 3.05)	-	-	-	-	1.75 (1.17, 2.61)	-	-	-	-
VCFD at any time point	-	1.60 (1.10, 2.33)	-	-	-	-	1.85 (1.35, 2.53)	-	-	-
Sequential or simultaneous presence of VCI and VCFD across the 3 time points	-	-	2.29 (1.37, 3.83)	-	-	-	-	2.12 (1.36, 3.31)	-	-
New VCFD preceded by VCI	-	-	-	3.01 (1.76, 5.13)	-	-	-	-	2.17 (1.32, 3.56)	-
Absence of VCI or VCFD across the 3 time points	-	-	-	-	0.62 (0.43, 0.89)	-	-	-	-	0.56 (0.41, 0.76)
Treatment (infliximab)	1.29 (0.68, 2.44)	1.26 (0.66, 2.39)	1.28 (0.67, 2.43)	1.32 (0.70, 2.50)	1.30 (0.68, 2.49)	1.15 (0.63, 2.11)	1.29 (0.72, 2.31)	1.20 (0.66, 2.18)	1.08 (0.59, 2.01)	1.21 (0.66, 2.22)
Gender (male)	2.50 (0.83, 7.51)	2.36 (0.80, 6.97)	2.48 (0.85, 7.26)	2.47 (0.83, 7.33)	2.29 (0.77, 6.77)	3.19 (1.03, 9.91)	2.70 (0.92, 7.88)	3.12 (1.03, 9.50)	3.20 (1.05, 9.74)	2.64 (0.90, 7.80)
Syndesmophyte/ankylosis at baseline	4.11 (1.56, 10.8)	4.22 (1.58, 11.2)	4.19 (1.60, 11.0)	4.14 (1.58, 10.9)	4.18 (1.56, 11.2)	5.45 (2.00, 14.9)	5.65 (2.03, 15.7)	5.50 (2.02, 15.0)	5.54 (2.03, 15.1)	5.53 (1.97, 15.5)

*Results are shown for a selected set of MRI case-definitions and for the adjustment variables: treatment (forced into the model) and gender and presence of syndesmophytes/ankylosis at baseline (the only two other variables significantly associated with new bone formation in univariable analysis); models also adjusted for within-patient correlation by VU-level and MRI-reader. adjOR, adjusted odds ratio; VCI, vertebral corner inflammation; VCFD, vertebral corner fat deposition.

absence of VCI or VCFD across the three TPs was negatively associated with new bone formation (OR 0.33 to 0.49, always statistically significant, figure 3E, F), in agreement with the above positive associations.

The last two MRI case definitions in supplementary table 3 explore two additional settings: new VCFD preceded by VCI (sequence analysis, VCI→VCFD) and the coexistence of

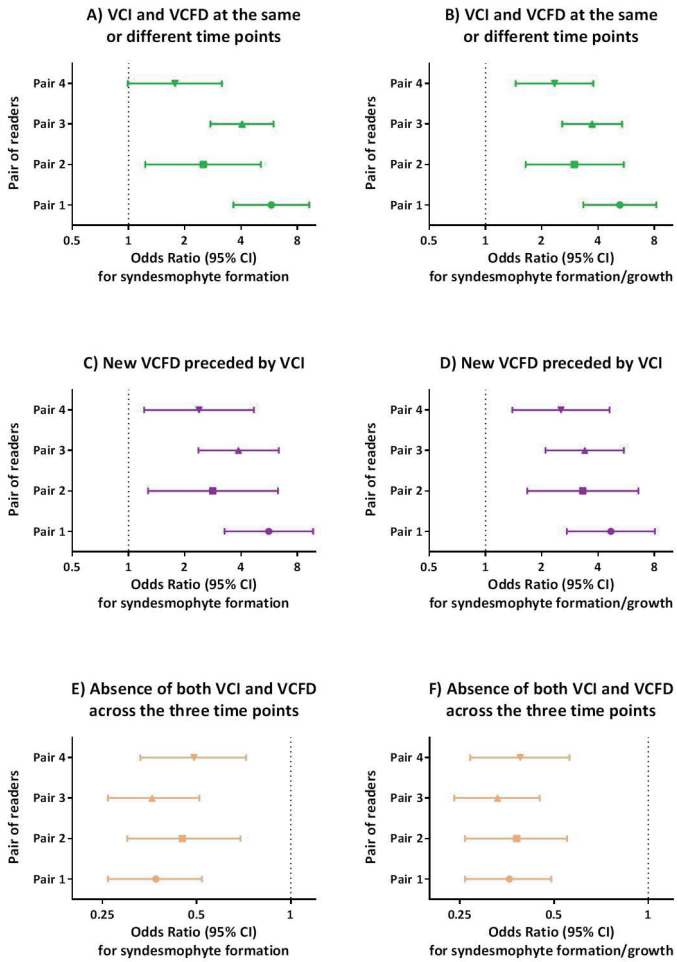

Figure 3. OR (95% CI) of selected combined vertebral corner inflammation (VCI) and vertebral corner fat deposition (VCFD) MRI case definitions for the outcome syndesmophyte formation (left panel) or syndesmophyte formation/growth (right panel) according to all possible pairs of readers in the two-way analysis. (A) MRI case definition: sequential or simultaneous presence of VCI and VCFD across the three time points (ie, presence of VCI and VCFD at the same or different time points), outcome: syndesmophyte formation. (B) MRI case definition: sequential or simultaneous presence of VCI and VCFD across the three time points, outcome: syndesmophyte formation/growth. (C) MRI case definition: new VCFD preceded by VCI, outcome: syndesmophyte formation. (D) MRI case definition: new VCFD

VCFD and VCI at the same TP. VCs in which fat deposition developed de novo and was preceded by VCI showed the highest probability of developing new bone formation (OR 2.38 to 5.62, always statistically significant, figure 3C, D). This relationship was slightly weaker for the coexistence of VCFD and VCI at the same TP (OR 0.85 to 6.00, statistically significant in 5/8 scenarios).

Despite these associations, a large proportion of new bone still developed in VCs without visible MRI inflammation or fat deposition at any of the three assessed TPs (40–66%, depending on the combination of MRI and X-ray reader) (supplementary table 3, percentages can be obtained by using syndesmophyte formation/growth rather than MRI lesions as denominator).

Multilevel GEE analyses

Overall, results of the GEE analyses (supplementary tables 4 and 5) confirmed that both VCI and VCFD are associated with radiographic progression after 102 weeks of follow-up. Results were similar for the outcome syndesmophyte formation and for the outcome syndesmophyte formation/growth combined. The strength and significance of the associations varied depending on the MRI and radiographic case definition. Furthermore, GEE results confirmed that the sequential or simultaneous presence of VCI and VCFD further increases the probability of developing new bone formation, particularly when new VCFD is preceded by VCI (sequence analysis, VCI→VCFD→new bone formation). Some of the most consistent results were observed for VCI at any TP (adjOR 1.75 to 1.98), for VCFD at any TP (adjOR 1.60 to 2.32), for the sequential or simultaneous presence of VCI and VCFD across the three TP (adjOR 2.12 to 2.73) and for new VCFD preceded by VCI (adjOR 2.12 to 3.01). GEE analyses also confirmed that the absence of VCI or VCFD across all TPs 'protects' against new bone formation (adjOR 0.45 to 0.62). These associations were always statistically significant.

The other variables significantly associated with radiographic progression in the GEE multivariable analyses were gender and the presence of syndesmophytes/ankylosis at baseline (at the patient level). Table 2 shows the adjOR for the MRI case definitions most consistently associated with new bone formation as well as the adjOR of the adjustment factors (treatment, gender and the presence of syndesmophytes/ankylosis at baseline). The adjOR for the presence of syndesmophytes/ankylosis at baseline ranged from 2.81 to 5.65, always statistically significant. The adjOR for male gender ranged from 2.36 to 3.39, statistically significant in the majority of cases.

DISCUSSION

In the present study, we have confirmed that MRI VCI is associated with radiographic progression in AS, and we have shown that VCFD is also associated with radiographic progression. In addition, we have shown that the combination of fat and inflammation either at the same TP or sequentially further increases the probability of radiographic progression. Furthermore, VCFD that develops de novo can be preceded by VCI, and this sequence of events is also associated with progression of structural damage. However, VCI, VCFD and this particular sequence only partially explain the development of new bone in AS, as a large proportion of new syndesmophytes/bridging still occurred in VCs without either inflammation or fat deposition across three TPs.

The association between spinal MRI inflammation and radiographic progression after 2 years of follow-up has been reported in four previous studies, including ours.[15–18] OR ranged from 1.7 to 8.6, and differences could be related to methodological aspects such as sample size, type of population (trial/observational cohort, TNF-blocker/standard treatment) and anatomical approach (VC/vertebral unit/vertebral edge). One study has indicated that new syndesmophytes are more likely to develop at VCs where inflammation has completely resolved than at VCs without inflammation at baseline or follow-up.[18] It has also been suggested that VCs with persistent inflammation are less likely to develop new syndesmophytes.[17,18]

The relationship between spinal MRI inflammation, fat deposition and radiographic progression has been assessed in three previous AS studies.[20–22] Chiowchanwisawakit et al[20] showed that VCs that were simultaneously positive for inflammation and fat at baseline had an OR of 7.6 for the development of new syndesmophytes after 2 years of follow-up. Baseline fat and inflammation were both associated with radiographic progression in univariate analysis. However, in multivariable analysis, only the presence of VCI was associated with syndesmophyte formation (OR 5.8). Maksymowych et al[22] studied 'advanced VCI' (defined by the presence of inflammation and concomitant fat, erosion or sclerosis), 'early VCI' (defined by the presence of inflammation only) and VCFD in relation to syndesmophyte formation. When adjusted for the baseline level of damage (at the patient level), only 'advanced VCI' (OR 3.9) and VCFD (OR 4.8) were associated with the development of new syndesmophytes after 2 years of follow-up. However, when both variables were tested in the same model, this association was statistically significant only for VCFD (OR 4.0). Finally, Baraliakos et al[21] found that vertebral edges with both inflammation and fat deposition at baseline had the highest OR (3.7) for syndesmophyte formation after 5 years of follow-up (the reference being vertebral edges without either inflammation or fat at baseline and 2 years). Interestingly, in an axial spondyloarthritis population, Song et al[19] described a significant relationship between the disappearance of inflammation (at the vertebral unit level and using whole-

body MRI) and the development of fat deposition.

It is interesting to discuss our results in relation to the question whether TNF-blockers are capable of inhibiting the progression of structural damage in AS or not. The unexpected lack of inhibition of structural damage by TNF-blockers has fueled the discussion about the relationship between inflammation and new bone formation.[29,30] These initial trial data have recently been challenged by observational studies suggesting a protective effect of TNF-blockers on radiographic progression.[31,32] However, these observational data have important methodological limitations, and this is still an unsolved question.[8] Our observation that the sequence VCI→VCFD is valid and contributes to new bone formation in AS could be supportive of the hypothesis that TNF-blocker treatment in AS may only be effective in protecting from structural damage once newly developed VCI is prevented (after long-term treatment), while the immediate effects of TNF-blocker treatment could paradoxically contribute to new bone formation following the abrupt suppression of VCI and the development of VCFD at the same vertebral corner. However, this equation is more complex because the biological effects of TNF-blockers are not limited to the suppression of inflammation and TNF-blockers have also been associated with osteoproliferation in animal models.[33]

The occurrence of VCFD at baseline only was an infrequent event in our study, and the presence of VCFD at baseline only was not associated with new bone formation. It is possible that in the minority of cases where resolution of VCFD occurs the risk of developing new bone becomes similar to the risk in VCs that never had VCFD. We also observed that VCFD increased at follow-up compared with baseline. Since we analysed a TNF-blocker treated population, this finding would be consistent with the hypothesis that VCFD is more likely to develop at VCs where inflammation resolves compared with VCs with persistent or no inflammation at baseline/follow-up; alternatively, this finding could also simply reflect the natural history of disease, with VCFD being prone to increase over time, irrespective of inflammation.

Consistent with previous studies, we have shown that a significant part of new bone formation occurs in VCs without either traceable inflammation or fat deposition. However, this does not necessarily mean that these VCs do not have inflammation/fat deposition at the microscopic level because MRI may not be sensitive enough to capture all areas of inflammation/fat deposition[34] and because the time between MRI assessments may not be short enough to capture the potential fluctuation of these lesions, particularly inflammation. Conversely, these results could suggest that the mechanisms of new bone formation in AS are still largely unknown and that the triggering of osteoproliferation may be completely or partially independent of inflammation (and fat deposition).[7]

Our study has limitations. First, we analysed a clinical trial cohort of patients with long-standing disease treated with TNF-blockers. Therefore, results cannot be generalised

to patients in earlier disease stages or treated with first line treatments only. Second, two factors that have been shown to influence radiographic progression in AS — non-steroidal anti-inflammatory drug consumption[35 37] and smoking status[38] — could not be adjusted for in our analyses because this information was not available in sufficient detail in the database. Finally, although we have performed MRI assessments at three TPs, additional assessments at shorter intervals may be needed to completely elucidate the dynamics of inflammation and fat deposition over time.

Strengths of our study are the uniquely large population of patients with AS, the large number of imaging readers, the fully unbiased nature of the imaging scoring, the fact that three MRI TPs were analysed (as opposed to one or two TPs as in the majority of previous studies), the fact that we have adjusted for multiple potential confounders using a statistical approach that adjusts for the dependence of observations in the same patient and the comprehensive list of scenarios (case definitions) that have been tested. These strengths make our study the most robust and comprehensive study investigating the relationship between VCI, VCFD and new bone formation to date.

In summary, we have shown that fat deposition in VCs (with or without concomitant inflammation) is associated with radiographic progression and that this association is stronger than for the presence of inflammation alone. Furthermore, inflammatory lesions can precede fat lesions, suggesting the possibility of a window of opportunity to prevent new bone formation. While the longitudinal absence of inflammation and fat deposition was negatively associated with radiographic progression, a significant proportion of new bone still developed at these sites. If this is indeed true and not a consequence of missing inflammation as described above, this suggests that inflammation/fat deposition and new bone formation may reflect independent pathways of the same disease, implying that new therapies specifically targeting osteoproliferation may need to be developed in order to prevent radiographic progression. Interesting future questions are how to incorporate MRI in future clinical trials and long-term observational studies, whether MRI criteria should be incorporated in future treat-to-target treatment strategies and whether new drugs with different mechanisms of action, such as drugs targeting the interleukin (IL)-23/IL-17 axis, will have a different effect in inflammation, fat deposition and structural damage.

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Supplementary table 1. Two-way analysis to test the association between MRI vertebral corner inflammation and new bone formation after 2 years of follow-up*

	New syndesmophyte (X-ray reader 1)		**New syndesmophyte (X-ray reader 2)**		**New syndesmophyte or growth of existing syndesmophyte (X-ray reader 1)**		**New syndesmophyte or growth of existing syndesmophyte (X-ray reader 2)**	
	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)
Case-definition 1: Vertebral corner inflammation at baseline, irrespective of inflammation status at other time points (MRI reader 1)								
Yes	30 (13.6)	191 (86.4)	12 (5.6)	202 (94.4)	32 (14.3)	191 (85.7)	16 (7.3)	202 (92.7)
No	122 (3.9)	3005 (96.1)	91 (2.9)	3029 (97.1)	146 (4.6)	3005 (95.4)	112 (3.6)	3029 (96.4)
OR (95% CI)	3.87 (2.53, 5.92)		1.98 (1.07, 3.67)		3.49 (2.29, 5.19)		2.14 (1.25, 3.69)	
Case-definition 1: Vertebral corner inflammation at baseline, irrespective of inflammation status at other time points (MRI reader 2)								
Yes	38 (9.8)	350 (90.2)	15 (3.9)	368 (96.1)	43 (10.9)	350 (89.1)	24 (6.1)	368 (93.9)
No	114 (3.9)	2846 (96.1)	88 (3.0)	2863 (97.0)	135 (4.5)	2846 (95.5)	104 (3.5)	2863 (96.5)
OR (95% CI)	**2.71 (1.85, 3.98)**		1.33 (0.76, 2.32)		**2.59 (1.81, 3.72)**		**1.80 (1.14, 2.84)**	
Case-definition 2: Vertebral corner inflammation at baseline only (MRI reader 1)								
Yes	24 (14.5)	141 (85.5)	10 (6.3)	148 (93.7)	26 (15.6)	141 (84.4)	12 (7.5)	148 (92.5)
No	123 (4.2)	2791 (95.8)	89 (3.1)	2823 (96.9)	147 (5.0)	2791 (95.0)	110 (3.8)	2823 (96.2)
OR (95% CI)	3.86 (2.42, 6.17)		2.14 (1.09, 4.21)		3.50 (2.23, 5.49)		2.08 (1.12, 3.86)	
Case-definition 2: Vertebral corner inflammation at baseline only (MRI reader 2)								
Yes	29 (9.7)	270 (90.3)	13 (4.5)	278 (95.5)	33 (10.9)	270 (89.1)	16 (5.4)	278 (94.6)
No	118 (4.2)	2662 (95.8)	86 (3.1)	2693 (96.9)	140 (5.0)	2662 (95.0)	106 (3.8)	2693 (96.2)
OR (95% CI)	**2.42 (1.58, 3.71)**		1.46 (0.81, 2.66)		**2.32 (1.56, 3.47)**		1.46 (0.85, 2.51)	
Case-definition 3: Vertebral corner inflammation at baseline and another time point (MRI reader 1)								
Yes	6 (12.8)	41 (87.2)	2 (4.3)	45 (95.7)	6 (12.8)	41 (87.2)	4 (8.2)	45 (91.8)
No	146 (4.4)	3146 (95.6)	101 (3.1)	3177 (96.9)	172 (5.2)	3146 (94.8)	124 (3.8)	3177 (96.2)
OR (95% CI)	**3.15 (1.32, 7.55)**		1.40 (0.34, 5.84)		**2.68 (1.12, 6.39)**		2.28 (0.81, 6.43)	
Case-definition 3: Vertebral corner inflammation at baseline and another time point (MRI reader 2)								
Yes	9 (11.5)	69 (88.5)	2 (2.5)	79 (97.5)	10 (12.7)	69 (87.3)	8 (9.2)	79 (90.8)
No	143 (4.4)	3116 (95.6)	101 (3.1)	3141 (96.9)	168 (5.1)	3116 (94.9)	120 (3.7)	3141 (96.3)
OR (95% CI)	**2.84 (1.39, 5.81)**		0.79 (0.19, 3.25)		**2.69 (1.36, 5.31)**		**2.65 (1.25, 5.61)**	

	New syndesmophyte (X-ray reader 1)		New syndesmophyte (X-ray reader 2)		New syndesmophyte or growth of existing syndesmophyte (X-ray reader 1)		New syndesmophyte or growth of existing syndesmophyte (X-ray reader 2)	
	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)
Case-definition 4: Vertebral corner inflammation at any time point (MRI reader 1)								
Yes	36 (14.3)	215 (85.7)	13 (5.4)	229 (94.6)	38 (15.0)	215 (85)	17 (6.9)	229 (93.1)
No	112 (3.9)	2742 (96.1)	86 (3.0)	2768 (97.0)	136 (4.7)	2742 (95.3)	105 (3.7)	2768 (96.3)
OR (95% CI)	4.10 (2.75, 6.12)		1.83 (1.01, 3.33)		3.56 (2.42, 5.24)		1.96 (1.15, 3.32)	
Case-definition 4: Vertebral corner inflammation at any time point (MRI reader 2)								
Yes	43 (9.7)	400 (90.3)	16 (3.7)	419 (96.3)	48 (10.7)	400 (89.3)	25 (5.6)	419 (94.4)
No	106 (4.0)	2559 (96.0)	83 (3.1)	2580 (96.9)	127 (4.7)	2559 (95.3)	98 (3.7)	2580 (96.3)
OR (95% CI)	**2.60 (1.79, 3.76)**		1.19 (0.69, 2.05)		**2.42 (1.71, 3.43)**		**1.57 (1.00, 2.47)**	
Case-definition 5: Vertebral corner inflammation at all three time points (MRI reader 1)								
Yes	1 (25.0)	3 (75.0)	0 (0.0)	4 (100.0)	1 (25.0)	3 (75.0)	0 (0.0)	4 (100.0)
No	151 (4.5)	3208 (95.5)	103 (3.1)	3241 (96.9)	177 (5.2)	177 (5.2)	128 (3.8)	3241 (96.2)
OR (95% CI)	7.08 (0.73, 68.48)		NA		6.04 (0.63, 58.37)		NA	
Case-definition 5: Vertebral corner inflammation at all three time points (MRI reader 2)								
Yes	1 (16.7)	5 (83.3)	0 (0.0)	6 (100.0)	1 (16.7)	5 (83.3)	0 (0.0)	6 (100.0)
No	150 (4.5)	3207 (95.5)	103 (3.1)	3240 (96.9)	176 (5.2)	3207 (94.8)	127 (3.8)	3240 (96.2)
OR (95% CI)	4.28 (0.50, 36.83)		NA		3.64 (0.42, 31.36)		NA	

*In the table cells, the percentage uses new bone formation as numerator and the various definitions of MRI vertebral corner inflammation at the 3 combined time points as denominator. Statistically significant OR ($p<0.05$) are highlighted in **bold.** NA, not applicable.

Supplementary table 2. Two-way analysis to test the association between MRI vertebral corner fat deposition and new bone formation after 2 years' follow-up*

	New syndesmophyte (X-ray reader 1)		**New syndesmophyte (X-ray reader 2)**		**New syndesmophyte or growth of existing syndesmophyte (X-ray reader 1)**		**New syndesmophyte or growth of existing syndesmophyte (X-ray reader 2)**	
	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)
Case-definition 1: Vertebral corner fat deposition at baseline, irrespective of fat deposition status at other time points (MRI reader 1)								
Yes	25 (9.4)	240 (90.6)	19 (7.2)	244 (92.8)	32 (11.8)	240 (88.2)	27 (10.0)	244 (90.0)
No	127 (4.1)	2956 (95.9)	84 (2.7)	2987 (97.3)	146 (4.7)	2956 (95.3)	101 (3.3)	2987 (96.7)
OR (95% CI)	2.43 (1.55, 3.80)		2.77 (1.66, 4.63)		2.70 (1.80, 4.05)		3.27 (2.10, 5.10)	
Case-definition 1: Vertebral corner fat deposition at baseline, irrespective of fat deposition status at other time points (MRI reader 1)								
Yes	54 (9.6)	508 (90.4)	34 (6.1)	524 (93.9)	65 (11.3)	508 (88.7)	45 (7.9)	524 (92.1)
No	98 (3.5)	2688 (96.5)	69 (2.5)	2707 (97.5)	113 (4.0)	2688 (96.0)	83 (3.0)	2707 (97.0)
OR (95% CI)	2.92 (2.06, 4.12)		2.55 (1.67, 3.88)		3.04 (2.21, 4.19)		2.80 (1.93, 4.07)	
Case-definition 2: Vertebral corner fat deposition at baseline only (MRI reader 1)								
Yes	0 (0.0)	11 (100)	1 (8.3)	11 (91.7)	0 (0.0)	11 (100.0)	1 (8.3)	11 (91.7)
No	147 (4.8)	2921 (95.2)	98 (3.2)	2960 (96.8)	173 (5.6)	2921 (94.4)	121 (3.9)	2960 (96.1)
OR (95% CI)	NA		2.75 (0.35, 21.48)		NA		2.22 (0.29, 17.37)	
Case-definition 2: Vertebral corner fat deposition at baseline only (MRI reader 2)								
Yes	4 (10.0)	36 (90.0)	1 (2.4)	40 (97.6)	4 (10.0)	36 (90.0)	1 (2.4)	40 (97.6)
No	143 (4.7)	2896 (95.3)	98 (3.2)	2931 (96.8)	169 (5.5)	2896 (94.5)	121 (4.0)	2931 (96.0)
OR (95% CI)	2.25 (0.79, 6.41)		0.75 (0.10, 5.49)		1.90 (0.67, 5.41)		0.61 (0.08, 4.44)	
Case-definition 3: Vertebral corner fat deposition at baseline and another time point (MRI reader 1)								
Yes	25 (10.1)	223 (89.9)	18 (7.3)	227 (92.7)	32 (12.5)	223 (87.5)	26 (10.3)	227 (89.7)
No	127 (4.1)	2967 (95.9)	85 (2.8)	2998 (97.2)	146 (4.7)	2967 (95.3)	102 (3.3)	2998 (96.7)
OR (95% CI)	2.62 (1.67, 4.11)		2.80 (1.65, 4.73)		2.92 (1.94, 4.38)		3.37 (2.14, 5.29)	
Case-definition 3: Vertebral corner fat deposition at baseline and another time point (MRI reader 2)								
Yes	48 (9.5)	457 (90.5)	33 (6.6)	469 (93.4)	59 (11.4)	457 (88.6)	42 (8.2)	469 (91.8)
No	102 (3.6)	2724 (96.4)	70 (2.5)	2747 (97.5)	117 (4.1)	2724 (95.9)	84 (3.0)	2747 (97.0)
OR (95% CI)	2.81 (1.96, 4.01)		2.76 (1.81, 4.23)		3.01 (2.17, 4.17)		2.93 (2.00, 4.30)	

	New syndesmophyte (X-ray reader 1)		New syndesmophyte (X-ray reader 2)		New syndesmophyte or growth of existing syndesmophyte (X-ray reader 1)		New syndesmophyte or growth of existing syndesmophyte (X-ray reader 2)	
	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)
Case-definition 4: Vertebral corner fat deposition at any time point (MRI reader 1)								
Yes	51 (9.5)	487 (90.5)	31 (5.8)	508 (94.2)	62 (11.3)	487 (88.7)	46 (8.3)	508 (91.7)
No	101 (3.9)	2475 (96.1)	69 (2.7)	2497 (97.3)	116 (4.5)	2475 (95.5)	79 (3.1)	2497 (96.9)
OR (95% CI)	2.57 (1.81, 3.64)		2.21 (1.43, 3.41)		2.72 (1.97, 3.75)		2.86 (1.97, 4.17)	
Case-definition 4: Vertebral corner fat deposition at any time point (MRI reader 2)								
Yes	85 (8.9)	869 (91.1)	50 (5.2)	907 (94.8)	103 (10.6)	869 (89.4)	69 (7.1)	907 (92.9)
No	67 (3.1)	2109 (96.9)	50 (2.3)	2111 (97.7)	75 (3.4)	2109 (96.6)	56 (2.6)	2111 (97.4)
OR (95% CI)	3.08 (2.21, 4.28)		2.33 (1.56, 3.47)		3.33 (2.45, 4.53)		2.87 (2.00, 4.12)	
Case-definition 5: Vertebral corner fat deposition at all three time points (MRI reader 1)								
Yes	17 (8.2)	190 (91.8)	16 (7.7)	193 (92.3)	23 (10.8)	190 (89.2)	22 (10.2)	193 (89.8)
No	131 (4.2)	3007 (95.8)	86 (2.8)	3035 (97.2)	151 (4.8)	3007 (95.2)	103 (3.3)	3035 (96.7)
OR (95% CI)	2.05 (1.21, 3.48)		2.93 (1.68, 5.09)		2.41 (1.52, 3.83)		3.36 (2.07, 5.44)	
Case-definition 5: Vertebral corner fat deposition at all three time points (MRI reader 2)								
Yes	31 (9.1)	309 (90.9)	24 (6.9)	322 (93.1)	38 (11.0)	309 (89.0)	31 (8.8)	322 (91.2)
No	119 (4.0)	2884 (96.0)	78 (2.6)	2905 (97.4)	138 (4.6)	2884 (95.4)	96 (3.2)	2905 (96.8)
OR (95% CI)	2.43 (1.61, 3.67)		2.78 (1.73, 4.45)		2.57 (1.76, 3.75)		2.91 (1.91, 4.44)	

*In the table cells, the percentage uses new bone formation as numerator and the various definitions of MRI vertebral corner fat deposition at the 3 combined time points as denominator. Statistically significant OR ($p<0.05$) are highlighted in **bold.** NA, not applicable.

Supplementary table 3. Two-way analysis to test the association between the various combinations of MRI vertebral corner inflammation and fat deposition taking the three time points into account and new bone formation after 2 years follow-up*

	New syndesmophyte (X-ray reader 1)		**New syndesmophyte (X-ray reader 2)**		**New syndesmophyte or growth of existing syndesmophyte (X-ray reader 1)**		**New syndesmophyte or growth of existing syndesmophyte (X-ray reader 2)**	
	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)
Case-definition 1: Sequential or simultaneous presence of vertebral corner inflammation and fat deposition across the 3 time points (MRI reader 1)								
Yes	26 (20.0)	104 (80.0)	9 (7.3)	114 (92.7)	28 (21.2)	104 (78.8)	13 (10.2)	114 (89.8)
No	122 (4.1)	2831 (95.9)	90 (3.0)	2861 (97.0)	146 (4.9)	2831 (95.1)	109 (3.7)	2861 (96.3)
OR (95% CI)	5.80 (3.64, 9.25)		2.51 (1.23, 5.11)		5.22 (3.33, 8.18)		2.99 (1.64, 5.48)	
Case-definition 1: Sequential or simultaneous presence of vertebral corner inflammation and fat deposition across the 3 time points (MRI reader 2)								
Yes	39 (14.1)	237 (85.8)	14 (5.2)	254 (94.8)	43 (15.4)	237 (84.6)	22 (8.0)	254 (92.0)
No	110 (3.9)	2702 (96.1)	85 (3.0)	2725 (97.0)	132 (4.7)	2702 (95.3)	101 (3.6)	2725 (96.4)
OR (95% CI)	**4.04 (2.74, 5.96)**		1.77 (0.99, 3.16)		**3.71 (2.57, 5.37)**		**2.34 (1.45, 3.77)**	
Case-definition 2: Presence of vertebral corner inflammation but not fat deposition across the 3 time points (MRI reader 1)								
Yes	10 (10.1)	89 (89.9)	4 (4.1)	93 (95.9)	10 (10.1)	89 (89.9)	4 (4.1)	93 (95.9)
No	138 (4.6)	2846 (95.4)	95 (3.2)	2882 (96.8)	164 (5.4)	2846 (94.6)	118 (3.9)	2882 (96.1)
OR (95% CI)	2.32 (1.18, 4.55)		1.31 (0.47, 3.62)		**1.95 (1.00, 3.82)**		1.05 (0.38, 2.91)	
Case-definition 2: Presence of vertebral corner inflammation but not fat deposition across the 3 time points (MRI reader 2)								
Yes	4 (2.7)	143 (97.3)	2 (1.4)	145 (98.6)	5 (3.4)	143 (96.6)	3 (2.0)	145 (98.0)
No	145 (4.9)	2796 (95.1)	97 (3.3)	2834 (96.7)	170 (5.7)	2796 (94.3)	120 (4.1)	2834 (95.9)
OR (95% CI)	0.54 (0.20, 1.48)		0.40 (0.10, 1.65)		0.58 (0.23, 1.42)		0.49 (0.15, 1.56)	
Case-definition 3: Presence of vertebral corner fat deposition but not inflammation across the 3 time points (MRI reader 1)								
Yes	21 (5.6)	356 (94.4)	21 (5.5)	364 (94.5)	30 (7.8)	356 (92.2)	30 (7.6)	364 (92.4)
No	127 (4.7)	2579 (95.3)	78 (2.9)	2611 (97.1)	144 (5.3)	2579 (94.4)	92 (3.4)	2611 (96.6)
OR (95% CI)	1.20 (0.75, 1.93)		**1.93 (1.18, 3.17)**		1.51 (1.00, 2.27)		2.34 (1.53, 3.58)	
Case-definition 3: Presence of vertebral corner fat deposition but not inflammation across the 3 time points (MRI reader 2)								
Yes	43 (6.8)	593 (93.2)	35 (5.4)	614 (94.6)	57 (8.8)	593 (91.2)	45 (6.8)	614 (93.2)
No	106 (4.3)	2346 (95.7)	64 (2.6)	2365 (97.4)	118 (4.8)	2346 (95.2)	78 (3.2)	2365 (96.8)
OR (95% CI)	1.61 (1.11, 2.31)		2.11 (1.38, 3.21)		1.91 (1.38, 2.66)		2.22 (1.52, 3.24)	

	New syndesmophyte (X-ray reader 1)		New syndesmophyte (X-ray reader 2)		New syndesmophyte or growth of existing syndesmophyte (X-ray reader 1)		New syndesmophyte or growth of existing syndesmophyte (X-ray reader 2)	
	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)	Yes, No (%)	No, No (%)
Case-definition 4: Absence of vertebral corner inflammation or fat deposition across the 3 time points (MRI reader 1)								
Yes	91 (3.7)	2386 (96.3)	65 (2.6)	2404 (97.4)	106 (4.3)	2386 (95.7)	75 (3.0)	2404 (97.0)
No	57 (9.4)	549 (90.6)	34 (5.6)	571 (94.4)	68 (11.0)	549 (89.0)	47 (7.6)	571 (92.4)
OR (95% CI)	0.37 (0.26, 0.52)		0.45 (0.30, 0.69)		0.36 (0.26, 0.49)		0.38 (0.26, 0.55)	
Case-definition 4: Absence of vertebral corner inflammation or fat deposition across the 3 time points (MRI reader 2)								
Yes	63 (3.1)	1966 (96.9)	48 (2.4)	1966 (97.6)	70 (3.4)	1966 (96.6)	53 (2.6)	1966 (97.4)
No	86 (8.1)	973 (91.9)	51 (4.8)	1013 (95.2)	105 (9.7)	973 (90.3)	70 (6.5)	1013 (93.5)
OR (95% CI)	0.36 (0.26, 0.51)		0.49 (0.33, 0.72)		0.33 (0.24, 0.45)		0.39 (0.27, 0.56)	
Case-definition 5: New vertebral corner fat deposition preceded by vertebral corner inflammation (MRI reader 1)								
Yes	18 (20.2)	71 (79.8)	7 (8.2)	78 (91.8)	18 (20.2)	71 (79.8)	10 (11.4)	78 (88.6)
No	129 (4.3)	2861 (95.7)	92 (3.1)	2893 (96.9)	155 (5.1)	2861 (94.9)	112 (3.7)	2893 (96.3)
OR (95% CI)	5.62 (3.26, 9.71)		2.82 (1.27, 6.29)		4.68 (2.72, 8.05)		3.31 (1.67, 6.57)	
Case-definition 5: New vertebral corner fat deposition preceded by vertebral corner inflammation (MRI reader 2)								
Yes	21 (14.8)	121 (85.2)	10 (6.9)	134 (93.1)	22 (15.4)	121 (84.6)	13 (8.8)	134 (91.2)
No	126 (4.3)	2811 (95.7)	89 (3.0)	2837 (97.0)	151 (5.1)	2811 (94.9)	109 (3.7)	2837 (96.3)
OR (95% CI)	3.87 (2.36, 6.36)		2.38 (1.21, 4.68)		3.39 (2.09, 5.49)		2.53 (1.39, 4.60)	
Case-definition 6: Coexistence of vertebral corner fat deposition and inflammation at the same time point (MRI reader 1)								
Yes	10 (21.7)	36 (78.3)	2 (4.9)	39 (95.1)	12 (25)	36 (75)	3 (7.1)	39 (92.9)
No	137 (4.5)	2899 (95.5)	97 (3.2)	2935 (96.8)	161 (5.3)	2899 (94.7)	119 (3.9)	2935 (96.1)
OR (95% CI)	**5.88 (2.86, 12.09)**		1.55 (0.37, 6.52)		**6.00 (3.06, 11.76)**		1.90 (0.58, 6.23)	
Case-definition 6: Coexistence of vertebral corner fat deposition and inflammation at the same time point (MRI reader 2)								
Yes	20 (13.2)	132 (86.8)	4 (2.8)	140 (97.2)	23 (14.8)	132 (85.2)	10 (6.7)	140 (93.3)
No	128 (4.4)	2806 (95.6)	95 (3.2)	2837 (96.8)	151 (5.1)	2806 (94.9)	113 (3.8)	2837 (96.2)
OR (95% CI)	**3.32 (2.01, 5.49)**		0.85 (0.31, 2.35)		**3.24 (2.02, 5.19)**		**1.79 (0.92, 3.50)**	

*In the table cells, the percentage uses new bone formation as numerator and the various definitions of combined MRI vertebral corner inflammation and fat deposition as denominator. Statistically significant OR ($p<0.05$) are highlighted in **bold.**

Supplementary table 4. GEE results (adjOR; 95% CI; p values) for the outcome syndesmophyte formation (upper section) and for the outcome syndesmophyte formation or growth of existing syndesmophytes (lower section) according to X-ray reader 1 or reader 2

Definitions of VCI or VCFD	Syndesmophyte formation according to X-ray reader 1 or reader 2	
	Adjustment for within-patient correlation by VU-level and MRI-reader	**Multivariable adjustment***
Definitions based on the presence of VCI and taking the 3 TPs into account		
VCI at baseline, irrespective of inflammation status at other TPs	2.23 (1.65, 3.00); p<0.001	1.95 (1.45, 2.62); p<0.001
VCI at baseline only	2.04 (1.48, 2.82); p<0.001	1.90 (1.37, 2.63); p<0.001
VCI at baseline and another TP	1.89 (1.04, 3.42); p=0.036	1.62 (0.91, 2.90); p=0.102
VCI at any TP	2.21 (1.68, 2.93); p<0.001	1.98 (1.49, 2.62); p<0.001
Definitions based on the presence of VCFD and taking the 3 TPs into account		
VCFD at baseline, irrespective of inflammation status at other TPs	2.66 (2.08, 3.41); p<0.001	2.47 (1.93, 3.17); p<0.001
VCFD at baseline only	1.92 (0.85, 4.34); p=0.118	1.76 (0.75, 4.12); p=0.193
VCFD at baseline and another TP	2.65 (2.05, 3.41); p<0.001	2.45 (1.90, 3.17); p<0.001
VCFD at any TP	2.59 (2.07, 3.24); p<0.001	2.32 (1.85, 2.91); p<0.001
VCFD at all TPs	2.49 (1.87, 3.31); p<0.001	2.30 (1.73, 3.06); p<0.001
Combined definitions based on the presence of VCI and VCFD and taking the 3 TPs into account		
Sequential or simultaneous presence of VCI and VCFD across the 3 TPs	3.02 (2.22, 4.12); p<0.001	2.73 (2.00, 3.74); p<0.001
Presence of VCI but not VCFD across the 3 TPs	1.04 (0.62, 1.75); p=0.883	0.97 (0.57, 1.64); p=0.905
Presence of VCFD but not VCI across the 3 TPs	1.76 (1.38, 2.24); p<0.001	1.60 (1.25, 2.04); p<0.001
Absence of VCI or VCFD across the 3 TPs	0.40 (0.32, 0.50); p<0.001	0.45 (0.36, 0.56); p<0.001
New VCFD preceded by VCI	2.59 (1.76, 3.80); p<0.001	2.45 (1.66, 3.60); p<0.001
Coexistence of VCFD and VCI at the same TP	2.64 (1.73, 4.02); p<0.001	2.37 (1.55, 3.63); p<0.001

Definitions of VCI or VCFD	Syndesmophyte formation or growth according to X-ray reader 1 or reader 2	
	Adjustment for within-patient correlation by VU-level and MRI-reader	**Multivariable adjustment***
Definitions based on the presence of VCI and taking the 3 TPs into account		
VCI at baseline, irrespective of inflammation status at other TPs	2.10 (1.58, 2.78); p<0.001	1.88 (1.42, 2.50); p<0.001
VCI at baseline only	1.76 (1.29; 2.40); p<0.001	1.70 (1.24, 2.33); p=0.001
VCI at baseline and another TP	2.10 (1.25; 3.53); p=0.005	1.83 (1.09, 3.04); p=0.021
VCI at any TP	2.01 (1.55, 2.62); p<0.001	1.84 (1.41, 2.41); p<0.001
Definitions based on the presence of VCFD and taking the 3 TPs into account		
VCFD at baseline, irrespective of inflammation status at other TPs	2.59 (2.07, 3.26); p<0.001	2.46 (1.95, 3.10); p<0.001
VCFD at baseline only	1.83 (0.86, 3.88); p=0.118	1.63 (0.73, 3.66); p=0.233
VCFD at baseline and another TP	2.59 (2.05, 3.27); p<0.001	2.45 (1.93, 3.12); p<0.001
VCFD at any TP	2.47 (2.00, 3.04); p<0.001	2.27 (1.83, 2.81); p<0.001
VCFD at all TPs	2.44 (1.88, 3.17); p<0.001	2.31 (1.77, 3.01); p<0.001
Combined definitions based on the presence of VCI and VCFD and taking the 3 TPs into account		
Sequential or simultaneous presence of VCI and VCFD across the 3 TPs	2.77 (2.07, 3.72); p<0.001	2.58 (1.91, 3.48); p<0.001
Presence of VCI but not VCFD across the 3 TPs	0.92 (0.56, 1.51); p=0.732	0.87 (0.52, 1.45); p=0.590
Presence of VCFD but not VCI across the 3 TPs	1.74 (1.40, 2.18); p<0.001	1.63 (1.29, 2.05); p<0.001
Absence of VCI or VCFD across the 3 TPs	0.43 (0.35, 0.53); p<0.001	0.47 (0.38, 0.58); p<0.001
New VCFD preceded by VCI	2.16 (1.49, 3.13); p<0.001	2.12 (1.46, 3.08); p<0.001
Coexistence of VCFD and VCI at the same TP	2.58 (1.75, 3.82); p<0.001	2.40 (1.61, 3.57); p<0.001

*Adjustment for within-patient correlation by VU-level and MRI-reader and adjustment for treatment, gender and presence of syndesmophytes or ankylosis at baseline (at the patient level). adjOR, adjusted odds ratio; TP, time point; VCI, vertebral corner inflammation; VCFD, vertebral corner fat deposition.

Supplementary table 5. GEE results (adjOR; 95% CI; p values) for the outcome syndesmophyte formation (upper section) and for the outcome syndesmophyte formation or growth of existing syndesmophytes (lower section) according to X-ray reader 1 and reader 2

Definitions of VCI or VCFD	Syndesmophyte formation according to X-ray reader 1 and reader 2	
	Adjustment for within-patient correlation by VU-level and MRI-reader	**Multivariable adjustment***
Definitions based on the presence of VCI and taking the 3 TPs into account		
VCI at baseline, irrespective of inflammation status at other TPs	2.11 (1.27, 3.52); p=0.004	1.90 (1.16, 3.09); p=0.010
VCI at baseline only	2.33 (1.40, 3.90); p=0.001	2.20 (1.34, 3.61); p=0.002
VCI at baseline and another TP	0.68 (0.14, 3.33); p=0.630	0.63 (0.16, 2.49); p=0.507
VCI at any TP	2.09 (1.30, 3.35); p=0.002	1.93 (1.22, 3.05); p=0.005
Definitions based on the presence of VCFD and taking the 3 TPs into account		
VCFD at baseline, irrespective of fat deposition status at other TPs	1.29 (0.79, 2.11); p=0.317	1.18 (0.74, 1.90); p=0.483
VCFD at baseline only	1.22 (0.25, 5.99); p=0.808	1.13 (0.26, 4.91); p=0.868
VCFD at baseline and another TP	1.30 (0.78, 2.17); p=0.311	1.19 (0.73, 1.94); p=0.480
VCFD at any TP	1.74 (1.18, 2.57); p=0.006	1.60 (1.10, 2.33); p=0.014
VCFD at all TPs	1.70 (1.00, 2.88); p=0.050	1.59 (0.96, 2.61); p=0.070
Combined definitions based on the presence of VCI and VCFD and taking the 3 TPs into account		
Sequential or simultaneous presence of VCI and VCFD across the 3 TPs	2.53 (1.49, 4.32); p=0.001	2.29 (1.37, 3.83); p=0.002
Presence of VCI but not VCFD across the 3 TPs	1.25 (0.56, 2.80); p=0.583	1.22 (0.57, 2.60); p=0.609
Presence of VCFD but not VCI across the 3 TPs	1.18 (0.76, 1.85); p=0.463	1.10 (0.72, 1.69); p=0.650
Absence of VCI or VCFD across the 3 TPs	0.57 (0.39, 0.84); p=0.004	0.62 (0.43, 0.89); p=0.009
New VCFD preceded by VCI	3.39 (1.93, 5.95); p<0.001	3.01 (1.76, 5.13); p<0.001
Coexistence of VCFD and VCI at the same TP	0.77 (0.24, 2.46); p=0.653	0.72 (0.25, 2.13); p=0.556

Definitions of VCI or VCFD	Syndesmophyte formation or growth according to X-ray reader 1 and reader 2	
	Adjustment for within-patient correlation by VU-level and MRI-reader	**Multivariable adjustment***
Definitions based on the presence of VCI and taking the 3 TPs into account		
VCI at baseline, irrespective of inflammation status at other TPs	1.83 (1.16, 2.87); p=0.009	1.63 (1.06, 2.50); p=0.027
VCI at baseline only	2.10 (1.34, 3.29); p=0.001	1.95 (1.26, 3.02); p=0.003
VCI at baseline and another TP	0.69 (0.19, 2.55); p=0.575	0.62 (0.20, 1.95); p=0.408
VCI at any TP	1.91 (1.27, 2.89); p=0.002	1.75 (1.17, 2.61); p=0.006
Definitions based on the presence of VCFD and taking the 3 TPs into account		
VCFD at baseline, irrespective of inflammation status at other TPs	1.70 (1.16, 2.49); p=0.006	1.57 (1.09, 2.26); p=0.017
VCFD at baseline only	1.10 (0.27, 4.44); p=0.894	1.04 (0.29, 3.80); p=0.949
VCFD at baseline and another TP	1.67 (1.12, 2.48); p=0.012	1.53 (1.04, 2.23); p=0.030
VCFD at any TP	2.04 (1.47, 2.82); p<0.001	1.85 (1.35, 2.53); p<0.001
VCFD at all TPs	1.91 (1.24, 2.92); p=0.003	1.77 (1.18, 2.66); p=0.006
Combined definitions based on the presence of VCI and VCFD and taking the 3 TPs into account		
Sequential or simultaneous presence of VCI and VCFD across the 3 TPs	2.36 (1.49, 3.74); p<0.001	2.12 (1.36, 3.31); p=0.001
Presence of VCI but not VCFD across the 3 TPs	1.04 (0.50, 2.16); p=0.914	1.00 (0.50, 2.02); p=0.981
Presence of VCFD but not VCI across the 3 TPs	1.49 (1.05, 2.12); p=0.027	1.38 (0.98, 1.93); p=0.064
Absence of VCI or VCFD across the 3 TPs	0.51 (0.37, 0.70); p<0.001	0.56 (0.41, 0.76); p<0.001
New VCFD preceded by VCI	2.40 (1.41, 4.08); p=0.001	2.17 (1.32, 3.56); p=0.002
Coexistence of VCFD and VCI at the same TP	1.20 (0.54, 2.65); p=0.652	1.09 (0.51, 2.30); p=0.829

*Adjustment for within-patient correlation by VU-level and MRI-reader and adjustment for treatment, gender and presence of syndesmophytes or ankylosis at baseline (at the patient level). adjOR, adjusted odds ratio; TP, time point; VCI, vertebral corner inflammation; VCFD, vertebral corner fat deposition.

Chapter 12

Summary and conclusions

SUMMARY AND CONCLUSIONS

The work presented in this thesis focuses on the assessment and monitoring of health and imaging outcomes in axial spondyloarthritis (SpA) and the relationship between these outcomes. Four major contributions to the understanding of axial SpA and to its management have been made: 1) we have contributed to improving and facilitating the assessment of disease activity in axial SpA using the Ankylosing Spondylitis (AS) Disease Activity Score (ASDAS), for which we have defined cut-off levels for disease activity states and improvement criteria and in addition we have studied mathematical properties of the ASDAS formula resulting in further practical advice about its calculation; 2) we have contributed to increasing the knowledge about the mutual relationships between health outcomes in axial SpA, having looked at treatment responses and a comprehensive list of assessments and related health outcomes, namely health related quality of life (HRQoL), physical function, clinical disease activity, spinal mobility, structural damage and magnetic resonance imaging (MRI) of the spine; 3) we have contributed to increasing the knowledge about the factors that influence phenotypic variability in axial SpA, namely Human Leukocyte Antigen B27 (HLA-B27) positivity (a genetic factor), smoking (an environmental factor) and the presence of psoriasis (an extra-articular manifestation); and 4) we have provided further insight into understanding the processes that drive structural progression in axial SpA and into elucidating the link between inflammation and structural damage, by specifically looking at the relationship between MRI inflammation, MRI fat deposition and new bone formation in axial SpA.

The studies presented in this thesis were conducted in three cohorts: the AS Study for the Evaluation of Recombinant infliximab Therapy (ASSERT) cohort,[1] the Norwegian Disease Modifying Anti-Rheumatic Drug (NOR-DMARD) cohort,[2] and the *Devenir des Spondyloarthropathies Indifférenciées Récentes* (DESIR) cohort.[3] ASSERT was a 24-week randomised controlled trial with a tumour necrosis factor alpha (TNF) blocker, with an open extension until 102 weeks with all patients on the TNF-blocker. Demographic, clinical and MRI data were collected at baseline, 24 weeks and 102 weeks, while radiographic data was collected at baseline and 102 weeks. ASSERT was the main population studied in this thesis. NOR-DMARD is a Norwegian register from 5 centres that includes consecutive patients with axial SpA (according to the treating rheumatologist) starting a new synthetic or biological DMARD regimen. Patients from the NOR-DMARD register are considered an appropriate representation of patients with axial SpA as seen by rheumatologists in Norway. DESIR is a longitudinal prospective cohort that includes adults aged over 18 and less than 50 years from 25 regional centres in France. Patients have inflammatory back pain with symptom duration more than 3 months and less than 3 years and symptoms suggestive of SpA according to the opinion of the local investigator.

In this final chapter we will summarise the main findings of the studies presented in this thesis and we will also discuss future perspectives as well as a research agenda for the topics that we have studied.

Assessment of disease activity in axial SpA using the ASDAS

In **chapter 2** we determined cut-off values for disease activity states and response criteria according to the ASDAS. We developed the cut-offs in the NOR-DMARD cohort,[2] and validated the cut-offs in the same population at a different time-point and in an independent cohort, the ASSERT cohort.[1] Four disease activity states were defined: inactive disease, moderate-, high-, and very high disease activity. Both the patient and physician global assessments of disease activity at pre-defined levels (<1, <3 and >6 on a 0-10 scale) were used as external anchors to define the three disease activity cut-offs: 1.3, separating 'inactive disease' from 'moderate disease activity'; 2.1, separating 'moderate disease activity' from 'high disease activity'; and 3.5, separating 'high disease activity' from 'very high disease activity'. The Assessment of Spondyloarthritis international Society (ASAS) partial remission criteria were also used as an additional external anchor for 'inactive disease'. Regarding response criteria, the external anchor in the receiver operating characteristic (ROC)-curve analysis was a 'global rating of change' after starting treatment, with the health change defined by the patient in five Likert-type categories: 'much worse', 'worse', 'unchanged', 'better' and 'much better'. This resulted in the definition of two cut-offs for the magnitude of response: 'clinically important improvement' (external construct: patients reporting to be 'better' or 'much better'), defined as a decrease in ASDAS greater or equal to 1.1, and 'major improvement' (external construct: patients reporting to be 'much better'), defined as a decrease in ASDAS greater or equal to 2.0.

In **chapter 3**, we analysed the DESIR cohort, and contributed to further standardisation of the ASDAS and to a more homogeneous and reproducible application of this new index by demonstrating that: i) when the conventional CRP (cCRP) value is below the limit of detection, a CRP value of 2mg/L should be used to calculate ASDAS with CRP (ASDAS-CRP), and ii) when the high sensitivity CRP (hsCRP) value is below 2mg/L, the constant value of 2mg/L should also be used to calculate ASDAS-CRP. This study fulfilled a gap in the methodology of ASDAS calculation, since ASDAS-CRP had been developed using the cCRP and evidence-based guidance on how to calculate the ASDAS when the cCRP is below the threshold of detection or when using the hsCRP was lacking.

Further discussion and future perspectives

Chapter 2 is an important chapter from a methodological point of view since it highlights several key aspects of cut-off development, namely the fact that the cut-off selection

procedure should be an informed decision that takes into account the clinical (eg, treatment implications of the cut-off) and epidemiological context of the disease (eg, frequency of the various disease states in the target population) and the relative consequences of false-negative and false-positive test results compared to an external anchor ('gold standard', which may differ across contexts).[4,5] Importantly, we developed the ASDAS cut-offs both on clinical and statistical grounds and found a remarkable consistency between the various external constructs that we tested. Regarding improvement cut-offs, the availability of a global rating of change questionnaire in NOR-DMARD allowed us to use an adequate gold-standard for this purpose, with the cut-off for minimal clinically important improvement being beyond the limits of measurement error according to all tested methods.[6-8] Consistency of results was also shown between ASDAS-CRP and ASDAS with erythrocyte sedimentation rate (ASDAS-ESR), with the cut-offs being applicable to both formulae (however, the formulae are not interchangeable). ASDAS cut-offs showed excellent psychometric properties, with the ASDAS response criteria being more discriminative between treatment groups than classical response criteria. The two currently available remission-like states in axial SpA were also compared, ASDAS inactive disease being more discriminative than ASAS partial remission criteria.

Cut-offs are important because they give a meaning to a continuous index, to be used in an individual patient. 'Disease activity states' may help for instance to decide about the need to change treatment, they can be used as selection criteria for patient participation in research studies or they can be used as therapeutic targets (eg, aiming at remission/inactive disease). 'Response criteria' allow measuring the impact of a treatment, namely if the treatment results in clinically relevant improvement. Therefore the development of cut-offs for the ASDAS was a critical step in the ASDAS implementation plan, allowing translating mean group-effects into individual patient effects.

The ASDAS cut-offs were subsequently endorsed by ASAS and the Outcome Measures in Rheumatology (OMERACT) group and its use in clinical practice, observational studies and clinical trials has continued to increase since then.[9-16] They have been shown to have excellent measurement properties and its widespread use across different settings will allow combining results from different studies, for example for meta-analysis, or to audit results and to define and improve standards of care. ASDAS categories will also facilitate studying the impact of disease activity states on prognosis. Subsequent evidence has also suggested that the ASDAS better reflects the inflammatory disease processes in axial SpA than the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), namely at the biological level (correlation with biomarkers of inflammation, angiogenesis, cartilage and bone turnover)[17] and at the MRI level (correlation with MRI inflammation scores).[9,18,19] Furthermore, ASDAS high disease activity (ASDAS $\geq$2.1) might be a better threshold than the historically used BASDAI elevation cut-off level

(BASDAI ≥4) for the selection of patients for treatment with TNF-blockers, particularly because it selects a higher number of patients with characteristics predictive of a good response to these therapies.[13,20-22] This threshold has already been adopted by some national rheumatology societies as an additional criterion to select patients for treatment with biological therapies[23,24] and has been included in the ASAS/European League Against Rheumatism (EULAR) recommendations for the management of axial SpA.

Excellent examples of how ASDAS categories can facilitate studying the impact of disease activity states on prognosis are two recently published articles looking at this topic. The first article showed a longitudinal association between disease activity and progression of radiographic damage in AS.[25] This study included patients from the Outcome in AS International Study (OASIS) cohort that were clinically and radiographically evaluated every 2 years up to a period of 12 years. Radiographic progression increased in parallel with increase in the ASDAS disease activity state with for example a patient with very high disease activity (ASDAS>3.5) being estimated to have an additional progression of 2.3 modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) units in the subsequent 2 years in comparison to a patient with inactive disease (ASDAS<1.3). Several measures of disease activity (ASDAS, BASDAI, CRP) were significantly associated with an increase in the mSASSS but the ASDAS statistical model was the one that best fitted the data. Another recent study using the GErman SPondyloarthritis Inception Cohort (GESPIC) showed similar findings.[26] In this study, the authors also found that disease activity was associated with radiographic spinal progression in a population in an earlier disease stage compared to OASIS. Time-averaged ASDAS was significantly associated both with mSASSS worsening by ≥2 points and syndesmophyte formation/bridging over 2 years.[26] These data add to the validity (and predictive value in terms of progression of structural damage) of the ASDAS[25] and provide an additional argument to pursue a treat-to-target strategy in axial SpA, with ASDAS inactive disease potentially being the best target.

For the purpose of defining a remission-like state in axial SpA, ASDAS inactive disease seems to provide a more appropriate definition than the ASAS partial remission criteria because ASDAS inactive disease is independent of physical function, while ASAS partial remission criteria include physical function as one of its items, which implies that some patients with long-standing disease and severe structural damage and physical limitations may never fulfil ASAS partial remission criteria despite the disease being clinically and biologically inactive.[27] In a recent study reporting the outcomes of TNF-blocker treatment over a period of 2 years, achievement of ASDAS inactive disease or ASDAS major improvement was also significantly associated with greater improvements in the 36-Item Short Form Survey (SF-36) physical and mental component scores´ as well as in work productivity compared to patients that did not meet these treatment targets.[15] These data show that an ASDAS response translates into improvements in HRQoL and

health economic outcomes and again suggest that achieving ASDAS inactive disease should be considered a major treatment goal in patients with axial SpA.[15,28]

The ASDAS formula is rather complex and it is not possible to mentally calculate the index. However, this is not different from the Disease Activity Score (DAS) that has been successfully implemented in rheumatoid arthritis and in fact, compared to the DAS, the ASDAS benefits from not requiring a joint count. Rheumatologists are already familiarised with this type of indices and with the strategies that have been put in place to overcome their complexity: the availability of online, desktop, hand-held and smartphone calculators. The ASAS group has developed such tools (available at www.asas-group.org) for the ASDAS as well as a 'quick ASDAS calculation form', a 2-page form that gives the possibility to quickly calculate the ASDAS without the need of an electronic calculator. The availability of these instruments will facilitate the implementation of the ASDAS in clinical practice.

Regarding the research agenda in this area, evidence for the benefits of a treat-to-target strategy over standard treatment in axial SpA is still scarce and further studies are required; further research is needed to confirm if selecting patients for TNF-blocker treatment according to the ASDAS instead of BASDAI will result in improved long-term treatment outcomes; the definition of flare in axial SpA needs to be further explored and flare cut-offs for the currently available indices need to be established; the role of MRI in assessing and monitoring disease activity as well in selecting axial SpA patients for TNF-blocker treatment requires further investigation; finally, it needs to be confirmed whether a reduction of disease activity according to ASDAS by therapeutic intervention will be associated with reduction of radiographic spinal progression in axial SpA.

Relationship between health outcomes in axial SpA

Progressive restriction in spinal mobility is a hallmark health outcome of axial SpA and a predictor of poor long-term prognosis. In **Chapter 4** we showed that spinal mobility impairment in AS is independently determined by irreversible spinal damage as well as by reversible spinal inflammation, a finding that is consistent with clinical data reporting the improvement of both spinal inflammation and spinal mobility after treatment with TNF-blockers[1,29-31] and with studies showing an association between radiographic damage of the spine and spinal mobility impairment at the group level[32-36] but not always at the individual level.[36]

In **Chapter 5**, we studied in detail the relationships between several AS outcome measures and proposed a stratified model for health outcomes in this disease. According to this model, HRQoL is determined by physical function and disease activity, physical function is determined by spinal mobility and disease activity, and spinal mobility is determined by structural damage and inflammation of the spine (this last relationship

being based on the data presented in **Chapter 4**).

In **Chapter 6**, we showed that, cross-sectionally, MRI inflammation correlates better with CRP than with other measures of disease activity, but also correlates with the ASDAS, which includes the CRP in its formula. Furthermore, at the longitudinal level, improvement in MRI inflammation correlated with improvements in CRP and ASDAS, and a greater improvement in spinal inflammation was seen for those with higher CRP or ASDAS values at baseline. Importantly, other measures of disease activity, namely fully patient-driven measures such as the BASDAI, individual BASDAI questions and patient global, did not correlate with MRI inflammation.

The ASSERT cohort was studied in **Chapters 4, 5 and 6**.

Further discussion and future perspectives

Data from **Chapter 4** confirmed that spinal inflammation could be an explanation for the cases of discordance between the level of spinal mobility impairment and the degree of radiographic damage. Moreover, the results of this study also showed that spinal mobility impairment is more influenced by spinal inflammation in early disease, and by structural damage in later disease, which raises the suggestion that spinal mobility may better be maintained by an early- as compared to a delayed intervention. By showing that inflammatory changes (and not only structural changes) contribute to spinal mobility impairment, this study gave a new and original meaning to MRI spinal inflammation, further elucidating its role in the burden of disease. Since the mSASSS only accounts for the structural damage in the anterior corners of the cervical and lumbar spine, future research should focus on the role of damage of the thoracic spine and of the posterior elements of the spine, as well as on the role of MRI inflammation of the facet joints, vertebral ligaments and soft tissues (none of which are included in the MRI assessment at the vertebral unit level that was done in this study), in determining spinal mobility.

The model presented in **Chapter 5** explained a large percentage of the variation in the health outcomes, but not the entire variation, suggesting that other variables such as psychological, social, cultural, ethnical and educational factors should also be taken into account in future studies. However, the relations that we described are indisputable and consistent with the conceptual 'continuum of outcome measures' proposed by Tennant,[37] and suggest that in order to optimise HRQoL, both physical function and disease activity should be considered major goals in the treatment of axial SpA and optimal physical function-preserving therapy should focus not only on improving disease activity but also on maintaining spinal mobility, which on its own requires both the elimination of spinal inflammation and the prevention of structural damage. This stratified model nicely explains why optimal treatment of axial SpA should be multimodal, not only involving non-steroidal anti-inflammatory drugs (NSAIDs) and anti-TNF therapy (drugs that have

shown to improve patient-reported disease activity, while regarding MRI inflammation of the spine the effect is only clear for anti-TNF) but also therapies more specifically addressing spinal mobility (such as physical therapy) and progression of structural damage (for which no specific therapies have been developed and regarding which there is conflicting and/or inconclusive data regarding the capacity of NSAIDs and TNF-blockers to prevent the progression of structural damage).[38-41]

The associations that we described may also serve as the framework for future longitudinal studies in which temporal relationships may be tested. An association does not necessarily imply causation and only longitudinal studies can evaluate if a change in an outcome measure translates into a subsequent change in the associated measure. As we learn more about how to measure axial SpA, our knowledge about the disease improves and we can make better decisions on how to assess and treat the disease. The model we proposed is useful not only for the design and interpretation of clinical trials but also for daily clinical practice and may contribute to guide best practice in the assessment and treatment of patients with axial SpA. Since we studied a population with established AS, future research should also focus on earlier disease stages.

Data presented in **Chapter 6**, allowed us to better understand the relationship between clinical disease activity and MRI inflammation, both cross-sectionally as well as longitudinally, by assessing treatment responses and changes in MRI inflammation after TNF-blocker therapy. We concluded that ASDAS better reflects the spinal inflammatory disease process in AS than BASDAI, both as a status- and as a response measure. These results added to the construct validity of ASDAS and provided further evidence that ASDAS is an appropriate tool for monitoring patients with axial SpA. By including both CRP and patient-reported outcomes in its formula, ASDAS has the advantage of providing combined information on objective and subjective measures. Nevertheless, we found weak to moderate correlations between CRP/ASDAS and MRI inflammation scores. Therefore, these clinical and laboratory measures should not be used to replace MRI assessment of spinal inflammation, which has become a useful tool in the management of patients with axial SpA. We have shown that the various measures have additive value. In the future, it will be interesting to see if more advanced (and quantitative) MRI techniques that may be more sensitive to inflammatory changes will result in different (and potential better) correlations with clinical and laboratory measures of disease activity. Another question still under debate relates to the role of MRI in the management of patients with axial SpA, especially in cases in which there is dissociation between clinical, laboratory and imaging findings. MRI may have a role in treatment adjustments but the benefit of this approach is still to be shown. It could also be debated if MRI should be used as an additional criterion to classify patients as being in remission, rather than just using clinical and laboratory criteria (or a combination of clinical and laboratory variables in the same formula such as it happens with ASDAS

inactive disease).

Phenotypic variability in axial SpA

In **Chapter 7**, our aim was to clarify the influence of HLA-B27 status on the phenotype of axial SpA. The results provided important information about the contribution of HLA-B27 to disease spectrum manifestations in axial SpA. We found that the presence of HLA-B27 was associated with an earlier age of onset of inflammatory back pain and with less delay in diagnosis. In addition, HLA-B27 was associated with axial inflammation (spine and sacroiliac joints [SIJ]). Moreover, SIJ inflammation seemed to be an intermediate variable between HLA-B27 and radiographic sacroiliitis.

In **Chapter 8**, we aimed to clarify the impact of smoking in the axial SpA spectrum. We found that in young axial SpA patients with short disease duration, smokers had an earlier onset of inflammatory back pain, higher disease activity, increased axial inflammation and structural damage, poorer functional status and poorer quality of life.

In **Chapter 9**, we compared AS patients with and without psoriasis. We found that demographic characteristics, disease activity, spinal mobility, physical function, structural damage and quality of life measures were comparable between AS patients with and without psoriasis.

The DESIR cohort was studied in **Chapters 7 and 8**, and the ASSERT cohort was studied in **Chapter 9**.

Further discussion and future perspectives

HLA-B27 positive patients differ from HLA-B27 negative patients in clinical presentation and imaging. Previous studies had looked at patients with longer duration of symptoms[42,43] and also reported an association between HLA-B27 and an earlier age of disease onset, supporting the concept of axial SpA as a continuous spectrum. Our imaging analyses yielded new and relevant findings. Our models showed that HLA-B27 positivity was independently associated with MRI inflammation of the SIJ (and the spine), while MRI inflammation of the SIJ was independently associated with radiographic sacroiliitis. Interestingly, when MRI inflammation of the SIJ was removed from the models, HLA-B27 positivity was also found to be associated with radiographic sacroiliitis, suggesting that HLA-B27 may contribute to SIJ inflammation which in turn may lead to subsequent structural damage; inflammation as an intermediate factor between HLA-B27 and SIJ structural damage. In this study it was also noteworthy that ASDAS-CRP was positively associated with MRI inflammation of the spine, while BASDAI was negatively associated with MRI inflammation of the SIJ. These results also add to the validity of ASDAS-CRP as a measure for clinical disease activity in early axial SpA, and are in line with results from **Chapter 6**, obtained in a population with AS.

The adverse effects of smoking on AS disease parameters had been reported in previous studies, and were confirmed by us more robustly in an early disease stage population. In addition, we have demonstrated a new association with the presence of MRI inflammation. On radiographs, smoking was only associated with spinal, but not with SIJ damage.

The analyses in patients with and without psoriasis can be added to previous studies performed in heterogeneous populations (early inflammatory back pain, axial psoriatic arthritis and AS patients) that had showed conflicting results.[44-49] One of the advantages of our study is the large number of disease variables that were studied. We investigated a population with AS and futures studies should focus on the entire spectrum of axial SpA patients, including patients with not only radiographic but also non-radiographic axial SpA.[50] This topic was subsequently studied by other authors in the DESIR cohort.[51] In this more recent study psoriasis was associated with more active axial disease and frequent concomitant enthesitis and dactylitis. Studying the differences between patients with and without specific extra-articular manifestations (namely differences regarding treatment responses and associated comorbidities) may help us to better stratify patients and individualize treatments. Differences between TNF-blockers regarding their efficacy on extra-articular manifestations have already been described (while all TNF-blockers block TNF alpha *in vivo*, they differ significantly in structure and exact mechanism of action). New therapies to treat axial SpA are now emerging, namely therapies targeting the IL-23/IL-17 pathway, and understanding how certain extra-articular manifestations influence other disease characteristics and the response to therapies with different mechanisms of action (from the axial disease perspective as well as from the perspective of peripheral disease and the extra-articular manifestation itself) may contribute to more personalized treatment approaches.

Our studies on HLAB-27 and smoking have fuelled the discussions about gene-environment interactions in axial SpA, and particularly about the role of smoking as a prognostic factor in axial SpA, a concept that was only beginning to emerge when we published our results. Interestingly, a recently published 2-year prospective study performed also in the DESIR cohort showed that genetic (HLA-B27), environmental (smoking status) and inflammatory factors (presence of MRI inflammation of the SIJ) are independent predictors of radiographic progression of the SIJ.[52] Inflammation, represented by either abnormal CRP or MRI inflammation, had been previously reported as a predisposing factor for subsequent radiographic SIJ progression.[53] In the same previous study, the risk of progression was reported to be particularly high in case of co-existence of HLA-B27 positivity and inflammatory lesions of the SIJ.[53] The association between elevated CRP and radiographic progression of the SIJ had also been suggested in the GESPIC cohort but was not confirmed in the recently published DESIR study.[54] In another GESPIC study, smoking had been reported to be a risk factor

for structural progression at the spinal level with a potential dose related effect.[55] In the field of axial SpA, smoking has also been related to a higher incidence of the disease and a worse response to biologics. Taking into account that smoking is a potentially modifiable lifestyle factor, axial SpA patients who smoke should be strongly advised to quit this habit, since there may be disease-specific harms of smoking that go beyond the well-known risks described for the general population (axial SpA patients may have an increased cardiovascular risk by the inflammation). Of note, the demonstration of an increased risk of smoking does not necessarily imply that stopping (modifying risk behaviour) will have measurable beneficial effects.

It is interesting to speculate on the mechanisms by which smoking may confer these increased risks. Apart from rheumatoid arthritis, the pathogenic basis of the influence of smoking in rheumatic and musculoskeletal diseases including axial SpA remains largely unclear to date. Poor health behaviour, increased osteoporotic fractures and impaired cardiorespiratory function in smokers have been proposed as reasons for the negative impact of smoking on disease activity, functional status and quality of life measures.[56-58] In such explanations smoking is a risk indicator rather than a causal factor. However, this negative impact might also be mediated by a direct toxic effect of smoking. Cigarette smoke has pro-inflammatory effects, via various proposed mechanisms: smokers have an increased level of pro-inflammatory molecules such as TNF, interleukin (IL) 1, IL-6, IL-8 and granulocyte-macrophage colony-stimulating factor;[59,60] an increased concentration of free radicals;[61] augmentation of autoreactive B cells;[62] increased circulating polymorphonuclear neutrophil[63,64] and T-lymphocyte counts;[65] and smoking is associated with triggering of the nuclear factor κB pathway and promotion of pro-inflammatory cytokine gene expression.[66]

Periodontitis may also play a role in axial SpA,[67] and smoking is associated with periodontitis and its severity in a dose-dependent manner.[68] Smoking may also interfere with gut physiology, a factor that may in turn play a role in the pathogenesis of SpA.[69] Smoking was demonstrated to alter intestinal microbiota both in inflammatory bowel disease and in healthy subjects.[70] The IL-23/IL-17 pathway is pathophysiologically important in SpA[71] and in animal models, and it has been demonstrated that chronic cigarette smoke exposure is associated with an increase in lung Th17 cell prevalence and Th17-related cytokines (IL-17A, IL-6, IL-23). These data are compatible with an activation of the IL-23/IL-17 pathway by smoking.[72] In addition, some data suggest an effect of smoking on messanger ribonucleic acid (mRNA) expression of bone morphogenetic proteins (BMP) in the periosteum.[73] BMP and osteoblast signalling pathway markers (Wnt for example) and their inhibitors (dickkopf-1)[41] play a role in new bone formation in axial SpA.

Unravelling of the mechanisms underlying the relationship between smoking and health outcomes in axial SpA is an important item in the axial SpA research agenda.[74] Many questions about this topic remain unanswered. Factors linked to smoking should be investigated and, since cigarette smoking is a complex mixture of numerous agents, it needs to be determined which compound(s) in cigarette smoke is/are responsible for the deleterious effects of smoking in axial SpA. It also needs to be investigated if smoking is only a risk indicator or also a causal factor in axial SpA. Clinical trials evaluating the impact of smoking cessation in long-term health and imaging outcomes are needed, as the benefits of smoking cessation in patients with rheumatic diseases has never been prospectively assessed.

Relationship between MRI lesions and radiographic progression in axial SpA

In **Chapter 10**, we showed that MRI inflammation in a vertebral unit slightly increases the likelihood of finding a new syndesmophyte in the same vertebral unit two years later. However, the majority of syndesmophytes (in absolute numbers) developed in vertebral units without any sign of inflammation on MRI, suggesting that the relationship between MRI inflammation and syndesmophyte formation is not straightforward. Furthermore, the subtle association between MRI inflammation and new syndesmophytes at the vertebral unit level did not translate into a statistically significant association at the patient level, although a trend was also observed.

In **Chapter 11**, we confirmed that MRI vertebral corner inflammation is associated with radiographic progression in AS, and we showed that vertebral corner fat deposition is also associated with radiographic progression. The combination of fat and inflammation either at the same time point or sequentially further increased the probability of radiographic progression. Furthermore, vertebral corner fat deposition that developed *de novo* was sometimes preceded by vertebral corner inflammation, and this sequence of events had an even stronger association with progression of structural damage. However, vertebral corner inflammation, vertebral corner fat deposition and this particular sequence only partially explained the development of new bone in AS, as a large number of new syndesmophytes/bridging still occurred in vertebral corners without either inflammation or fat deposition across three time points that were assessed in this study.

The ASSERT cohort was studied in **Chapters 10 and 11.**

Further discussion and future perspectives

When we started the analyses presented in **Chapter 10**, two studies had been published showing a statistical association between MRI inflammation and syndesmophyte formation at the same the site of inflammation after 2 years of follow-up.[75,76] The strength of the association was slightly higher in these studies as compared to our study, but also

in these studies there were far more new syndesmophytes in non-inflamed vertebral sites as compared to inflamed vertebral sites. A third study by Pedersen et al was subsequently published,[77] also suggesting that sites with inflammation are more likely to develop new syndesmophytes than sites without inflammation. In addition, it has been proposed that syndesmophytes are more likely to develop at vertebral corners in which inflammation resolves compared to those where inflammation persists.[76,77] Resolving inflammation has also been associated with fat deposition.[78] In turn, fat deposition, with or without concomitant inflammation, has been associated with the formation of new syndesmophytes.[79-81]

Given the extensive debate and controversy about this topic, as well as the new data published after we performed the analyses described in **Chapter 10**, we aimed to expand our analytical studies about the association between inflammation and new bone formation by investigating the relationship between MRI inflammation and fat deposition at a vertebral corner and the subsequent development of new bone at the same corner. We focused on a detailed sequence analysis, addressing the hypothesis that vertebral corner inflammation 'leads to' fat deposition which in turn 'leads to' bone formation, and we could indeed confirm the rationality of this sequence.

It is interesting to discuss these results in relation to the question whether TNF-blockers are capable of inhibiting the progression of structural damage in axial SpA or not. The unexpected lack of inhibition of structural damage by TNF-blockers has fuelled the discussion about the relationship between inflammation and new bone formation. Initial trial data had suggested that TNF-blockers do not have an effect on spinal structural damage.[82-84] These data have recently been challenged by observational studies suggesting a protective effect of TNF-blockers on spinal radiographic progression.[85,86] However, these observational data have important methodological limitations and this is still an unsolved question.[41] Our observation that the sequence 'vertebral corner inflammation → vertebral corner fat deposition' is a rational sequence that may contribute to new bone formation in axial SpA is in agreement with the hypothesis that TNF-blocker treatment in axial SpA will only protect from structural damage if the (new) development of vertebral corner inflammation in previously unaffected vertebrae is prevented (that means: after long-term treatment), while in contrast an immediate effect of TNF-blocker treatment could even evoke new bone formation because of the abrupt suppression of vertebral corner inflammation and the subsequent development of vertebral corner fat deposition (repair reaction) at the same vertebral corner. Undoubtedly this explanation is a simplification of the truth, because the biological effects of TNF-blockers are not limited to the suppression of inflammation and TNF-blockers have also been associated with osteoproliferation in animal models.[87]

The question whether anti-TNF may retard new bone formation in axial SpA is difficult to answer. Radiographic progression is very slow in axial SpA and ethically it would be unacceptable to perform a long-term randomised controlled trial comparing the structural outcome in patients treated with- and those not treated with a TNF-blocker as this would imply delaying effective treatment in patients who might need it. Thus, we are left with observational studies to address this question. The analysis of such cohorts requires complex statistical methods and a great deal of caution in dealing with potential biases. These considerations should be taken into account in future studies about this topic. Ideally, multiple time points (annual or biennial assessments with long duration of follow-up) with complete demographic, clinical and radiographic data should be analysed in longitudinal models, taking into account time-varying variables (including changes in treatments, disease activity and acute phase reactants), potential confounders and interactions. In sequential radiographs of the same patient structural damage is highly correlated and therefore these longitudinal models should also account for within-patient correlation in order to avoid spurious results.[41] Given that an IL-17-blocker has now been approved to treat patients with axial SpA, a randomised controlled study comparing the structural effects of TNF-blocker *versus* IL-17-blocker therapy would also be informative. Moreover, the availability of low-dose computed tomography (CT) scans may help to increase the sensitivity of the imaging methods to detect progression of structural damage potentially and to allow the reduction of the length of the trial.

Consistent with previous studies, we have shown that a significant part of new bone formation occurs in vertebral corners without traceable inflammation or fat deposition. However, this does not necessarily mean that these vertebral corners do not have inflammation/fat deposition at the microscopic level because MRI may not be sensitive enough to capture all areas of inflammation/fat deposition[88] and because the time between MRI assessments may not be short enough to capture the potential fluctuation of these lesions, particularly inflammation. Conversely, these results suggest that the mechanisms of new bone formation in axial SpA are still largely unknown and that the triggering of osteoproliferation may be completely or partially independent of inflammation (and fat deposition).[89]

Interesting future questions are how to incorporate MRI in future clinical trials and long-term observational studies, whether MRI criteria should be incorporated in future treat-to-target treatment strategies, and whether new drugs with different mechanisms of action, such as drugs targeting the IL-23/IL-17 axis, will have different effects on inflammation, fat deposition and structural damage. Studies looking at additional time-points and at shorter intervals may also help to further elucidate the relationship between inflammation and syndesmophyte formation.

Final comments

In this thesis we have studied a large number of health and imaging outcomes in axial SpA. The positive emotion with which the ASDAS has been received by the axial SpA scientific community is particularly noticeable. Such a quick and wide implementation and acceptance of a new disease activity index has rarely been seen. Our clinical research has fuelled other research in the field, with research on the effects of smoking as a particularly relevant example. Our detailed studies about the relationship between MRI lesions and new bone formation on radiographs are among the most comprehensive and robust to date as they have used a uniquely large population of patients, multiple imaging readers, fully-unbiased imaging scoring methods, and three time points of assessment with adjustment for the dependence of observations in the same patient. In conclusion, our studies have contributed to a better understanding of the disease axial SpA and of the measures that we use to evaluate it and to monitor its course.

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Chapter 13

Samenvatting en conclusies

SAMENVATTING EN CONCLUSIES

Spondylartritis (SpA) is een veelzijdige aandoening met axiaal (wervelkolom en sacro-iliacale gewrichten) en/of perifere (perifere gewrichten) betrokkenheid. SpA kan veel klinische manifestaties hebben zoals chronische rugpijn, artritis (ontsteking van de gewrichten), enthesitis (ontsteking van de structuren tussen de ligamenten en het bot), dactylitis (ontsteking van een hele vinger of teen), en er zijn ook extra-articulaire manifestaties zoals psoriasis (huidziekte), uveitis (oogziekte) en inflammatoire darmziekte (ziekte van Crohn of colitis ulcerosa).[1]

De inhoud van dit proefschrift richt zich op de evaluatie en de monitoring van het beloop van gezondheid en afwijkingen op beeldvormend onderzoek bij axiale SpA en de relatie hiertussen. Vier grote bijdragen zijn geleverd aan het begrijpen van axiale SpA en de behandeling ervan: 1) we hebben bijgedragen aan het verbeteren en het vergemakkelijken van de beoordeling van de ziekteactiviteit in axiale SpA met behulp van de Disease Activity Score (ASDAS) voor de Ziekte van Bechterew of Ankyloserende Spondylitis (AS); We hebben afkapwaarden voor de ASDAS voor de verschillende niveaus van ziekteactiviteit gedefinieerd en criteria om respons te meten ontwikkeld. Bovendien hebben we de mathematische eigenschappen van de ASDAS-formule bestudeerd, wat resulteerde in een praktisch advies over de berekening; 2) we hebben bijgedragen aan het vergroten van de kennis over de onderlinge relaties tussen de effecten op de gezondheid in axiale SpA. We hebben hierbij zowel de behandeleffecten alsook een uitgebreide lijst met andere gezondheidseffecten bekeken, inclusief aan gezondheid gerelateerde kwaliteit van leven (HRQoL), fysiek functioneren, klinische ziekteactiviteit, spinale mobiliteit, structurele schade en 'magnetische resonantie imaging' (MRI) van de wervelkolom; 3) we hebben bijgedragen aan kennis over factoren die de variabiliteit van de klinische uitingen van axiale SpA beinvloeden, waaronder Human Leukocyte Antigen B27 (HLA-B27) positiviteit (een genetische factor), roken (een omgevingsfactor) en de aanwezigheid van psoriasis (een extra-articulaire manifestatie); en 4) we hebben meer inzicht gegeven in het begrijpen van het proces dat tot structurele progressie (botveranderingen, met name de vorming van nieuw bot en fusie van de wervels van de wervelkolom) in axiale SpA leidt en in de link tussen ontsteking en structurele schade. Dit hebben we gedaan door specifiek te kijken naar de relatie tussen MRI-afwijkingen (MRI-ontsteking en MRI-vet) en botnieuwvorming bij axiale SpA.

De onderzoeken in dit proefschrift werden uitgevoerd in drie cohorten: de AS Study for the Evaluation of Recombinant infliximab Therapy (ASSERT) studie,[2] het Noorse Disease Modifying Anti-Rheumatic Drug (NOR-DMARD) cohort,[3] en het Franse *Devenir des Spondyloarthropathies Indifférenciées Récentes* (DESIR) cohort.[4] ASSERT was een gerandomiseerde studie van 24 weken met een geneesmiddel dat is gericht tegen tumornecrosisfactor-alfa (TNF) en daarom TNF-blokker wordt genoemd in vergeljking

met placebo. Deze studie had een langere follow-up duur tot 102 weken waarbij alle patiënten werden behandeld met een TNF-blokker. Demografische, klinische en MRI-gegevens werden verzameld bij de start, na 24 weken en na 102 weken, terwijl radiologische gegevens ('X-rays') werden verzameld bij de start en na 102 weken. ASSERT was de belangrijkste populatie die in dit proefschrift bestudeerd werd. NOR-DMARD is een Noors register van patiënten uit 5 centra waaronder patiënten met axiale SpA (volgens de behandelende reumatologen) die zijn gestart met een synthetisch of biologisch DMARD, (langwerkende medicatie die wordt gebruikt om patiënten met inflammatoire reumatische aandoeningen te behandelen). Patiënten uit het NOR-DMARD-register worden gezien als een goede afspiegeling van patiënten met axiale SpA die door reumatologen in Noorwegen behandeld worden. DESIR is een longitudinaal prospectief cohort bestaande uit volwassenen die ouder zijn dan 18 maar jonger dan 50 jaar, afkomstig uit 25 regionale centra in Frankrijk. Patiënten hebben inflammatoire rugpijn (rugpijn die een ontsteking als oorzaak doet vermoeden) met een symptoomduur van meer dan 3 maanden en minder dan 3 jaar, en voorts symptomen die SpA suggereren volgens de mening van de plaatselijke onderzoeker.

In dit hoofdstuk zullen we de belangrijkste bevindingen samenvatten.

Beoordeling van ziekteactiviteit met behulp van de ASDAS

In **hoofdstuk 2** hebben we de afkapwaarden bepaald voor de mate van ziekteactiviteit en voor de responscriteria volgens de ASDAS. We hebben de afkapwaarden ontwikkeld in het NOR-DMARD cohort,[3] en deze vervolgens gevalideerd in dezelfde studie op een ander tijdstip en in een onafhankelijk cohort, het ASSERT cohort.[2] Vier niveaus van ziekteactiviteit werden gedefinieerd: inactieve ziekte, matige, hoge en zeer hoge ziekteactiviteit. Beoordelingen van ziekteactiviteit op vooraf gedefinieerde niveaus (<1, <3 en >6 op een schaal van 0-10) van zowel de patiënt als de arts werden gebruikt als externe ankers (externe referentie) om de drie afkapwaarden van ziekteactiviteit te bepalen: 1.3 onderscheidt 'inactieve ziekte' van 'matige ziekteactiviteit'; 2.1, onderscheidt 'matige ziekteactiviteit' van 'hoge ziekteactiviteit'; en 3.5 onderscheidt 'hoge ziekteactiviteit' en 'zeer hoge ziekteactiviteit'. De 'bijna-remissie' criteria van de Assessment of Spondyloarthritis international Society (ASAS) (reeds gepubliceerde remissie-achtige criteria) werden ook gebruikt als een aanvullend extern anker voor 'inactieve ziekte'. Wat de responscriteria betreft was het externe anker een 'globale meting van verandering' na de start van de behandeling, waarbij het effect op de gezondheid, zoals door de patiënt beoordeeld, wordt gedefinieerd in vijf categorieën: 'veel erger', 'erger', 'onveranderd', 'beter' en 'veel beter'. Deze werden gebruikt in een (receiver operating characteristic) ROC-curve analyse (een statistische methode om afkapwaarden voor een continue maat te bepalen). Dit resulteerde in de definitie van twee afkapwaarden voor de grootte van de respons: Ten eerste een 'belangrijke

klinische verbetering' (extern anker: patiënten geven aan dat ze zich 'beter' of 'veel beter' voelen), gedefinieerd als een afname in ASDAS die groter of gelijk aan 1.1 is; en ten tweede een 'grote verbetering' (extern anker: patiënten geven aan dat ze zich 'veel beter' voelen), gedefinieerd als een afname in ASDAS die groter of gelijk aan 2.0 is.

Een van de ASDAS-formules bevat de CRP-waarde (CRP is een laboratoriumtest om ontstekingsactiviteit te meten). Er zijn conventionele laboratoriumtesten die het CRP (cCRP) meten met matige gevoeligheid terwijl andere hoog-sensitieve testen het CRP met veel hogere gevoeligheid meten (hsCRP). In het kort gezegd ligt het verschil tussen hsCRP en cCRP niet zozeer in de bepaling zelf als wel in de prestaties van de test; hsCRP-testen hebben een meetbereik dat zich uitstrekt tot onder het typische meetbereik van de meeste cCRP-testen (gevoeliger voor lage testuitslagen).

In **hoofdstuk 3** hebben we het DESIR-cohort geanalyseerd en hebben we bijgedragen aan de verdere standaardisatie van de ASDAS Dit hebben we gedaan door aan te tonen dat: i) wanneer de cCRP-waarde onder de detectiegrens ligt, een CRP-waarde van 2mg/l gebruikt moet worden om ASDAS met CRP (ASDAS-CRP) te berekenen, en ii) wanneer de hsCRP-waarde onder 2mg/l is, de constante waarde van 2mg/l gebruikt moet worden om ASDAS-CRP te berekenen. Deze studie vult een leemte in de methodologie van ASDAS-berekeningen daar ASDAS-CRP wered ontwikkeld is met gebruikmaking van de cCRP en aanwijzingen over hoe de ASDAS berekend moet worden wanneer de cCRP onder de detectiegrens ligt, of wanneer de hsCRP gebruik wordt, ontbraken.

Bespreking

Hoofdstuk 2 is een belangrijk hoofdstuk vanuit methodologisch oogpunt omdat het verschillende belangrijke aspecten van de bepaling van afkapwaarden aanhaalt, met name het feit dat de selectieprocedure van afkapwaarden een gefundeerde beslissing moet zijn. Deze moet rekening houden met de klinische context (bijvoorbeeld behandelingsimplicaties volgend uit het gebruik van de afkapwaarde), de epidemiologische context van de ziekte (bijvoorbeeld frequentie van de verschillende niveaus van de ziekte bij de doelpopulatie) en de eventuele gevolgen van vals-negatieve en vals-positieve testresultaten in vergelijking met een extern anker ('gouden standard', die kan verschillen afhankelijk van de context).[5,6] Belangrijk is dat we de ASDAS-afkapwaarden hebben ontwikkeld op zowel klinische als statistische gronden en dat we een opmerkelijke samenhang hebben gevonden tussen de verschillende externe ankers die we hebben getest. Wat de verbetering van afkapwaarden betreft liet de beschikbare vragenlijst over globale veranderingsmeting in NOR-DMARD ons toe om het best mogelijke anker te gebruiken: minimale klinisch belangrijke verbetering die boven de grens van meetfouten lag volgens alle geteste methodes.[7-9] Meet- of observatiefouten zijn gedefinieerd als het verschil tussen een gemeten waarde en de echte waarde; in de statistiek is een meetfout geen 'fout' aangezien de variabiliteit een

inherent onderdeel is van het meetproces. Er werd ook consistentie aangetoond tussen afkapwaarden die van toepassing zijn op de formules van de ASDAS-CRP en ASDAS met een andere maat voor ontsteking, de bezinkingssnelheid van erytrocyten (ASDAS-ESR), (echter, de formules zijn niet uitwisselbaar). ASDAS-afkapwaarden hadden uitstekende meeteigenschappen. De ASDAS-responscriteria maken beter onderscheid tussen behandelingsgroepen (groepen patiënten die verschillende behandelingen toegewezen krijgen) dan klassieke (eerder gepubliceerde) responscriteria. Bij de vergelijking van twee maten die momenteel beschikbaar zijn om remissie in axiale SpA te meten bleek dat de maat 'ASDAS inactieve ziekte' een beter onderscheid kon maken tussen twee groepen dan de ASAS 'bijna-remissie' criteria.

Afkapwaarden zijn belangrijk want ze geven meer (klinische) betekenis aan een continue maat en ze zijn te gebruiken bij een individuele patiënt. Een 'ziekteactiviteits-status' kan bijvoorbeeld bijdragen aan de beslissing of een andere behandeling moet worden ingesteld, om te beoordelen of een patiënt in onderzoekstudies moet worden ingesloten, of kan dienen als behandelingsdoel (vb. remissie/inactieve ziekte). Met 'responscriteria' wordt de impact van een behandeling gemeten, met name of de behandeling tot een klinisch relevante verbetering leidt. Daarom is de ontwikkeling van afkapwaarden voor de ASDAS een cruciale stap, waarmee gemiddelde groepseffecten vertaald kunnen worden naar individuele patiënteffecten. De ASDAS-afkapwaarden werden vervolgens goedgekeurd door ASAS en de Outcome Measures in Rheumatology (OMERACT)-groep en sindsdien is het gebruik in de klinische praktijk, in observationele studies en in klinische trials toegenomen.[10-17] Daarenboven is ASDAS hoge ziekteactiviteit (ASDAS ≥2.1) een beter ingangscriterium dan de vroeger gebruikte BASDAI (BASDAI ≥4) voor het insluiten van patienten in trials met TNF-blokkers, vooral omdat zo een groter aantal patiënten wordt geselecteerd met eigenschappen die een goede respons op deze therapieën voorspellen[14,18-20]. Dit criterium is reeds geimplementeerd door sommige nationale verenigingen voor reumatologie en als richtlijn voor trials met biologische therapieën[21,22] en is daarenboven opgenomen in de ASAS/European League Against Rheumatism (EULAR) aanbevelingen voor de behandeling van axiale SpA.

De samenhang tussen diverse uitkomstmaten van axiale SpA

Geleidelijke beperking van de mobiliteit van de wervelkolom is een kenmerk van axiale SpA en voorspelt een slechte prognose op lange termijn. In **Hoofdstuk 4** hebben we aangetoond dat een beperking van deze spinale mobiliteit bij patiënten met AS onder meer wordt bepaald door onomkeerbare schade aan de wervelkolom en door ontsteking van de wervels.

In **Hoofdstuk 5** hebben we de onderlinge samenhang tussen verschillende AS-uitkomsten in detail bestudeerd en hebben we een model voorgesteld dat de gezondheid bij patiënten met axiale SpA beter verklaart. Volgens dit model wordt 'kwaliteit van leven'

verklaard door 'fysiek functioneren' en door 'ziekteactiviteit';, 'fysieke functioneren op zijn beurt door 'spinale mobiliteit' en 'ziekteactiviteit'; en 'spinale mobiliteit' wordt verklaard door 'structurele schade' en 'ontsteking van de wervelkolom' (**Hoofdstuk 4**).

In **Hoofdstuk 6** hebben we aangetoond dat ontsteking te zien op MRI van de wervelkolom beter correleert met de ontstekingsmaat CRP (in het bloed) dan met andere maten van ziekteactiviteit. MRI-ontsteking correleert ook met de ASDAS (waarin CRP immers is opgenomen). Bovendien ging een verbetering van MRI-ontsteking samen met verbeteringen in CRP en ASDAS en werd bij patiënten met hogere CRP of ASDAS-waarden bij de start van de studie méér verbetering van MRI-ontsteking gedurende de studie gezien. Belangrijk is verder dat andere maten van ziekteactiviteit, met name die maten die door de patiënt worden gerapporteerd (bv. BASDAI), niet correleerden met MRI-ontsteking.

Bespreking

Gegevens in **Hoofdstuk 4** suggereren dat de aan-of afwezigheid van ontsteking in de wervelkolom zou kunnen verklaren waarom spinale mobiliteit zo matig samenhangt met radiologisch gemeten schade van de wervelkolom: Spinale mobiliteit werd het meest beïnvloed door spinale ontsteking bij patiënten met vroege ziekte en het meest door aanwezige structurele schade bij patiënten met meer gevorderde ziekte, wat suggereert dat een acceptabele spinale mobiliteit wellicht kan worden onderhouden door een vroegtijdige behandeling. Omdat deze studie heeft aangetoond dat er een belangrijke bijdrage van het ontstekingsproces zelf (en niet alleen de structurele schade) aan het verminderen van spinale mobiliteit is, heeft deze studie een nieuwe betekenis gegeven aan het belang van MRI-ontsteking bij patiënten met axiale SpA.

Ons model legt fraai uit waarom een optimale behandeling van axiale SpA zich zou moeten richten op meerdere aspecten van de ziekte, niet alleen middels geneesmiddelen gericht tegen ontsteking (zoals niet-steroïdale anti-inflammatoire geneesmiddelen (NSAID's) en anti-TNF-therapie) maar ook middels therapieën die meer specifiek gericht zijn op de spinale mobiliteit (zoals fysiotherapie) en op progressie van structurele schade (mogelijk hebben de hiervoor genoemde NSAIDs een beschermend effect).[1,23-25] De samenhang tussen verschillende uitkomstmaten die we hier hebben beschreven kan voorts dienen als startpunt voor toekomstige studies waarbij diezelfde samenhang moet worden onderzocht op basis van *veranderingen* in de tijd.

De gegevens die in **Hoofdstuk 6** worden gepresenteerd bieden ons meer inzicht in de relatie tussen klinische ziekteactiviteit en MRI-ontsteking, ook al omdat de behandelingsrespons in samenhang met veranderingen in MRI-ontsteking na behandeling met TNF-blokkers werd geëvalueerd. We hebben geconcludeerd dat ASDAS het ontstekingsproces bij AS beter weerspiegelt dan BASDAI. Door het CRP

alsmede door de patiënt gerapporteerde maten op te nemen in de formule voor ASDAS, weerspiegelt de ASDAS zowel objectieve als subjectieve aspecten van de ziekte. Desalniettemin correleren ook CRP en ASDAS slechts matig met MRI-ontstekingsscores. We hebben aangetoond dat de verschillende metingen van ziekteactiviteit (ASDAS en MRI-ontsteking) een aanvullende waarde hebben bij patiënten met axiale SpA.

Verschillen in de klinische presentatie van axiale SpA

In **Hoofdstuk 7** was ons doel om de invloed van HLA-B27-status op de fenotypische variabiliteit (dat wil zeggen: verschillen in klinische verschijnselen en bij beeldvormend onderzoek) van axiale SpA. De resultaten bevestigden dat HLA-B27 de manifestaties van axiale SpA in belangrijke mate 'stuurt' . We zagen dat de aanwezigheid van HLA-B27 is geassocieerd met een vroegere beginleeftijd van inflammatoire rugpijn en met een snellere diagnose ('diagnostische marker'). Daarnaast bleek dat HLA-B27 samenhangt met de aanwezigheid van met MRI-ontsteking (van wervelkolom en sacro-iliacale [SI] gewrichten). Het lijkt er op dat MRI-ontsteking van de SI-gewrichten voorafgaat aan radiologische sacro-iliitis, en dan vooral bij HLA-B27-positieve patiënten.

In **Hoofdstuk 8** hebben we getracht om de impact van roken op de ziekte te onderzoeken. We vonden dat bij jonge SpA-patiënten met een relatief korte ziekteduur rokers op jongere leeftijd last kregen van inflammatoire rugpijn, meer ziekteactiviteit hadden, meer axiale MRI-ontsteking en meer structurele schade, alsmede een slechtere functionele status en minder kwaliteit van leven.

In **Hoofdstuk 9** hebben we AS-patiënten met en zonder psoriasis met elkaar vergeleken. We vonden dat demografische eigenschappen, ziekteactiviteit, spinale mobiliteit, fysieke functie, structurele schade en levenskwaliteit vergelijkbaar waren.

Bespreking

HLA-B27-positieve en HLA-B27-negatieve patiënten verschillen van elkaar in klinische presentatie en met betrekking tot uitkomsten van beeldvormend onderzoek. In oudere studies van patiënten met een langere symptoomduur dan de onze[26,27] werd ook een verband gerapporteerd tussen HLA-B27 en een vroege beginleeftijd van de ziekte. Onze analyses van het beeldvormend onderzoek hebben voor nieuwe en interessante bevindingen gezorgd: HLA-B27-positiviteit is geassocieerd met MRI-ontsteking van de SI-gewrichten en de wervelkolom, en MRI-ontsteking van de SI gewrichten is geassocieerd met radiologische sacroiliitis. HLA B27 draagt dus niet alleen bij aan ontsteking van SI-gewrichten, maar ook aan structurele schade, en MRI-ontsteking van de SI-gewrichten fungeert daarbij als 'tussenstap' tussen HLA-B27 en structurele schade. Opmerkelijk was dat ASDAS-CRP positief geassocieerd is met MRI-ontsteking van de wervelkolom, terwijl BASDAI eigenlijk niet geassocieerd is met MRI-ontsteking van de SI. Al deze resultaten dragen ertoe bij dat ASDAS-CRP heden ten dage kan

worden beschouwd als de beste maat voor klinische ziekteactiviteit bij patiënten met vroege axiale SpA.

Het schadelijke effect van roken op parameters van ziekteactiviteit bij patiënten met AS werd al vermeld in eerdere studies en werd door ons bevestigd bij patiënten in een vroege fase van de ziekte. Nieuw is dat we we een nieuw verband hebben aangetoond tussen roken en de aanwezigheid van MRI-ontsteking. Op röntgenfoto's werd roken alleen geassocieerd met schade van de wervelkolom maar niet met schade van de SI-gewrichten.

De analyses van patiënten met en zonder psoriasis passen in een breed palet van studies die verricht zijn bij heterogene populaties van patiënten (patiënten met vroege inflammatoire rugpijn, met axiale artritis psoriatica, en patiënten met AS-patiënten) en tegenstrijdige resultaten hebben opgeleverd.[28-33] Een van de voordelen van ons onderzoek is het grote aantal ziektevariabelen dat we bestudeerd hebben. Wij onderzochten een populatie met AS maar toekomstige studies moeten zich richten op het gehele spectrum van patiënten met axiale SpA, met inbegrip van patiënten met niet-radiologische SpA.[34] Dit onderwerp werd ook door andere auteurs in het DESIR-cohort onderzocht.[35] In deze recentere studie werd psoriasis geassocieerd met actievere axiale ziekte en het gelijktijdig optreden van enthesitis en dactylitis. Het bestuderen van de verschillen tussen patiënten met- en zonder specifieke extra-articulaire manifestaties (met name verschillen met betrekking tot behandelingsrespons en geassocieerde co-morbiditeiten) kan ons verder helpen om patiënten beter in te delen en de behandelingen meer te individualiseren. Verschillen in de doelmatigheid van TNF-blokkers met betrekking tot de behandeling van extra-articulaire manifestaties werden al beschreven). Recent zijn er nieuwe therapieën ontwikkeld voor de behandeling van axiale SpA, die zich richten op het remmen van IL-23/IL-17, in plaats van direct op het remmen van TNF-alfa, en die licht kunnen werpen op het belang van verschillende aangrijpingspunten. Wellicht bepaalt bijvoorbeeld de aanwezigheid van sommige extra-articulaire manifestaties op welke vorm van therapie bij een individuele patiënt de beste respons te verwachten is.

Dergelijke ontwikkelingen kunnen bijdragen aan een meer op de persoon gerichte behandeling, met een grotere kans op succes en een kleinere kans op bijwerkingen.

Samenhang tussen MRI-laesies en radiologische progressie in axiale SpA

In **Hoofdstuk 10** hebben we aangetoond dat MRI-ontsteking in een wervelunit (bestaande uit de onderkant van een bovenliggende wervel, de hieronder liggende kraakbeenschijf en de bovenkant van de onderliggende wervel) de kans op een nieuw syndesmofiet (botaangroei in de wervel die kan leiden tot verbening en overbrugging van wervels) op dezelfde plek na twee jaar vergroot. De meeste nieuwe syndesmofieten

ontstonden echter in wervels zonder enig teken van MRI-ontsteking, hetgeen aangeeft dat de relatie tussen MRI-ontsteking en syndesmofiettvorming nog steeds onvolledig wordt begrepen.

In **Hoofdstuk 11** hebben we bevestigd dat MRI-ontsteking is geassocieerd met radiologische progressie bij patiënten met AS, en hebben we aangetoond dat vetdepositie op MRI op precies dezelfde plaats in de wervel waar ook ontsteking optreedt eveneens geassocieerd is met radiologische progressie. De combinatie van vetdepositie en ontsteking, al dan niet op hetzelfde tijdstip, verhoogt de kans op radiologische progressie. En vetdepositie in de wervelhoek lijkt soms (maar niet altijd) te worden voorafgegaan door ontsteking op die plaats. Wij vonden dat als deze sequentie achtereenvolgens optrad, de kans op radiologische progressie het grootst was. Echter, veel syndemofieten ontstonden zonder voorafgaande ontsteking of vetdepositie zodat kan worden geconcludeerd dat het proces van syndesmofietvorming nog steeds niet volledig wordt begrepen.

Bespreking

Toen we begonnen met de analyses in **Hoofdstuk 10** waren er twee studies gepubliceerd die een statistisch verband aantoonden tussen MRI-ontsteking en syndesmofiet-vorming na 2 jaar follow-up.[36,37] Onderzoek door Pedersen et al.[38] suggereerde vervolgens dat wervels met ontsteking meer geneigd zijn tot syndesmofiet vorming dan wervels zonder ontsteking. Gesuggereerd werd dat syndesmofieten zich vaker ontwikkelen in wervels waar de ontsteking is opgelost dan in wervels waar de ontsteking aanhoudt.[37,38,39-41]

In het licht van de controverse rond dit thema, en op basis van de gegevens die zijn gepubliceerd nadat we de analyses die beschreven werden in **Hoofdstuk 10** hadden uitgevoerd, hebben we getracht de associatie tussen ontsteking en nieuwe botvorming uit te breiden met onderzoek naar de relatie tussen MRI-ontsteking en vetdeposities in wervels, en de daaropvolgende syndesmofietvorming.

We hebben ons gericht op de hypothese dat ontsteking van de wervelhoek leidt tot vetopslag die op zijn beurt leidt tot syndesmofiet, en we hebben deze sequentie inderdaad kunnen bevestigen.

Het is interessant om deze resultaten te bespreken in het licht van de vraag of TNF-blokkers de progressie van structurele schade bij patiënten met axiale SpA kunnen remmen.. Initiële onderzoeksgegevens hebben gesuggereerd dat TNF-blokkers geen effect hebben op radiologische progressie in de wervelkolom.[42-44] Recente observationele studies hebben echter juist een beschermend effect van TNF-blokkers gesuggereerd.[45,46] Echter, deze observationele studies hebben belangrijke methodologische beperkingen en het vraagstuk blijft vooralsnog onopgelost.[25] Onze observatie dat de sequentie

'ontsteking → vetdepositie' vooruitloopt op nieuwe botvorming bij axiale SpA zou kunnen impliceren dat behandeling met TNF-blokkers beschermt tegen syndesmofietvorming in onaangetaste wervels, omdat de ontsteking van die wervels wordt voorkomen, maar niet in wervels die al ontsteking en/of syndesmofieten hebben (waarin immers het proces reeds in gang is gezet). IN theorie zou een behandeling met TNF-blokkers zelfs tot syndesmofietvorming kunnen leiden door de abrupte onderdrukking van de ontsteking en het ingang zetten van een proces van vetdepositie gevolgd door botnieuwvorming. Deze uitleg is zonder twijfel een vereenvoudiging van de werkelijkheid omdat de biologische effecten van TNF-blokkers niet beperkt zijn tot onderdrukking van de ontsteking en TNF-blokkers inderdaad ook direct (dat wil zeggen: zonder ontsteking) zijn geassocieerd met botnieuwvorming bij dieren.[47]

Interessante klinische vragen voor de toekomst zijn hoe MRI kan worden geïncorporeerd in toekomstige klinische wetenschappelijk onderzoek; of MRI-criteria van belang is voor 'treat-to-target' behandelingsstrategieën; en of middelen met andere werkingsmechanismen andere effecten hebben op de ontsteking, vetdepositie en syndesmofietvorming. Studies met meer tijdspunten en kortere intervallen tussen de tijdspunten kunnen helpen om de relatie tussen ontsteking en syndesmofiet vorming verder op te helderen.

Ter afsluiting

In het onderzoek beschreven in dit proefschrift hebben we heel veel data bestudeerd die iets zeggen over manifestaties van de ziekte axiale SpA. De resultaten van dit klinisch onderzoek leiden waarschijnlijk tot aanvullend onderzoek in het veld, met het onderzoek naar de effecten van roken als relevant voorbeeld. Onze gedetailleerde analyses naar de relatie tussen MRI-ontsteking, vetdepositie en syndesmofietvorming behoren tot de meest omvangrijke en robuuste op hun gebied gezien de uitzonderlijk grote patiëntenpopulatie, de methode van scoren (onafhankelijk, zonder voorkennis en onpartijdig), de evaluatie op meerdere tijdsstippen en de gehanteerde analysemethodiek. Kortom, onze studies hebben bijgedragen tot een beter begrip van de ziekte axiale SpA.

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CURRICULUM VITAE

Pedro Machado was born on the 2nd of August 1978 in Porto, Portugal. He studied Medicine at the University of Coimbra in Portugal and obtained his medical degree in October 2002. He obtained his MSc in Rheumatology at the same University in November 2010 (title of the thesis: 'Performance of osteoporosis risk assessment tools in Portuguese postmenopausal women: a cost-effectiveness analysis'). He trained in Rheumatology at the Department of Rheumatology of Coimbra University Hospital, in Coimbra, Portugal. As part of his training he did a 3-month rotation in musculoskeletal rehabilitation at the Royal National Orthopaedic Hospital, in Stanmore, London, United Kingdom (UK), another 3-month rotation in neuromuscular diseases at the National Hospital for Neurology and Neurosurgery, in London, UK, and a 6-month rotation in clinical research at the Department of Rheumatology of Leiden University Medical Centre (LUMC), in Leiden, The Netherlands. This rotation at the LUMC was instrumental for him to choose a clinical academic career and undertake the research work that resulted in this thesis at the same institution, focusing on the assessment (including imaging assessment) and prediction of outcomes in axial spondyloarthritis. He obtained his specialist accreditation in Rheumatology in Portugal (2013) and in the UK (2014). He has (co)-authored 70 articles (original articles, reviews and editorials) and 2 book chapters. He has been awarded 4 fellowships and 11 scientific prizes. He is currently a National Institute for Health Research (NIHR) Researcher & Honorary Consultant Rheumatologist at University College London and University College London Hospitals, in London, UK.

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