Assessing disease activity and response to treatment in axial spondyloarthritis: The unmet clinical need and potential role for quantitative imaging

A thesis for the degree of Doctor of Medicine

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Declaration

I, Alexis Jones, confirm that the work presented in this thesis is my own. Where information has been retrieved from other sources, this has been indicated in the thesis.

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Abstract

Background

Objective assessments of disease activity and response to treatment in axial spondyloarthritis (axSpA) remain an area of unmet clinical need. Quantitative magnetic resonance imaging (qMRI) offers potential for more accurate measures of disease activity and therapeutic response.

Purpose

To critically appraise current methods of disease activity in axSpA and determine the responsiveness and validity of quantitative imaging biomarkers (QIBs) in patients with axSpA undergoing biologic therapy.

Methods

An observational cohort study was carried out to assess the specificity of our current disease activity measure on patients with axSpA. A systematic literature review was performed to assess the use of MRI in the assessment of axSpA. A prospective cohort study was carried out on 30 patients with axSpA undergoing biologic therapy or switching biologic therapy. Conventional and qMRI scans, including diffusion-weighted imaging (DWI) and chemical shift-encoded imaging (CSI) were carried out at baseline and after 12-16 weeks of treatment. Apparent diffusion coefficient (ADC) and proton density fat fraction (PDFF) maps were analysed using the partially-automated Bone Edema and Adiposity Characterisation with Histograms (BEACH) tool, which derives a series of quantitative imaging biomarkers (QIBs) for both ADC and PDFF. Conventional MR images were

assessed using established visual scoring methods. QIBs were assessed in terms of change after treatment and correlation with clinical and conventional MRI measures of disease activity.

Results

Current disease activity measures are not specific to axSpA and can be increased in a number of other spinal pathologies. ADC biomarkers are sensitive to changes in inflammation and show significant reductions following biologic therapy, while PDFF-based QIBs showed nonsignificant reductions. Responsiveness to therapy was moderate for ADC based biomarkers and small for conventional scoring systems. ADC and PDFF correlated well with conventional MRI scoring methods.

Conclusion

Quantitative MRI offers promise for a more accurate assessment of disease activity in axSpA.

Impact Statement

Precision medicine, that is the tailoring of medical treatment to the individual characteristics of each patient, has become a key objective in modern healthcare. Robust measures of disease activity form an essential component of precision medicine by providing an accurate assessment of patients' disease burden and their individual response to treatment. Current disease activity measures in axSpA rely on patient reported measures of pain, stiffness and fatigue. These are subjective and distorted by concomitant conditions such as chronic pain and/or mechanical spinal issues. There is a clear need for improvements in our assessment of axSpA to allow for accurate and objective measures of disease activity.

Whilst biologic therapy has revolutionised the treatment of axSpA, these are high cost drugs: In 2015/16, the NHS spent over £250 million on Adalimumab alone (Commissioning framework for biologic medicines Sept 2017). Furthermore, these medications are associated with increased risk of serious infections as well as infusion and allergic reactions. Clinicians need to be sure patients are eligible for these medications and have the confidence to start (and stop) treatment to avoid unnecessary expense and patient risk.

In this thesis, I highlight the limitations of our current disease activity measures in axSpA. I show that patients with axSpA want more accurate measures of their disease activity, which do not rely on questionnaires. I demonstrate the role of MRI and, specifically, qMRI for the future of disease monitoring in axSpA. I show that qMRI, that is MRI scans which translate tissue attributes such as cellularity, vascularity or fat content into a numerical

value, show significant response to treatment in axSpA and correlate well with conventional MRI scoring systems. Whilst this is a small pilot study, it highlights the scope of qMRI to improve our assessment of axSpA both for initiation of biologic treatment and assessment of response.

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List of Abbreviations

AI	artificial intelligence
AS	ankylosing spondylitis
ASDAS	ankylosing spondylitis disease activity score
ASspiMRI-a	ankylosing spondylitis spine magnetic resonance imaging score for activity
ADC	apparent diffusion coefficient
AIBD	arthritis associated with inflammatory bowel disease
ASAS	Assessment of Spondyloarthritis International Society
axSpA	axial spondyloarthritis
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
BASMI	Bath ankylosing spondylitis metrology index
BEACH	Bone oedema and adiposity characterisation with histograms
BMO	bone marrow oedema
BHPR	British health Professionals in Rheumatology
BSR	British Society for Rheumatology
CRP	c reactive protein
CS-MRI	chemical shift encoded magnetic resonance imaging
CWP	chronic widespread pain
DAS	disease activity score
DWI	diffusion weighted imaging
DVU	disco-vertebral unit
ER	endoplasmic reticulum
ERAP	endoplasmic reticulum aminopeptidase
ESR	erythrocyte sedimentation rate
EMA	European Medicines Agency
EPR	Electronic patient records
ESSG	European Spondyloarthropathy Study Group

EULAR	European League Against Rheumatism
FM	fibromyalgia
GWAS	genomic wide association studies
HLA	human leucocyte antigen
HLA	human leucocyte antigen
IBD	inflammatory bowel disease
IL	interleukin
JAK	janus kinase
KIR	killer-immunoglobulin-like receptors
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
mSASS	modified Stoke Ankylosing Spondylitis Spine Score
MSK	musculoskeletal
NASS	National Ankylosing Spondyloarthritis Society
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NK	natural killer
nr-axSpA	non-radiographic axial spondyloarthritis
NSAIDs	non-steroidal anti-inflammatories
OMERACT	outcome measures in rheumatology
PROMS	patient reported outcome measures
PDFF	proton density fat fraction
PsA	psoriatic arthritis
PPI	public and patient involvement
QIB	quantitative imaging biomarkers
qMRI	quantitative magnetic resonance imaging
RA	rheumatoid arthritis
RCT	randomised controlled trial
ReA	reactive arthritis
RMP	reference medicinal product
RoB	risk of bias

SE	sensitivty
STIR	short tau inversion recovery
SIJ	sacroiliac joint
SPARCC SSS	Spondyloarthritis Research Consortium of Canada structural score
SP	specificity
SpA	spondyloarthritis
SSS	spondyloarthritis structural score
SPARCC	Spondyloarthritis Research Consortium of Canada
TNF	tumour necrosis factor
UCLH	University College London Hospital
uSpA	undifferentiated spondyloarthritis
VAS	visual analogue score
WPAI	work productivity and activity impairment questionnaire
WHO	World Health Organisation

1 Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease, predominately affecting the spine and sacroiliac joints (SIJs) leading to pain, damage and disability. Two key areas of research have been central to our progress in the management of axSpA; namely, the development of biologic therapies and the use of magnetic resonance imaging (MRI).

Historically, axSpA has been associated with long delays in diagnosis; with an average of 8-10 years between onset of back pain to diagnosis by a rheumatologist[123]. This delay can be attributed to the ubiquity of back pain in the general population, the difficulties distinguishing inflammatory from mechanical back pain by the general practitioner and the absence of blood and imaging biomarkers for the disease. Historically, plain films have been used for diagnosis[4], however, radiographic lesions often manifest long after the onset of symptoms. The recognition that inflammatory lesions could be detected on magnetic resonance imaging (MRI) prior to any changes on plain radiographs[5], has led to the earlier detection of axSpA and, therefore, initiation of treatment.

Treatment in the form of biologic therapies, including anti-tumour necrosis factor (TNF) and, more recently, anti-interleukin (IL) 17A, herald a new era in the management of axSpA - a disease which was previously considered to be untreatable. Although biologic drugs are not a first line treatment option in axSpA, they are highly effective following lack of or incomplete response to physiotherapy and non-steroidal anti-inflammatory drugs (NSAIDs).

Whilst there have been significant advances in our ability to diagnose and treat axSpA, accurate measures of disease activity and response to treatment are an area of unmet clinical need. Robust measures of disease activity are not only essential for optimal care of patients but also support the development of novel therapeutic targets in clinical trials. Currently, we rely on patient reported measures of pain, stiffness and fatigue. Whilst these indices provide important information, they are subjective and distorted by associated conditions such as chronic pain and/or mechanical spinal issues. Biochemical parameters such as erythrocyte sedimentation rate (ESR) and c reactive protein (CRP) have been incorporated into recent indices of disease activity, however, they are less sensitive in axSpA compared with other rheumatic diseases. MRI scoring systems have been developed for axSpA, however, these are not applicable to routine clinical practice and their relationship with other parameters of disease activity has produced conflicting results.

Quantitative MRI incorporates a succession of scans which probe tissue characteristics and infer attributes such as cellularity, vascularity or fat content. Each picture element (pixel) in a qMRI image has a measurable numerical value that reflects the intrinsic properties of a tissue, rather than arbitrary signal intensity produced by standard MRI. The application of this techniques to patients with axSpA could provide more information on bone marrow pathophysiology and potentially provide a more robust assessment of disease activity and response to treatment.

The aim of this thesis is to review our current assessments of disease activity in axial spondyloarthritis, investigate potential biomarkers and, specifically, look at the use of MRI and qMRI as a novel imaging biomarker of disease activity and assessment of response to treatment in axSpA.

Research Hypothesis:

Quantitative imaging biomarkers (QIBs) correlate with clinical and conventional MRI measures of disease activity in axial spondyloarthritis and are sensitive to change after treatment with biological therapy.

In chapter 2, I review the pathogenesis, diagnosis and management of axSpA. I address the limitations of our current disease activity scores and discuss the complex symptom of pain in our assessment of disease activity in axSpA. In Chapter 3, I investigate the specificity of our most utilised disease assessment tool in axSpA, the Bath ankylosing spondylitis disease activity index (BASDAI), in an observational cohort study. In chapters 4 and 5, I review current MRI techniques and scoring systems for axSpA, before addressing the potential role of qMRI. As part of my research, I was eager to understand patient views on disease monitoring in axSpA. I organised two Public and Patient Involvement (PPI) events at UCLH to explore this. These are described in Chapter 6. The main body of my research (Chapter 7) investigates the use of qMRI in patients with axSpA undergoing biologic therapy. Carrying out qMRI scans before and three months after biologic therapy in patients with active axSpA, I look at the sensitivity of this tool to change and whether it can predict response to treatment. The final chapter of this thesis (Chapter 8) reviews the

potential application of my research to clinical practice and explores future research in imaging and axSpA.

2 Background

2.1 Overview

This chapter provides an overview of the classification, pathogenesis, clinical course and management of axial spondyloarthritis; as well as an analysis of current disease activity measures and biomarkers for the disease.

2.2 The Spondyloarthropathies

2.2.1 Background

Spondyloarthritis (SpA) encompasses a heterogeneous group of diseases which share common genetic, clinical and radiographic features. They are one of the most common varieties of inflammatory rheumatic disorders with an estimated prevalence of 0.1% to 1.4%[6]. SpA is characterised by the presence of spinal inflammation, peripheral arthritis, enthesitis, anterior uveitis and an association with human leucocyte antigen (HLA) B27.

Historically, there are five major subtypes of SpA: Ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), enteropathic or arthritis associated with inflammatory bowel disease (AIBD) and undifferentiated SpA (uSpA)(Figure 2-1). Owing to the degree of clinical overlap within these groups, the Assessment of Spondyloarthritis International Society (ASAS) established a classification of SpA based on the predominant clinical manifestations: axial (inflammatory back pain, sacroiliitis) versus peripheral (enthesitis and arthritis) SpA[7] (Figure 2-2).

The role of magnetic resonance imaging (MRI) in the detection of early inflammatory lesions in axial spondyloarthritis (axSpA) resulted in the subdivision of axSpA into two groups: Non-radiographic axSpA (nr-axSpA) and radiographic axSpA or AS. Non-radiographic SpA includes those patients with evidence of sacroiliitis on MRI but no clear structural damage on X-rays of the sacroiliac joints. Radiographic axSpA incorporates the prototype disease, AS, and includes patients with structural damage on conventional x-rays including radiographic sacroiliitis and/or syndesmophytes in the spine (Figure 2-7).

Figure 2-1 The Spondyloarthropathies

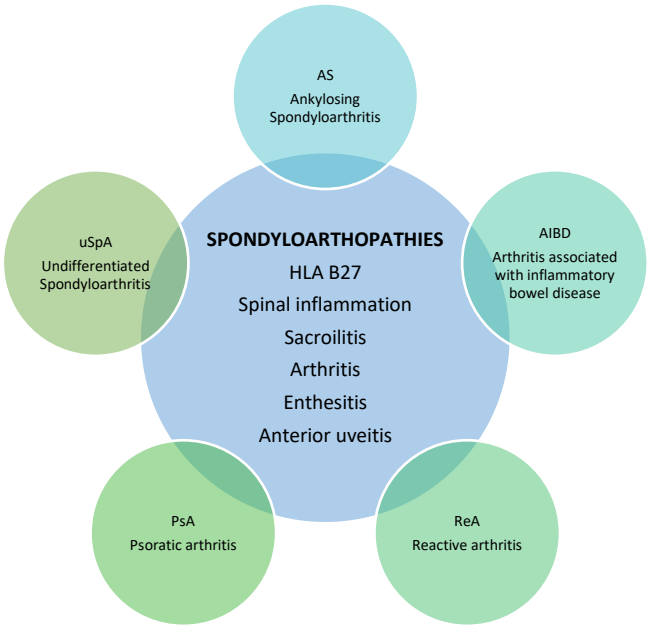
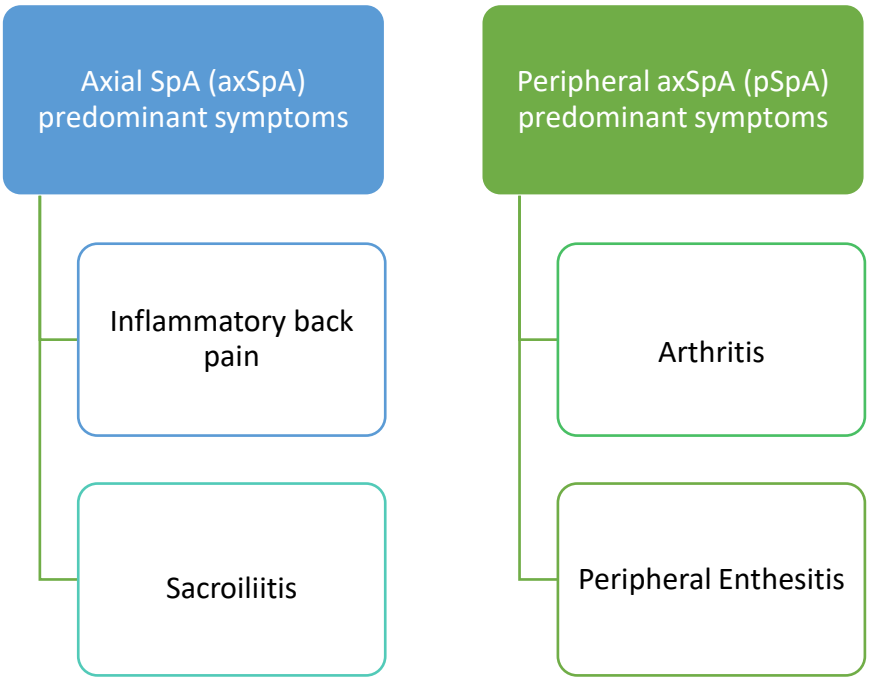


Figure 2-2 Axial versus peripheral spondyloarthritis



One of the main aims of the ASAS criteria was to encourage early detection of SpA, enabling earlier treatment of the disease and a subsequent reduction in morbidity. Although there has been a modest improvement with the wider use of MRI and implementation of ASAS criteria, time to diagnosis in axSpA compared with peripheral inflammatory arthritis, such as rheumatoid arthritis (RA), remains significantly worse [1–3]. It should be noted that the ASAS criteria are classification criteria, created for the purpose of identifying patient groups sharing similar clinical characteristics intended for the purpose of research. These are not diagnostic criteria – these will be discussed in later chapters.

2.2.2 Epidemiology

The global prevalence of axSpA ranges between 0.1% and 1.4%[6]. Geographic differences can partly be explained by the prevalence of the HLA B27, which is strongly associated with the development of axSpA[8]. The highest prevalence of HLA B27 is found in the Pawaia tribe in Papua New Guinea (53%)[9], followed by the Haida indigenous Americans in Western Canada (50%)[10]. In contrast, the lowest prevalence of HLA B27 positivity has been described in Japan (approximately 1%)[11].

There are limited studies evaluating the incidence of axSpA. A study published in 2005 showed an annual incidence rate of SpA in Norway of 7.26 per 100,000 patient years between 1960 and 1993[12]. In Canada, Haroon et al [13] conducted a retrospective analysis of provincial health administrative databases for residents of Ontario aged 15 or older with AS between 1995 and 2010. They found the incidence to be 14-15 per 100,000 patient years. Gerisson et al [13] performed a nationwide screening of hospital records and private

rheumatology services in Iceland for cases of AS in association with an ongoing genetic study. They reported an annual incidence from for 1947 to 2005 to be 0.44 to 5.48. Historically, AS has been regarded as a disease with a predilection for men. Male to female prevalence ratios have previously reported at 10:1[14]. Subsequent studies show that this ratio is closer to 3:1[15–17]. A study in Switzerland, reports a steady decline in the male-female ratio among patients with AS/axSpA from 2.57:1 in 1980, down to 1.03:1 by the end of 2016[18] and minimal gender difference has been found in the prevalence of nr-axSpA [19–21].

2.2.3 Clinical features and classification

The pathognomonic feature in peripheral and axSpA is inflammation at the insertion of tendon, ligament, joint capsule, or fascia to bone (enthesitis). In axSpA, enthesitis of the spine and sacroiliac joints (SIJs) leads to symptoms of inflammatory back pain which manifest as nocturnal wakening, early morning stiffness and improvement with movement; and buttock pain in the case of sacroiliitis. Patients may also have symptoms of peripheral enthesitis, arthritis (typically a large joint, asymmetrical oligo arthritis), dactylitis and/or anterior uveitis.

In the 1970s, the first set of diagnostic criteria was proposed to identify patients with AS. This was subsequently updated in 1984 to form the Modified New York criteria (mNY)[22] (Figure 2-3). Patients had to present with structural damage (radiographic sacroiliitis) and symptoms and signs of inflammatory spinal disease. These criteria were used for over 25 years for clinical studies, including clinical trials with biologics agents.

Figure 2-3 Modified New York Criteria for ankylosing spondylitis (1984)

Clinical criteria:

Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest.

Limitation of motion of the lumbar spine in the sagittal and frontal planes.

Limitation of chest expansion relative to normal values correlated for age and sex.

Radiological criterion:

Sacroiliitis grade ⩾2 bilaterally or grade 3–4 unilaterally.

Definite AS if the radiological criterion is associated with at least one clinical criterion

The Amor Classification Criteria for Spondyloarthropathy[23] and the European Spondyloarthropathy Study Group (ESSG) Classification Criteria for Spondyloarthropathy[24] were developed in the early 1990s in order to include patients with undifferentiated SpA who would not otherwise meet the Modified New York 1984 Diagnostic Criteria. The Amor criteria included, for the first-time, peripheral features and a good response to NSAIDs. Radiographic sacroiliitis was not mandatory (Figure 2-4).

Figure 2-4 Amor criteria for ankylosing spondyloarthritis

Inflammatory back pain	1 pt	Non GC GU infection	1 pt
Unilateral back pain	1 pt	Acute diarrheal illness	1 pt
Alternating buttock pain	2 pts	Psoriasis, Balanitis, IBD	2 pt
Enthesitis	2 pts	Sacroiliitis on x-ray	3 pt
Peripheral arthritis	2 pts	HLA B27+ or FH of SpA	2 pt
Dactylitis	2 pts	Good response to NSAIDs	2 pt
Acute anterior uveitis	2 pts		
Diagnosis of SpA if the sum of positive criteria ≥ 6 points			

GC gonococcal, GU genitourinary, HLA Human Leucocyte antigen, IBD inflammatory bowel disease, FH family history, NSAIDS Non-steroidal anti-inflammatories, SpA Spondyloarthritis

The European Spondyloarthropathy Study Group (ESSG) classification criteria for spondyloarthropathy (Figure 2-5) were designed with a hierarchy framework: Inflammatory spinal pain or synovitis must be present before any other criteria can be considered. The secondary criteria include sacroiliitis by plain radiography and positive family history of SpA in a 1st or 2nd degree relative with AS, psoriasis, acute uveitis, ReA or IBD. The presence of HLA-B27 is not on the criteria.

Figure 2-5 The European Spondyloarthropathy Study Group (ESSG) Classification Criteria for Spondyloarthropathy

Inflammatory spinal pain ***and one of the following***

- Positive family history of SpA
- Psoriasis
- Inflammatory bowel disease
- Urethritis, cervicitis or acute diarrhoea < 1 month before arthritis
- Alternating buttock pain
- Enthesitis
- Sacroiliitis by plain radiography

A universal feature of all these criteria is the inclusion of inflammatory back pain. Therefore, the definition of inflammatory back pain is a critical component of any diagnostic or classification criteria for axSpA. Inflammatory back pain has been defined with various clinical criteria over the past 40 years. However, the Calin criteria for Inflammatory Back Pain (Figure 2-6) have been the most frequently used and are the basis of the definition of inflammatory spinal pain and the ESSG classification criteria for spondyloarthropathy.

Figure 2-6 Calin criteria for Inflammatory back pain

1. Insidious onset
2. Patient younger than 40 years
3. Persisting for at least 3 months
4. Associated with morning stiffness
5. Improving with exercise

Presence of 4 of 5 features is 95% sensitive and 85% specific

In 2009, an international group of experts, the Assessment of Spondyloarthritis International Society (ASAS,) revised the classification criteria for SpA[25], to promote earlier recognition of the disease by including MRI abnormalities and an abnormal CRP level for the first time. This approach led to the classification criteria for SpA, both for axial and peripheral presentations (Figure 2-7) and the division of axSpA into radiographic and non-radiographic.

Figure 2-7 ASAS Classification criteria for axial spondyloarthritis (in patients with back pain for a duration of ≥ 3 months and age at onset <45 years)

Axial spondyloarthritis		
Sacroiliitis on imaging* plus ≥ 1 SpA feature**	OR	HLA-B27 plus ≥ 2 other SpA features**

***Sacroiliitis on imaging:** Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA or Definite radiographic sacroiliitis according to mod. New York criteria

****SpA features:** Inflammatory back pain, Arthritis, Enthesitis (heel), Uveitis, Dactylitis, Psoriasis, Crohn's disease/ulcerative colitis, Good response to NSAIDs, Family history for SpA, HLA-B27, Elevated CRP

2.3 Pathogenesis

2.3.1 Genetics

Twin studies have shown that AS is highly heritable, with 90% of the risk thought to be due to genetic variation[26]. HLA B27 is a major histocompatibility complex class I (MHC I) molecule found in 80-90% of patients with AS versus 8-10% in the Caucasian population[27]. MHC I molecules are important for the initiation and propagation of immune responses.

The classical heterotrimeric MHC I molecule is composed of three non-covalently bound individual polypeptides: A highly polymorphic heavy chain, β2-microglobulin light chain and an oligopeptide, typically 8 to 10 residues in length[28].

The association between HLA B27 and AS remains one of the strongest of any common genetic variants within a human disease. Despite over 40 years of extensive research, the functional role of HLA B27 in the pathogenesis of SpA remains unclear. Three major theories have been proposed: The arthritogenic peptide theory, the misfolded HLA B27 hypothesis and the cell surface homodimers hypothesis.

One of the primary roles of HLA B27 is to bind with peptides in the endoplasmic reticulum (ER) and transport them to the cell surface where they are presented to the immune system. These peptides are often self-proteins and so HLA B27 is ignored by the immune system. The arthritogenic peptide theory proposes that HLA B27 may present peptides from microbial antigens to cytotoxic CD8+ T cells. These CD8+ cells, then recirculate and are activated in the joint by cross-reacting cartilage antigens. This hypothesis is supported by the identification of CD8+ T cell responses to both microbial antigens and self-antigens in patients with axial spondyloarthritis [29].

The observation that HLA B27 can misfold in the ER[30] has led to the misfolded HLA B27 theory. The theory supposes that misfolding of HLA B27 leads to ER stress, which in turn triggers a protein response and upregulation of IL 23 in dendritic cells. IL 23 has been found to be a significant cytokine in the inflammatory cascade in axSpA. This theory is

supported by the finding that in transgenic rats, HLA B27 misfolding in macrophages leads to upregulation of IL-23 [31].

The homodimers hypothesis is based on the ability of HLA B27 to aberrantly form homodimers. These aberrant forms of HLA B27 can be recognized by killer-immunoglobulin-like receptors (KIR). These receptors are predominately found on natural killer (NK) cells, but also CD4+ T cells. HLA B27 individuals with AS and HLA B27 healthy donors have been found to have a higher frequency of CD4+ T cells expressing this receptor. These cells are polarized towards a helper T cell 17 phenotype, which produce high levels of IL-17A, an important inflammatory cytokine in axSpA[32]

The HLA association of AS has turned out to be far more complex than originally thought. Analysis of HLA genes has demonstrated that in addition to HLA B27, associations with multiple other HLA risk alleles exist. Recent large scale HLA studies, have shown risk associations with HLA B13, B40-B47 and B51 (also associated with Bechet's disease) and protective association has been noted with B57 and B7[33]

2.3.2 Non-HLA genes

The identical twin concordance rate for AS is approximately 60%, for HLA-B27 dizygotic twins it is 22%, implying major non-HLA B27 genetic risk factors are also contributory. Genomic wide association studies (GWAS) have revealed several other MHC genes contributing to the disease risk. At least 113 genetic variants involved in AS have been identified to date, with 48 of these achieving genomic wide significance. A genetic study published in 2007, identified variants among non-HLA proteins as major risk factors for

AS, such as those involved in the IL 23 signalling pathway and those belonging to the M1 family of zinc metallopeptidases such as endoplasmic reticulum aminopeptidase 1 (ERAP1)[34]. The function of the proteins encoded by these genes is to trim peptides to appropriate length for presentation to HLA molecules. Of particular interest, is the finding that the main ERAP1 variant associated with AS is restricted to HLA B27 positive cases. Since the discovery of these variants, multiple non-HLA genes have been associated with AS [35].

2.3.3 Environmental factors in AS pathogenesis

2.3.3.1 The Microbiome

There is increasing evidence to suggest an association between the host gut microbiome and development of axSpA. In humans, sequencing-based profiling of the gut microbiome has demonstrated that AS cases have a different microbiome to healthy controls. A recent study of used 16S microbial sequencing to compare the microbiomes in terminal ileal biopsies from nine patients with AS with those of healthy volunteers found significant increases in several bacterial families in AS (*Lachnospiraceae, Ruminococcaceae, Rikenllaceae, Porphyromonadacae and Prevotellaceae*)[36]. Interestingly, germ-free housing of mouse and rat models of AS, ameliorates disease[37]. Many of the genes associated with AS are known to be either involved in bacterial sensing (TLR4, GPR35, GPR65, AHR, NOD2) or associated with alterations of the gut microbiome (FUT2). Diarrhoeal illness can trigger a spondyloarthritis as part of reactive arthritis - approximately 10% of those affected go on to develop axSpA. There is also a strong clinical relationship between axSpA and IBD and marked overlap between the genetics of the two conditions. Approximately 60% of axSpA cases have been reported to have subclinical terminal ileal inflammation, and if it were possible to conduct

studies of more proximal small intestine, this proportion may be even higher [38]. It has been postulated that alterations in the gut microbiome may alter immune responses directly or indirectly through altered barrier function or microbial metabolites. These factors might induce loss of tolerance and/or an increase in proinflammatory cytokines such as IL-23, triggering axSpA in susceptible people. In keeping with this theory, upregulation of mRNA for IL-23 has been found in the terminal ileum of patients with AS and those with Crohn's disease[39].

2.3.4 Cytokine pathways in axial spondyloarthritis

2.3.4.1 Tumour necrosis factor (TNF)

Tumour necrosis factor alpha (TNF- α) has been found to be overexpressed in the circulation, synovial fluid, and target tissue (sacroiliac and facet joints) in patients with axSpA. Furthermore, the phenotypes of several animal models overexpressing TNF- α more closely resemble SpA than RA. The efficacy of TNF- α inhibitors in patients with axSpA further supports the involvement of TNF in the pathophysiology of axSpA. However, it should be noted that TNF is also produced by certain T cells in response to IL-23, so this is compatible with the central role of the IL-23/IL-17 pathway (described later). In fact, the TNF inhibitors may be exerting many of their beneficial effects in axSpA by inhibiting this pathway.

2.3.4.2 TNF and bone formation

The relationship between inflammation and new bone formation in AS remains unclear, particularly in the context of TNF. TNF is an important inducer of osteoclast activity and

excess TNF activity leads to erosive disease, as observed in RA. TNF inhibitors strongly reduce or even arrest structural damage in RA. However, initial studies suggested this was not the case in AS, with evidence of radiographic progression, despite clinical response and reduction in inflammation. In contrast to RA, there is not only bony loss in AS, but also new bone formation in the form of syndesmophytes/enthesiophytes which, over time, can lead to ankylosis. MRI studies have shown that bone marrow oedema of vertebral endplates known as active corner inflammatory lesions, predict the development of syndesmophytes[40]. One possible explanation for the apparent lack of radiographic response with TNF inhibitors is that there may be persistent mild inflammation not detected by MRI or other means, which leads to ongoing radiographic progression. However, the recognition that syndesmophytes were more likely to develop at the sites of resolved corner inflammatory lesions rather than sites of persistent lesions, goes against this theory. The 'TNF brake' hypothesis proposes that while there is ongoing active inflammation, TNF suppresses new bone formation, via a number of regulatory pathways, but that when inflammation resolves (e.g. in response to treatment with TNF inhibitors), the brake is released, allowing tissue repair and new bone formation to occur. As a result of this uncoupling between inflammation and new bone formation, we could hypothesise that patients who otherwise respond well to anti-TNF therapy may appear to have radiographic progression due to the new bone formation (which would have occurred in many anyway, but at a later date, in the absence of TNF inhibition).

Additional research is needed to confirm whether progression is due to persistent, low-grade inflammation or to the release of the TNF brake once inflammation is effectively

treated, however, there is accumulating data to suggest that when patients are followed up for longer, treatment with TNF blockers results in slowing of radiographic progression, supporting the latter mechanism. Osteoimmunology is becoming a growing field of research, which may yield novel future therapeutic targets to directly target bone involvement in AS.

2.3.4.3 The Interleukin-23/17 axis

IL-17 and IL-23 are pro inflammatory cytokines strongly associated with the pathogenesis of axSpA. Th17 cells express IL-23R on their surface and IL-23 is essential for the differentiation and proliferation of Th17 cells, as well as maintenance of IL-17 production. GWAS studies have identified variants of the IL23R gene in association with axSpA, as well as IBD and psoriasis, implicating IL23R as a common susceptibility factor across the SpA spectrum [41–43]. Subsequently, several other genes whose products may influence IL-23 and Th17 development have been identified in association with axSpA, including *TYK2, STAT3, IL12B*, and *IL6R*. The gene *IL12B* encodes IL-12p40, the common subunit of IL-12 and IL-23, which is targeted by the monoclonal antibody, Ustekinumab, used in clinic for the treatment of psoriasis, psoriatic arthritis, and IBD[44]. The convergence of these gene products in the IL-23/IL-17 axis strongly implicates this pathway in the pathogenesis of AS and SpA conditions.

2.4 The clinical course of axial spondyloarthritis

A delay of up to 9 years or longer is frequently observed between the onset of symptoms and AS diagnosis[1] leading to worse clinical outcomes [45] and contributing to both physical and work-related disability. Overall, axSpA is considered a disabling condition [46] and the level of disability observed can be of the same magnitude as that of patients with RA[47].

In general, axSpA is a slowly progressing disease. However, patients with high ESR, hip arthritis, young age at onset, poor response to NSAIDs and extraspinal manifestations are predictors of more severe course [48]. CRP was identified as the only relevant parameter predicting progression from nr-axSpA to AS over two years[49]. Presence of syndesmophytes and smoking predict further progression of radiographic damage of the spine[50,51].

2.4.1 Disease burden of axial spondyloarthritis

The characteristic pathophysiological changes associated with axSpA result in persistent inflammation of the SIJs, causing chronic back pain and skeletal/postural changes. Symptoms of pain, stiffness and fatigue associated with progressive bony fusion of the spine are major contributors to disease burden and limit physical functioning. The physical limitations of axSpA can affect employment, mental health and interpersonal relationships[52,53].

Reduction in work productivity is an important component of the indirect costs of axSpA, which are typically calculated in terms of absenteeism and presenteeism using the Work Productivity and Activity Impairment Questionnaire (WPAI). In a UK study of 612 AS patients, employment rates were 14% lower than the UK national average, with 39.5% of patients of working age being unemployed, 44% of whom related this to poor health[54]. In an Italian study, axSpA employment rates were slightly lower than the general population (53% v 58%), 14% of patients reported axSpA-related discrimination at work and the proportion of patients receiving disability benefits was nearly five times higher than the general population (34% vs 7.3%)[55]. In a study of men with axSpA, 45% switched to a less physically

demanding job, and 24% retired early - at a mean age of 36 years because of the condition[56]. The economic impact of work limitations as a result of axSpA is substantial, compounded by the typically young age at diagnosis[57].

As spinal mobility is progressively lost or pain levels escalate, difficulty in performing simple physical routines places a huge burden on these patients and compromises the patient's social and psychological function. In a study of patients with axSpA, Kilic et al found that 45% were at high risk of depression, and 21% were at high risk of anxiety[58]. Notably, rates of depression are 80% higher in women and 50% higher in men with axSpA than in the general population[59].

A major component of the health economic burden of axSpA is fatigue, which increases steeply with disease activity[60]. Estimates suggest that up to 66% of patients with AS are affected by fatigue[61], comparable to the rate in other long term conditions such as RA[62]. The complex, multi-dimensional nature of fatigue associated with a range of rheumatological conditions has been distinguished from normal everyday tiredness by frequency, persistence, unpredictability and failure to be resolved by rest[63]. A study of disease burden in 1093 patients with RA, 365 patients with PsA, and 333 patients with axSpA, found that patients with axSpA and psoriatic arthritis experienced more pain and fatigue than those with RA and patients with axSpA had more overall and night time spinal pain than the other 2 groups [64].

2.4.2 Management of axial spondyloarthritis

Prior to the introduction of biologic therapies, treatment of axSpA was limited to NSAIDs and physical therapy. Both have demonstrated efficacy in improving symptoms of inflammatory back pain and NSAIDs can also be effective in reducing the level of acute phase reactants such as CRP [65]. Unfortunately, axial and entheseal manifestations of SpA do not respond well to conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs).

Infliximab was the first licensed biologic for the treatment of AS in the UK in 2008. Subsequently, four other TNF inhibitors were introduced for the treatment of AS. In December 2016, the IL-17 inhibitor, Secukinumab, was approved by the National Institute for Health and Care Excellence (NICE) for treatment of AS. Adalimumab, Etanercept, Certolizumab and Golimumab (health technology appraisal for Golimumab published in January 2018) are all licensed for the treatment of nr-axSpA. All, except Infliximab, have European Medicines Agency (EMA) approval for both rSpA and nr-axSpA. Biosimilars of Infliximab, Etanercept and Adalimumab have also been approved by the EMA. The IL-17 inhibitor, Secukinumab, has also been approved by the EMA but only for axSpA patients with radiographic sacroiliitis. In July 2021, NICE approved the use of Ixekizumab, human monoclonal antibody that binds to interleukin-17A, for the treatment of axSpA in patients where anti-TNF is not suitable or in patients who remain active despite anti-TNF treatment. Recently, Janus kinase (JAK) inhibitors have shown efficacy in the treatment of axSpA. This will be discussed later in this chapter. The majority of other biologics approved for the

treatment of RA; including those targeting T cells (Abatacept), B cells (Rituximab), IL-1(Anakinra) or IL-6 (Tocilizumab) failed to demonstrate clinical efficacy in AS.

The ASAS-EULAR guidelines (2016 update) recommend commencing anti-TNF therapy in those with high disease activity defined by either a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 or an Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥2.1 after two different NSAIDs for at least 4 weeks in total [66]. The British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines[67] and NICE guidelines [68] define high disease activity as a BASDAI and spinal pain visual analogue scale (VAS) score ≥4. According to the BSR, patients need to have failed two NSAIDs for at least two weeks each, unless contraindicated, and the BASDAI should be measured on two occasions at least 4 weeks apart. NICE guidelines, however, do not stipulate this requirement and patients can be started on biologic therapy if evidence of sustained high disease activity despite conventional treatment.

2.5 Currently approved biologic therapies, including biosimilars

2.5.1.1 Adalimumab

Adalimumab is a fully human monoclonal antibody that binds with high affinity to TNF. The ATLAS trial demonstrated clear efficacy of Adalimumab in active AS over the 24-week study period. In this study 58.2% patients achieved a 20% Assessment of Ankylosing Spondylitis (ASAS20) improvement in the adalimumab group compared to 20.6% in the placebo group by week 12 [69]. The use of Adalimumab in nr-axSpA was demonstrated by the ABILITY-1 study. In this study, ASAS40 response rates in the adalimumab treated

group were 36% compared to 15% in the placebo group at week 12 [70]. The long-term efficacy of adalimumab has been demonstrated in a 5 year follow-up study in patients with AS. In this study 70% of patients achieved ASAS40 [71].

2.5.1.2 Certolizumab

Certolizumab is a PEGylated Fc-free anti-TNF. A phase 3 double-blind, randomized study, evaluated the efficacy and safety of Certolizumab in patients with axSpA, including patients with AS and nr-axSpA. At week 12, ASAS20 response rates were significantly higher in the Certolizumab groups compared to placebo (57.7% (200mg) and 63.6% (400mg) vs 38.3% (placebo), p≤0.004). At week 24, patients in the certolizumab group showed significant differences in BASDAI, ASDAS, Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis Metrology Index (BASMI) scores. The results of this trial demonstrated that certolizumab led to rapid improvements in clinical signs and symptoms in axSpA [72]. The clinical efficacy of Certolizumab in axSpA has been demonstrated at 4-year follow-up in patients with axSpA including AS and nr-axSpA [73]. Sustained efficacy at the MRI level has been shown in a recently published 95-week study[74].

2.5.1.3 Etanercept

Etanercept is a recombinant TNF receptor p75 Fc fusion protein that acts competitively to inhibit cell surface receptor binding of TNF. Its safety and sustained clinical response in AS was studied in 277 patients who had participated in a previous randomised, double blind, placebo controlled 24 week trial that continued in an open label extension study for a total of 2 years. In the Etanercept group, 74% achieved an ASAS20 response after 96 weeks [75]. Its

efficacy in nr-axSpA was initially demonstrated in the ESTHER trial, where 50% of the patients (n=36) achieved remission in the etanercept group compared with 19% in the sulfasalazine group at week 48 [76]. The long-term efficacy and safety of etanercept was demonstrated in a 7-year follow-up study of patients with AS, where 31% of patients were in ASAS partial remission, and 44% had ASDAS inactive disease [77]. The EMBARK study was the pivotal study resulting in the market authorisation of Etanercept in nr-axSpA[78]. This study showed rapid, significant improvement in symptomatic disease activity, function, and systemic and skeletal inflammation over 12 weeks. Clinical and functional improvement was sustained over 24 weeks.

2.5.1.4 Infliximab

Infliximab is a monoclonal chimeric human anti-TNF antibody that binds with high affinity to TNF. The efficacy of Infliximab was demonstrated in the ASSERT trial; a multicentre, randomised study, where 61.2% of AS patients in the Infliximab group were ASAS20 responders compared with 19.2% of patients in the placebo group [79]. Persistent clinical efficacy and safety of infliximab was demonstrated after 8 years of follow-up in patients with active AS treated with Infliximab, where 24% of the patients were in partial remission (n=8) and 64% (n=21) had low disease activity (BASDAI <3) [80].

2.5.1.5 Golimumab

Golimumab is a humanised monoclonal antibody to TNF. In the GO-RAISE study, Golimumab was proven to be effective and well tolerated in a large cohort of patients with AS. At 14 weeks, about 60% achieved ASAS20 response in the golimumab treated patients

compared to 21.8% in the placebo group [81]. Golimumab has also been shown to be effective in nr-axSpA in the GO-AHEAD 16-week study, where the primary endpoint (ASAS20 at week 16) was achieved in 71.1% in the golimumab group versus 40.0% in the placebo group[82].

2.5.1.6 Secukinumab and Ixekizumab

Secukinumab is a monoclonal antibody of the IgG1/kappa isotype that targets interleukin-17A. It has recently been licensed for treatment of AS in patients who have failed NSAIDs or anti-TNF. The MEASURE trials demonstrated safety and efficacy of Secukinumab in patients who were anti-TNF naive and those who had previously failed anti-TNF. In MEASURE 1 (371 patients), the ASAS20 response rates at week 16 were 61%, 60% and 29% for subcutaneous Secukinumab at doses of 150 mg and 75 mg and for placebo, respectively ($p<0.001$). In MEASURE 2 (219 patients), the ASAS20 response rates were 61%, 41%, and 28% for subcutaneous Secukinumab at doses of 150 mg and 75 mg and for placebo, respectively ($p<0.001$ for the 150-mg dose and $p=0.10$ for the 75-mg dose). There were also statistically significant improvements in the BASDAI 50 (the proportion of patients achieving a 50% improvement in BASDAI score) and in the change from baseline BASFI scores in the Secukinumab arms of the trials compared with placebo [83]. COAST-V and COAST-W were 52-week, phase 3, randomized controlled trials evaluating the efficacy and safety of ixekizumab (IXE) in patients with rSpA who had not had a biologic before (COAST V) or had previously had at least one anti-TNF drug (COAST W). The COAST-V and COAST-W trials applied ASAS40 as the primary endpoint. In COAST V, more patients achieved ASAS40 at week 16 with ixekizumab given every two weeks (Q2W) (43 [52%] of

83; p<0·0001), ixekizumab every 4 weeks (Q4W) (39 [48%] of 81; p<0·0001), and adalimumab (32 [36%] of 90; p=0·0053) [84]. In COAST W, significantly higher proportions of IXE Q2W patients (n = 30 [30.6%]; P = 0.003) or IXE Q4W patients (n = 29 [25.4%]; P = 0.017) had achieved an ASAS40 response versus the placebo group (n = 13 [12.5%]) [85]

2.5.1.7 Biosimilars

Biologics have revolutionized the treatment of axSpA. However, these drugs are expensive resulting in wide inequalities in their use. The emergence of biosimilars offers the promise of substantial savings relative to the reference medicinal product (RMP) enabling more patients to access biologic therapy. A biosimilar is defined by the World Health Organisation (WHO) as a biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product[86]. It has been estimated that Germany, France and the UK each stand to save between €2.3 billion and €11.7 billion between 2007 and 2020 in response to the introduction of biosimilars [87].

Biosimilars of four RMPs, Adalimumab, Etanercept, Infliximab and Rituximab, have now been approved by the EMA for rheumatologic indications and those for which the bio-originator no longer is protected by patent, have been marketed. CTP-13, otherwise known as Remsima/Inflectra, was the first biosimilar approved by the EMA in September 2013. In January 2016, the EMA approved the first Etanercept biosimilar, SB4, otherwise known as Benepali. A further infliximab biosimilar, SB2/Flixabi, was approved in May 2016. In March 2017, the EMA approved the first Adalimumab biosimilar, SB5, otherwise known as

Amgevita/Solymbic. Currently, there are 700 biosimilar products in preclinical and clinical trials.

2.5.2 Predictors of response to biologic therapy

The biologics registries have shown that factors associated with clinical response include raised inflammatory markers, higher ASDAS score, lower BASFI, and younger age at baseline [88–90]. According to the Swedish register, male gender and presence of peripheral arthritis were also baseline predictors of continuation of anti-TNF therapy [91]. Similar findings have also been reported in a large cohort of AS patients treated with Adalimumab. In this study HLA-B27 positivity and anti-TNF naivety were associated with better response to Adalimumab (BASDAI50, ASAS40) [92]. Shorter disease duration [93] and active inflammatory lesions on MRI have also been shown to predict response to TNF therapy [94]. The use of corticosteroids has been associated with a poor response to Infliximab in a small retrospective study of 70 patients with AS treated with Infliximab over a five-year period. In this study 71.4% patients responded within the first 6 months of treatment [95].

Pederson et al [96] investigated the demographic, smoking status, presence of HLA B27, NSAID use and baseline CRP in 480 patients with AS commenced on anti-TNF therapy. They also assessed MRI at baseline, 3-6 months and annually. They found that the strongest predictor of treatment survival was normalised CRP or low disease activity within the first year of anti-TNF therapy. Sustained remission was more likely in patients achieving normal CRP with definite SIJ erosion and absence of ankylosis. Smoking was adversely associated with achieving sustained remission. Ciurea et al[97] assessed response rates to

anti-TNF in nr-axSpA versus AS in a SWISS cohort of 152 women and 267 men who fulfilled ASAS axSpA classification criteria. Interestingly, they found that a significantly lower number of women with nr-axSpA achieved an ASAS40 response with anti-TNF compared with those with AS. Responses were comparable in men with nr-axSpA and AS.

2.5.3 Switching biologics

Primary failure describes no response or inadequate efficacy in patients within 3-6 months of treatment with a biologic[98]. A prospective multicentre longitudinal observational study using the Norwegian register, NOR-DMARD, assessed 514 patients with AS treated with anti-TNF (including Infliximab, Etanercept, and Adalimumab) of whom 77 switched to a second anti-TNF agent. The reason for switching was adverse events in 44 patients (57.1%) and insufficient response in 30 (38.9%) of the 77 switchers. The insufficient response group had been treated with the first TNF blocker for a median of 294 days, and the adverse event group has been treated with the first anti-TNF agent for a median of 171 days. For the first anti-TNF, the 2-year drug survival rate was 65%, and for the second anti-TNF it was 60%. The 3-month BASDAI 50 and ASAS 40 responses were achieved by 49% and 38% of the non-switchers, by 25% and 30% of switchers after the first TNF blocker, and by 28% and 31% after the second TNF agent. This study shows that switching to a second anti-TNF can be an effective approach in AS, with around one-third of patients showing a good clinical response and more than half of patients continuing the treatment for more than 2 years [99].

Of the 1436 AS patients from the Danish biologics register (DANBIO), 30% of patients switched to a second biologic and 10% switched to a third biologic. Switchers were more

frequently women, had shorter disease duration, and higher BASDAI/BASFI and visual analogue scale (VAS) scores when they commenced their first anti-TNF agent. After 2 years of treatment, the response rates and drug survival were lower among switchers; however, 52% of them achieved response compared to 63% of non-switchers, therefore switching to another anti-TNF agent should be considered irrespective of the reason for discontinuation of the initial TNF blocker [100].

Of the 229 AS patients treated with biologics from the Finnish biologics register (ROB-FIN), 13 patients (7%) discontinued the first biologic due to lack of efficacy and 21 patients discontinued for unspecified reasons; 14 of these patients switched from Infliximab to Etanercept or Adalimumab. Adverse events occurred in 11% of the patients receiving their first biologic drug (25 of 229 patients). In this study, the dose of Infliximab was increased in more than a quarter of the patients in an attempt to improve response. There was also an extensive use of concomitant DMARDs such as Methotrexate and Sulfasalazine with biologic therapy, due to peripheral arthritis. The combination of DMARDs and Infliximab led to a rapid pain relief and improvement of patient's and physician's global assessments within six weeks, which was sustained at two years. A subgroup of AS patients with axial involvement only (n=46), had an ASAS20 response in 79%. The authors concluded that switching may be possible; however, the group of switchers in this study was small (13% of patients, n= 27) [101].

A retrospective analysis of 108 patients with severe AS on anti-TNF therapy showed that 15% were switched to a second anti-TNF agent, and two patients were switched to a third

anti-TNF agent. Inefficacy was the most common reason for switching (67%), followed by adverse events (28%). At 69 months, 86% of patients who switched to a second anti-TNF drug were continuing treatment. Switching due to adverse events led to better response than switching due to inefficacy. Sustained benefit in AS patients treated with a second anti-TNF is similar to the efficacy seen following the initial anti-TNF therapy [102] [103]

In a 54-week, open-label, prospective study of patients with AS treated with Infliximab who failed to achieve or maintain an ASAS20 clinical response or had adverse events, were switched to Etanercept. At week 54, ASAS20, ASAS50, and ASAS70 response rates were 74%, 61%, and 39% respectively. These figures suggest that switching to etanercept may be a good therapeutic option for patients who do not respond to Infliximab [104].

Some patients have a good initial response to biologic therapy which subsequently diminishes with time. This has been coined secondary failure and is defined as a loss of efficacy of a biologic agent after more than 6 months [98].

A longitudinal observational prospective study [105] evaluated the clinical response after switching from one anti-TNF agent to another in patients with AS and PsA over a 5-year period. A clinical response was seen in 75% of the patients who changed from Infliximab to Etanercept, and 57.1% who switched from Etanercept to Adalimumab. Patients who switched because of adverse events and lack or loss of efficacy, showed a similar clinical response; 70% and 61.5% respectively. In this study, 81.3% of patients who had switched from Infliximab to Etanercept continued the treatment, compared to only 57.1% of patients

who had changed from Etanercept to Adalimumab maintained the treatment. Two of the three patients who stopped Adalimumab because of inadequate response had already failed the other two anti-TNF agents. This observation suggests that the failure of two TNF inhibitors predicts ineffectiveness to the third, which has been seen in previous data on RA patients. Patients with SpA with inadequate response or adverse events to one anti-TNF agent may be successfully treated with another, regardless of the reason for switching

Switching to a second anti-TNF agent was necessary in 24% of the AS patients, and 11% of AS received a third anti-TNF in an observational study [98]. In this study, secondary failure was the main reason for switching to a second anti-TNF agent, followed by side effects and lack of efficacy, whereas the reasons for switching to a third anti-TNF were lack of efficacy, followed by side effects. As with the previous findings, patients with AS with loss of efficacy to the first anti-TNF who were switched to a second anti-TNF had an adequate response, suggesting that switching anti-TNF for secondary failure may be beneficial in this group of patients

In a cross-sectional study of 467 SpA patients drug survival and the reasons for switching anti-TNF therapy was studied [106]. Of the 467 patients who started anti-TNF therapy, 28% switched to a second and 8% switched to a third drug. The mean drug survival did not differ among the courses of anti-TNF. In this study, the main reasons for switching were lack or loss of efficacy and adverse events in 40% and 30% of switchers respectively. Switchers were more frequently women and had higher disease activity parameters

(BASDAI, ESR, and patient's visual analogue scale (VAS) for pain and for global state) at the time of the study than non-switchers

2.5.4 Do biologics affect radiographic progression?

Despite its clear clinical efficacy, there is controversy regarding biologic therapy and disease modification in axSpA. Studies have shown clear inhibition of radiographic progression in patients with rheumatoid arthritis and psoriatic arthritis. However, these findings have not been replicated in studies of axSpA.

Radiographic progression in AS develops slowly and may be detectable only after a minimum of two years. Ethically, it is difficult to justify a placebo arm of two years when the clinical benefits of the treatment are well known and occur shortly after it is commenced. Thus, studies assessing radiographic progression in axSpA have either used observational data or compared the open-label extension phase of RCT of TNF inhibitors with historical cohorts not treated with TNF inhibitors. These historical cohorts include the Outcome in Ankylosing Spondylitis International Study (OASIS), the German Spondyloarthritis Inception Cohort (GESPIC) and the Herne Cohort (HC).

Baraliakos et al [107] analysed radiographs of patients from a multi-centre, double-blind, placebo controlled trial in Germany which assessed the safety and efficacy of Infliximab over two years[108]. They compared radiographic images to the German AS Cohort (GESPIC) cohort who were treated conventionally; 82 patients were included in the study; 41 patients were randomly picked from the continuous treatment arm of the RCT and 41 patients were

randomly selected from the GESPIC cohort. The mean modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) change in the Infliximab group was less than in conventionally treated patients but not significantly so (p=0.085). Van der Heijde et al looked at radiographs at baseline and at week 96 from patients in the ASSERT trial and compared this to radiographs from patients from the OASIS cohort who were anti-TNF naive [109]. In this study Infliximab treated patients did not show a statistically significant difference in inhibition of structural damage progression at year 2, as assessed using the mSASSS scoring system, when compared with radiographic data from the historical control OASIS cohort.

Van der Heijde assessed a total of 257 patients treated with Etanercept and compared radiographs with 175 unselected patients from the OASIS study. No significant difference was found in the mean change (SD) in mSASSS from baseline among patients who received Etanercept 0.91 (2.45) versus those from the OASIS group 0.95 (3.18) [110]. The same group looked at radiographs from patients in the ATLAS study combined with a Canadian AS study (n=307). Radiographic progression from baseline to 2 years in the spine of these patients was compared to anti-TNF naive patients from the OASIS cohort (n=169). Again, mSASSS results were not significantly different between the Adalimumab cohort and the OASIS cohort after 2 years.

Baraliakos et al [111] assessed the rate of new bone formation after 8 years of Infliximab treatment in patients with AS. They compared the radiographic progression of 22 patients from the multi-centre DIKAS study [112]. In DIKAS, all patients were treated with 5mg/kg

Infliximab continuously every 6 weeks. They compared radiographic changes to those in the Herne Cohort. The selection of patients was made according to their availability of conventional radiographs of the cervical and lumbar spine at baseline and whether they continued anti-TNF for 8 years. Patients on Infliximab (n=22) and the Herne Cohort (n=34) did not differ in the baseline mSASSS status. Both showed significant radiographic progression after 8 years with a mean (SD) mSASSS of 20.2 (21.4) in DIKAS and 25.9 (17.8) in Herne Cohort. The mean mSASSS difference was similar in both groups between baseline and four years but radiographic progression between years 4 and 8 differed significantly between both treatment groups (p=0.01). The mean number of syndesmophytes, although similar at baseline differed significantly at 8 years (p=0.007). Adjustment for age, symptoms duration, HLA B27, BASDAI and Bath AS function index (BASFI) at baseline had no influence. This finding implies that delays in radiographic progression may occur but after a protracted period of time.

Haroon et al [113] designed a prospective study looking at all patients who satisfied the modified New York criteria for AS. The study found that those who received TNF inhibitors had a 50% reduction in odds progression to those who had not been on anti-TNF (OR: 0.52; CI 0.30-0.88 p = 0.02). The total duration of treatment was inversely associated with radiographic progression compared to those who has not been on TNF inhibitors (OR: 0.52; CI 0.30-0.88; p=0.02). Patients who were on biologics for more than 50% of their disease duration had lower odds of progression (OR 0.2 95% CI: 0.04-0.92; p=0.04) compared to patients who were not. Patients who were not on anti-TNF for the greater part of their disease duration, had higher rates of mSASSS progression. In the patients who were

on TNF-inhibitors, the rate of mSASSS progression increased with an increasing delay in starting treatment. This was the first study to show an association between the use of TNF inhibitors and progression of damage in AS. Haroon et al suggested that both the timing and duration of therapy could be important in rate of radiographic change. However, this study also raises methodological concerns, as it used a controversial definition of radiographic progression, the analyses did not take into account treatment changes and clinical changes between the 2 radiographic assessments and did not entirely account for time-varying variables in the statistical models [114].

A recent observational cohort study by Maas et al looked at 176 AS patients receiving long-term TNF inhibitors and showed a reduction in spinal radiographic progression after more than 4 years of follow-up [115]. These results may refer to a delayed effect of TNF inhibitors on radiographic progression. This finding supports the purported 'TNF brake hypothesis': That already-triggered repair processes can first lead to continuation of bone formation but long-term inhibition of inflammation by TNF inhibitors may result in a reduction of new bone formation over time.

2.5.5 Biologic therapies on the horizon

The TOPAS trial gave promise to the inhibition of IL23 and IL12 with Ustekinumab in the treatment of axSpA. This was a 28-week, prospective, open-label study in patients with AS and prompted 3 subsequent phase 3 placebo controlled trials (NCT02437162, NCT02438787 and NCT02407223) assessing the safety and efficacy of Ustekinumab in patients with both nr-axSpA and AS. However, this trial was withdrawn as it has failed to meet any of its

primary or secondary outcomes. Whilst JAK inhibitors are not biologic therapies, both tofacitinib (JAK1–3 inhibitor) and filgotinib (selective JAK1 inhibitor) have shown efficacy in the treatment of axSpA. In a phase III, randomised controlled trial of 269 patients with active AS, tofacitinib demonstrated significantly greater efficacy versus placebo. No new potential safety risks were identified[116]. Heijde et al showed that filgotinib was efficacious and safe for patients with active AS and inadequate response or intolerance to NSAIDs in a phase II study[117]. Upadacitinib, a selective JAK1 inhibitor was found to be efficacious and well tolerated in patients with active AS who had not responded to or had a contraindication to treatment with NSAIDs [118]. Apremilast is an oral phosphodiesterase 4 inhibitor that modulates inflammatory cytokines. It was evaluated in a double-blind, placebo-controlled, phase II study over 12 weeks in 38 patients with symptomatic AS with active disease on MRI. This small pilot study did not meet its primary end point; however Apremilast was associated with improvement in various clinical assessments including BASDAI, BASFI, and BASMI compared to placebo[119].

2.6 Measures of disease activity in axial spondyloarthritis – an area of unmet clinical need

The introduction of biologic therapy has transformed the management of axSpA, leading to significant improvements in patient morbidity. Whilst these treatments have significantly reduced the burden of disease, they are associated with considerable expense and are associated with an increased risk of serious infections compared with conventional DMARDs [120], as well as infusion and allergic reactions.

The average cost of biologic therapy varies, however, in our institution biologic therapies for axSpA cost in the region of 8,000-10,000 pounds per patient per annum. In 2015/16, the NHS spent over £250 million on Adalimumab alone (Commissioning framework for biologic medicines Sept 2017). Although the development of biosimilars will have reduced this amount substantially, improvements in our understanding and recognition of the disease will invariably lead to more patients being diagnosed with axSpA and commenced on therapy. Clinicians must, therefore, demonstrate both appropriate patient selection and accurate assessment of patient response to justify their ongoing administration.

A review of the report from the NICE Quality Standards Advisory Committee Meeting (Nov 2017) for Spondyloarthritis revealed that monitoring disease activity is an area of unmet clinical need. Queries from registered stake holders incorporating clinicians, national organisations and charities and members of industry, included uncertainty over the optimal time interval and need for clinical re-examination as monitoring and the use of repeat imaging. One stakeholder questioned the validity and reliability of the current disease activity score for long term monitoring and whether the NHS should be using

something different. It was noted that whilst there have been improvements in disease activity measurement in inflammatory arthritis, especially with RA where ultrasound can reliably detect "deep remission", there has not been the same the improvements for disease activity measurements in spondyloarthritis. During the NICE Quality Standards Advisory Committee Meeting, reference was made to the NICE spondyloarthritis guidelines which describe a range of different diagnostic criteria for the diagnosis of SpA but no mention of disease activity monitoring in the same way for RA.

Accurate measures of disease activity are not only applicable to clinical practice but essential in the assessment of novel therapies in in clinical trials. As the Outcome measures in Rheumatology (OMERACT) state in their mission statement, "Clinical trials are only as credible as their endpoints" [121]. The OMERACT group was established to help develop and validate clinical and radiological outcome measures in rheumatic disease. According to OMERACT, any instrument for patient assessment should meet the filter of 'truth', including content, construct and criterion validity, 'discrimination' providing reliability and sensitivity to change, and 'feasibility' reflecting the ease of use in clinical practice. Creating a disease activity scores in axSpA poses a significant challenge: Currently, we have no biomarker for the disease and a distinct lack of data from longitudinal epidemiological studies to help characterise the disease. At present, our assessment of disease activity is largely reliant on subjective feedback from patients regarding pain and stiffness.

2.7 Disease activity measures in axial spondyloarthritis

2.7.1 Clinical disease activity scores

Clinical outcomes can be divided into those that assess disease activity, patient function, mobility and health related quality of life. There are a number of different indices described for each.

2.7.1.1 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI has become the most utilised measure of disease activity for axSpA, both in clinical practice and in trials [69,122,123]. It is a fully patient reported measure which assesses a number of pertinent symptoms of axSpA; namely fatigue, back pain, joint pain/swelling, enthesitis, intensity and duration of morning stiffness; and aggregates these into a single score. For each question, patients must score their symptom on a 100mm Visual Analogue Scale (VAS) where 0 is no pain/stiffness/fatigue and 100 severe pain/stiffness/fatigue. The score was initially validated in a cohort of 473 patients with AS, where it was shown to be sensitive to change with treatment [124]. Subsequently, numerous clinical trials have demonstrated significant changes in BASDAI in response to biologic therapies [70,72,78,79].

NICE recommend that patients with axSpA starting biologics, should have should have failed at least two NSAIDs and demonstrate high disease activity defined by a BASDAI > 4 and spinal VAS > 4. Response to treatment should be measured at 3 months and determined by a reduction in BASDAI score to 50% of the pre-treatment value or by 2 or more units and a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.. Further BASDAI

criteria used in clinical trials include the BASDAI 50 (a major response criteria) defined as a 50% improvement in BASDAI score as well as BASDAI 20, defined as a 20% improvement in BASDAI score.

There are a number of criticisms regarding the BASDAI. Firstly, it measures only part of the disease reflected by pain and fatigue and excludes any measures of spinal mobility or objective measures of inflammation including ESR or CRP. Indeed, the index has shown poor correlation with CRP and ESR levels[125] . This might reflect the weakness of these markers to represent inflammation in axSpA, however, it may also demonstrate the inability of the BASDAI to represent disease activity accurately. Data shows that patients with high CRP and ESR are more likely to respond to biologic therapies [126] and are more likely to show radiographic progression.

The BASDAI reflects only patient reported outcomes. Studies have shown that patients and physician perspectives on disease activity can vary[127]. Patients rate symptoms of pain and fatigue and to a lesser extent, function, as important values defining disease activity. Physicians rate variables reflecting inflammation and severity, such as their own assessments and acute phase reactants, as most important in assessing disease activity instead of patient perception.

The BASDAI score does not weight individual clinical manifestations. Instead, variables are simply summed without taking the relative importance and dependency into account. In addition, the score does not account for variable redundancy - the phenomenon that separate variables cover the same aspect of the disease and may have high correlation.

Another major criticism of the BASDAI is its inability to distinguish axial inflammation from chronic widespread pain (CWP) and fibromyalgia (FM) which can often accompany axSpA.

The BASDAI cut-off point of ≥4 is the accepted standard on which to select patients for biologic therapy, however, the BASDAI threshold has been arbitrarily set and never thoroughly investigated. Accordingly, it has remained unclear whether patients with a lower BASDAI may also benefit from therapy with biologic agents. It has been shown that young male patients tend to report low BASDAI scores, even though they may have high CRP levels or strong evidence of axial inflammation by MRI [128]. A post-hoc analysis of the non-interventional, prospective, GO-NICE study in the subgroup of biologic-naive AS patients treated with golimumab demonstrated that patients with a BASDAI between 2.8 and <4 appeared to benefit significantly from golimumab treatment, while patients with BASDAI < 2.8 did not [129].

2.7.1.2 The Ankylosing Spondylitis Disease Activity Score (ASDAS)

The ASDAS is a score that combines elements of the BASDAI and patient global assessment with a laboratory measure of inflammation, either CRP or ESR. It is calculated with the following formula depending on whether using CRP or ESR.

ASDAS CRP = 0.121 x back pain score (mm) + 0.058 x duration of morning stiffness score (mm) + 0.110 x patient's global assessment score (mm) + 0.073 x peripheral pain/swelling score + 0.579 x Log (CRP+1)

ASDAS ESR = 0.113 x patient global + 0.293 x square root of ESR + 0.086 x peripheral pain/swelling + 0.069 x duration of morning stiffness + 0.079 x total back pain score

Good performance of ASDAS has been shown in several international datasets including randomized controlled trials and observational cohorts [130–132]. There are a number of studies demonstrating superior sensitivity of the ASDAS over the BASDAI with ASDAS showing a closer correlation to MRI [133]. In the 2017 update of the ASAS-EULAR management recommendations for axSpA, ASDAS is the preferred measure to define active disease.

One important criticism of ASDAS is the fact that it relies on acute phase reactants which are only elevated in 40% of patients with axSpA. It also takes into account peripheral pain or swelling, which is only seen in a subgroup of axSpA patients. Hence, the ASDAS is unlikely to represent true response in the absence of an elevated ESR/CRP or peripheral involvement. However, a study by Fagerli et al [134] compared ASDAS >2.1 with BASDAI >4 as an eligibility criterion for initiation of anti-TNF treatment in AS, and to investigate if ASDAS performs satisfactorily in patients without elevated CRP or without peripheral joint swelling. More patients were eligible for anti-TNF using the ASDAS than BASDAI eligibility criterion. ASDAS was also found to be applicable in subgroups without elevated CRP and without peripheral joint swelling. The results support the concept that ASDAS can be used as an outcome measure in all types of patients with AS, including patients with normal CRP and without peripheral joint swelling. However, the ASDAS remains heavily

reliant on patient reported measures of disease activity, which again, carry the same limitations as the BASDAI.

2.7.1.3 The Bath Ankylosing Spondylitis Metrology Index (BASMI)

Mobility in AS reflects a combination of disease activity as well as structural damage. The Bath Ankylosing Spondylitis Metrology Index (BASMI) is a combination of 5 measurements of spinal mobility that reflect axial disease. These include cervical rotation, tragus to wall distance, lateral lumbar flexion, modified Schober's and intermalleolar distance. All 5 measurements are then scored as 0, 1 and 2 using defined cut-offs. Each score is then added to give a total score of 0-10. This method was modified to allow a score range of 0-10 for each measure. A further modification to this converts the actual measurements into a linear scale of 0-10 called the BASMI-Linear. A small study of 30 Danish patients assessing reproducibility of BASMI linear by comparing results between a trained physiotherapist and an untrained nurse who underwent a one hour training session with the physiotherapist, found good intra-observer as well as inter-observer agreement [135]. However, the BASMI is arguably too time consuming for clinical practice and shows less response to change compared with other measures of disease activity.

2.7.1.4 The Bath Ankylosing Spondylitis Functional Index

The Bath ankylosing spondylitis functional index **(**BASFI) is a set of 10 questions designed to determine the degree of functional limitation in those with axSpA. The 10 questions were chosen with substantial input from patients with AS [136]. The questionnaire consists of 8 questions regarding patient function and 2 questions that assess the patient's ability to cope with axSpA. Each question is answered on a horizontal visual analogue scale of 0-10cm.

The results are then totalled and divided by 10 to obtain a final score. The BASFI has been shown to relate well with other functional indices such as the Dougados Functional Index (DFI) as well as with disease activity and radiological damage[137]. Both have also been shown to have a good test-re-test reliability. This questionnaire provides an important insight into patient's functional status but cannot be used in isolation to assess disease activity as it will dependent on a number of other variables including psychosocial factors. A number of other functional assessments have been created. The Functional Assessment of Chronic Illness Therapy (FACIT) was developed from the existing questionnaire: Functional Assessment of Cancer Therapy- General (FACT-G) used to assess quality of life in cancer patients[138] . The questions are divided into four quality of life domains - physical, social, emotional and functional well-being. It is self-administered either on paper or directly on the computer and has been validated as a tool in a number of different conditions including rheumatoid arthritis. Scores are calculated as a summation of the four individual components. There are a number of instruments measuring quality of life including the Short Form-36 (SF-36) Health Survey or Short Form-12 (SF-12). There are also a number of AS specific tools such as the AS Quality of Life (AS-QoL), European quality of life (EuroQoL), Patient Generated Index (PGI), Evaluation of Ankylosing Spondylitis quality of life (EASi-QoL). Other indices to assess function include the Health Assessment Questionnaire - Spondyloarthropathy (HAQ-S), the Assessment of Ankylosing Spondylitis Health Index (ASAS HI). Reduction in work productivity is an important component of the indirect costs of SpA, which are typically calculated in terms of absenteeism and presenteeism using the Work Productivity and Activity Impairment Questionnaire in AS (WAPI).

2.7.1.5 Bath Ankylosing Spondylitis- Global scale

The Bath ankylosing spondylitis global scale **(**BAS-G) was developed in 1996 as a measure of the effect of AS on the patient's well-being. This was measured on a horizontal VAS from 0–10cm with the patient marking how he/she felt over the last week and also over the last 6 months. This was shown to correlate best with BASDAI (r=0.73) followed by BASFI (r=0.54)[139]. However, this has been found to be less reliably reproducible than BASDAI or BASFI.

2.8 The problem with pain as a measure of disease activity in axSpA

Chronic widespread pain is a frequent and complex symptom in rheumatic disease. CWP can be thought of as a spectrum, including pain originating from a number of sources to severe global pain found in FM. It is considered to be the result of increased processing of pain by the central nervous system, a process termed pain sensitisation [140]. The prevalence of chronic pain in axSpA is high. A population based survey of 920 patients with AS or uSpA demonstrated that 45.3% of patients with AS and 49.3% with USpA met 1990 ACR criteria for CWP, with a higher prevalence among female patients (54.1% vs 41.2% $p<0.001$)[141].

In patients with axSpA and FM, it can be impossible for the physician to decipher whether a patient's pain is originating from the ongoing inflammation associated with active axSpA or as a result of pain sensitisation in FM; with both conditions causing axial pain, stiffness and fatigue. Unfortunately, PROMs also fail to differentiate symptoms secondary to chronic pain versus axSpA.

A cross sectional Spanish study of 462 patients with definite AS found that the BASDAI, BASFI and Bath AS Radiological Index (BASRI) were all greatly influenced by the presence of FM, with FM disease distorting the measures of disease activity and functional damage[142]. This group found that ASDAS was better able to discriminate chronic pain from inflammatory disease, which was felt to be attributed to the inclusion of CRP and/or ESR.

MacFarlane et al, 2017 [143] looked at patients on the BSR Biologics Register in AS (BSRBR-AS) who fulfilled the ASAS definition of axSpA. Of the 430 patients, 56 (20.4%) met the modified 2010 ACR criteria for FM. Patients who met FM criteria were more likely to be female, reported worse BASDAI, BASFI and depression, had more sleep problems and higher levels of fatigue. There was no difference in age or when they were commenced biologic therapy. Authors confirmed that FM may distort responses to some of the key patient-reported measures used in the BASDAI and BASFI, which also forms a component of the ASDAS.

Heikkila et al [144] looked at 24 patients with axSpA and 70 with FM. All patients were female. The investigators compared self-reported outcomes between the two groups including BASDAI. Patients with FM were found to have higher disease activity scores than patients with axSpA. Inflammation, as assessed by laboratory tests (ESR and CRP) and by the need for antirheumatic drugs, was more strongly associated with axSpA.

Increased prevalence of secondary FM among female SpA patients has been reported by

Aloush et al [145]. Eighteen women with AS were compared with 18 men with AS and assessed for age, duration of symptoms, time to diagnosis, degree of SIJ involvement, history of peripheral arthritis, patient global assessment, Health Assessment Questionnaire, level of diffuse pain, BASDAI and BASFI. Physical examination included the number of tender points and enthesitis sites, Schober's test, distance between occiput and wall, chest expansion, lateral spinal flexion, and the intermalleolar distance. Inflammatory activity was measured by the ESR. Of all the test parameters, the ones with significant differences between the groups were time between symptom onset and AS diagnosis (longer for women), FM incidence and the number of tender points and enthesitis sites (higher for women) BASDAI (higher in women and correlated with FM and the number of tender points but not with ESR), and BASFI and BASDAI scores (increased in FM patients). FM was present in 50% of women in AS and associated with higher DAS (BASDAI and BASFI) and not related to severity of physical findings or ESR. Aloush et al, therefore, questioned the reliability of well-accepted assessment tools of AS, such as BASDAI and BASFI, in evaluating AS activity in women due to the confounding effect of FM.

Salaffi et al [146] investigated the prevalence of FM in patients with AS or PsA characterized by axial involvement (axial-PsA). They also assessed the discriminative ability of different versions of the ASDAS and BASDAI in measuring disease activity in all three different cohorts of patients with axSpA, FM or both FM + axSpA. The study consisted of two parts. Firstly, 402 patients with definite AS or axial-PsA were examined to diagnose FM and estimate its prevalence. 419 patients, including 11 with axial-SpA, 248 with FM, and over 60 with axSpA + FM were evaluated using different versions of ASDAS and BADAI. The

overall prevalence of FM in the axSpA population was 14.9%. FM was significantly higher among women (< 0.0001); the estimated prevalence of FM in AS 12.7% and in axial-PsA was 17.2%. Although the BASDAI scores correlated with those of ASDAS-CRP and ASDAS ESR (p<0.0001), only ASDAS had sufficient discriminatory ability to assess disease activity.

Macfarlane et al [147] looked at the influence of co-morbid FM on DAS and response to anti-TNF in axSpA. Patients with axSpA and FM had only modestly higher DAS and worse QoL, after adjustment for disease indices, demographic and socio-economic factors. Poor QoL was more strongly determined by a high score on the FM criteria, indicating a high burden of somatic symptoms. Those with FM had higher BASDAI scores on commencement of anti-TNF and throughout the 12 month follow up, although the difference in magnitude decreased over the period of treatment.

2.9 Biomarkers of disease activity in axial spondyloarthritis

Finding a robust laboratory or imaging biomarker for axSpA would limit our dependence on subjective patient reported outcome measures. The National Institute of Health study group defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [148]. In this section, we look at potential inflammatory, serological and genetic biomarkers as well as imaging indices of disease activity in axSpA.

2.9.1 Inflammation biomarkers

CRP is currently the only laboratory biomarker used in clinical practice to help select patients for treatment and assess response. Studies show that CRP is associated with clinical DAS [149], demonstrates significant response to treatment [150,151], can predict response to anti-TNF [152] and is associated with a greater probability of radiographic progression [153]. However, CRP is elevated in only one third of patients with established SpA, thus its usefulness as a biomarker is limited [150]. High ESR levels predict structural damage but are not associated with clinical disease parameters nor show response to treatment [154]

2.9.2 Serum Amyloid A

Serum amyloid A (SAA) is an apoprotein synthesized by activated monocytes and macrophages in the liver. Jang et al [155] found that levels were higher in axSpA and correlate well with CRP as well as clinical parameters of disease activity but do not have any performance advantages over CRP. Another study comparing ESR, CRP and SAA in 155 AS patients before and after anti-TNF therapy, found significant decrease in all 3 acute phase reactants with treatment and showed a correlation to disease activity measured by BASDAI. Elevated baseline CRP and SAA values were most predictive of a response to anti-TNF therapy[156].

2.9.3 Interleukins

A number of pro-inflammatory cytokines and anti-inflammatory cytokines have been found to be elevated in axSpA. Here, we discuss the most common cytokines found in axSpA and studies assessing their role as a biomarker of disease activity.

2.9.3.1 Interleukin - 6 (IL-6)

IL-6 is the major driver of CRP production and has been extensively investigated in rheumatic disease. Elevated IL-6 levels have been found in cartilage, synovial fluid and connective tissue in SIJ biopsies of patients with axSpA[157] and serum levels have been shown to be significantly elevated in patient with AS compared to controls [158]. High levels of baseline IL-6 were found to be associated with a response to anti-TNF therapy and reductions in IL-6 were associated with improvements in disease activity and spinal inflammation on MRI[159]. In the GO RAISE study, moderately strong correlations were observed between baseline IL-6 and CRP and baseline ASDAS.

2.9.3.2 Interleukin 23 and Interleukin 17

A major advance in our understanding of the pathogenesis of axSpA has been the identification of a crucial role for the IL-23 and IL-17 pathway cytokines. IL-17 and peripheral TH17 cells are reported to be reduced following successful anti-TNF treatment[160] and IL-17 correlates with CRP and disease activity indices, such as BASDAI [161]. However, other authors failed to find correlation between IL-17 levels and inflammatory indices, disease activity or MRI changes [162]. Very similar findings have been found for IL-23 in the same studies. Chen *et al.*, showed that IL-17 and IL-23 performed even better compared to ESR and CRP in discriminating patients with disease activity, assessed by BASDAI [162].

2.9.3.3 Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a driver of angiogenesis, a process occurring in inflammation and bone remodelling. Drouart et al studied the potential use of VEGF as a biomarker of disease by measuring levels in 105 SpA patients versus 50 RA and 64 healthy volunteers [163]. They found serum VEGF levels were significantly higher in AS and RA

patients. VEGF levels correlated with BASDAI, ESR and CRP but were not associated with syndesmophytes or grade of sacroiliitis[125]. Similar findings have been found in further studies predicting radiographic progression [164] and show response to treatment [159].

2.9.4 Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases involved in the degradation of extracellular matrix proteins. Higher serum levels of metalloproteinase 3 (MMP3) have been shown to reflect disease activity and treatment response in axSpA[165]. MMP3 has also been shown to be an independent predictor of structural damage progression in patients with AS [166]. One study found MMP8 and MMP9 (but not MMP3) is better associated with disease activity [167]. However, a more recent study found that MMP3 is raised in AS and a significant drop in MMP3 levels was seen with anti-TNF therapy[168].

2.9.5 Calprotectin

Calprotectin is a heterodimeric protein produced by neutrophils, monocytes, and epithelial cells. It is now an established marker of whole gut inflammation. There have been contradictory results on the expression of calprotectin in axSpA. Calprotectin was found to be significantly higher in SpA patients compared to healthy controls and levels were found to decrease rapidly after treatment [169]. Some studies have shown that serum calprotectin levels are predictive for the progression of structural damage in the spine in axSpA[170]. However, other studies have shown no differences in serum calprotectin between the AS patients and healthy controls were found [171].

2.9.6 Bone and cartilage biomarkers

There has been growing attention on biomarkers of bone metabolism as indicators of disease activity. In particular, wingless-type (Wnt)/beta-catenin pathway, which is responsible for new bone formation. Bone formation is a central process in the pathogenesis of axSpA, leading to characteristic syndesmophyte formation and ankylosis.

Klingberg et al showed that patients with AS had significantly higher serum levels of Wnt3a ($p< 0.001$) and lower levels of sclerostin ($p = 0.014$) compared with the controls[172]. Similar findings have been replicated in other studies of sclerostin in patients with axSpA[50,56,64] and an association with disease activity has also been shown.[49,51]. Further studies suggest a prognostic value for sclerostin with baseline levels in AS and axSpA associated with new syndesmophyte formation[50–52].

Dickkopf-1 (Dkk-1) is another inhibitor of the Wnt pathway, which one would expect to be low in axSpA. However, studies have shown higher levels in patients with AS compared to healthy controls[173] leading to the hypothesis that Dkk-1 may be aberrant in axSpA[174]. Dkk-1 has not been show to correlate with CRP level[175] and anti TNF treatment does not affect its levels[176].

2.10 Imaging biomarkers

Owing to the anatomical structure of the axial skeleton, overt inflammation of the spine and SIJs cannot be detected by physical examination in the same way as peripheral joints in

rheumatoid arthritis. Therefore, imaging has played a crucial role in the detection of axial inflammation..

2.10.1 Conventional Radiography

X-rays are important in demonstrating structural changes in the SIJs and spine. A number of scores have been devised to assess the spine, however, the most widely used is the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)[177]. This score assesses the anterior site of vertebrae from lower border of C2 to the upper border of T1 and the lower border of T12 to the upper border of S1 on lateral spinal films. A score of 0-3 is given according to the presence or absence of vertebral endplate changes. The maximum score is 72. However, X-ray changes rely on the presence of new bone formation and not inflammatory lesions, therefore, assessing response to treatment over short periods of time is not possible. Even after 2 years of treatment with infliximab, adalimumab or etanercept, no significant difference in mSASSS scores was found [178–180]. This finding has been replicated in radiographic scores for SIJs. Radiographic progression in axSpA is a controversial topic and there is evidence to suggest that new bone formation in axial spondyloarthritis occurs independent of reduction of inflammation with biologic therapy.

2.10.2 Ultrasonography

The development of musculoskeletal (MSK) ultrasound has significantly improved the early detection of synovitis in peripheral inflammatory arthritis and is routinely used to confirm deep remission in RA. Inflammation is associated with neo-vascularisation and flow in these blood vessels are detected by doppler ultrasound. Conventional doppler ultrasound cannot detect neovascularisation in deep structures such as the spine and SIJS, however, colour doppler has been found to be more sensitive.

Colour doppler assesses the restrictive index (RI) calculated as the peak systolic velocity-end diastolic velocity/peak systolic velocity. In the presence of inflammation, the peak systolic velocity is low and end diastolic velocity may be higher and hence RI falls. Therefore, resolution of inflammation is associated with a rise in RI. To date, there are only 2 studies that have attempted to assess changes in RI in arteries supplying the spine and sacroiliac joints. The first paper was published by Arslan et al[181] . This study visualized blood vessels in and around the sacroiliac joints in 21 patients with active sacroiliiitis of varied aetiology. They compared the RI at baseline to a control group of 6 patients with osteoarthritis and 8 healthy volunteers. They found that the RI in patients with active sacroiliiitis was significantly lower than in the control group. They went on to repeat the scans after treatment and showed that RI increased significantly. A subsequent study by Unlu et al [182] studied RI in blood vessels in SI joints, lumbar spine and thoracic spine in a more homogenous group of 39 AS patients compared with 14 healthy controls. They then treated the AS patients, 11 of whom received anti-TNF therapy and repeated the scans at 12 weeks. They found that RI values for the SI joints, thoracic and lumbar spine were lower in AS patients when compared to controls. Patients were stratified according to disease activity. Those with active disease had a lower RI of the thoracic and lumbar spine, than those with inactive disease. Treatment with anti-TNF therapy in this group resulted in a significant increase in RI in the SI joints and lumbar spine but not in the thoracic spine. The authors proposed that this could be used as a biomarker of response to therapy. However, these are small pilot studies and no comparison was made with MRI findings.

A Spanish study [183] assessed the validity of spectral Doppler in sacroiliitis as defined by presence of Doppler signal within the sacroiliac joint with a resistive index below 0.75. They studied 108 patients of which 53 had SpA with symptoms suggestive of sacroiliitis, 26 SpA patients without symptoms and a third group of 27 which consisted of healthy volunteers and patients with mechanical back pain. US scans picked up Doppler signal in 37 patients of which 33 were symptomatic SpA patients. This technique had a positive predictive value of 70.5% and a negative predictive value of 84.5%. It showed a sensitivity of 68.6% and a specificity of 85.7%). These results are inferior to MRI studies, which will be discussed in Chapter 4.

2.10.3 Computerised Tomography

Computerised Tomography (CT) is useful for the detection of structural damage in the SIJs and spine including fatty change, erosions and ankylosis, however, does not detect bone inflammation or bone marrow oedema. Dual energy CT, also known as spectral CT, uses two separate x-ray photon energy spectra, allowing for the detection of different attenuation properties at different energies. Spectral CT can detect both calcium and water concentration within a tissue and some studies have demonstrated its capacity for quantitative analyses of the bone-marrow oedema within the SIJs [184–186] . However, the assessment of bone marrow oedema is still considered to be superior with MRI, which does not also impose the risk of ionising radiation.

3 The specificity of the BASDAI score: A prospective observational cohort study

Introduction:

In Chapter 2, the incidence of CWP and FM in axSpA was discussed: in particular, the significant overlap in symptoms, which can hinder an accurate assessment of disease activity. Mechanical back pain arising from a number of sources including degenerative intervertebral discs, facet joint synovitis and spondylolisthesis are common in the general population[187] and can occur concomitantly with axSpA. Many symptoms of mechanical back pain mimic those of axSpA making it difficult to assess the burden of inflammatory disease clinically. The current clinical assessments of disease activity in axSpA are PROMS; with the BASDAI being the most utilised assessment of disease activity. Studies demonstrating the limitation of this score are discussed in 2.8.

In this study, I assess how specific the BASDAI score is for symptoms of axSpA. Patients were asked for their consent to be approached by a member of the research team by their attended physiotherapist. I was then responsible for gaining verbal consent from each participant to take part in the study. Data collection and analysis were completed by myself.

3.1 Methods

This study received ethical approval from the London Riverside Ethics Committee (IRAS 208355).

The electronic patient records (EPR) of patients attending the MSK physiotherapy and hypermobility services at UCLH from January to July 2018 were screened for patients with backpain from all causes, fibromyalgia and hypermobility. Patients eligible for the study were highlighted to the attending physiotherapist. Verbal consent to be approached by a researcher was gained by the attending physiotherapist. Patients were subsequently approached (on the same day) and verbally consented to complete a paper questionnaire incorporating demographic and diagnostic information and a BASDAI questionnaire. This took approximately 5 minutes to complete and was returned in a sealed envelope (provided) to the physiotherapist. The term "ankylosing spondylitis" in the BASDAI questionnaire was replaced with "back pain" to represent those patients without this diagnosis. Patients with confirmed axSpA and no concomitant chronic pain were taken from the MRI study cohort (Chapter 7). These patients had high disease activity by virtue of being eligible for this study.

3.2 Results

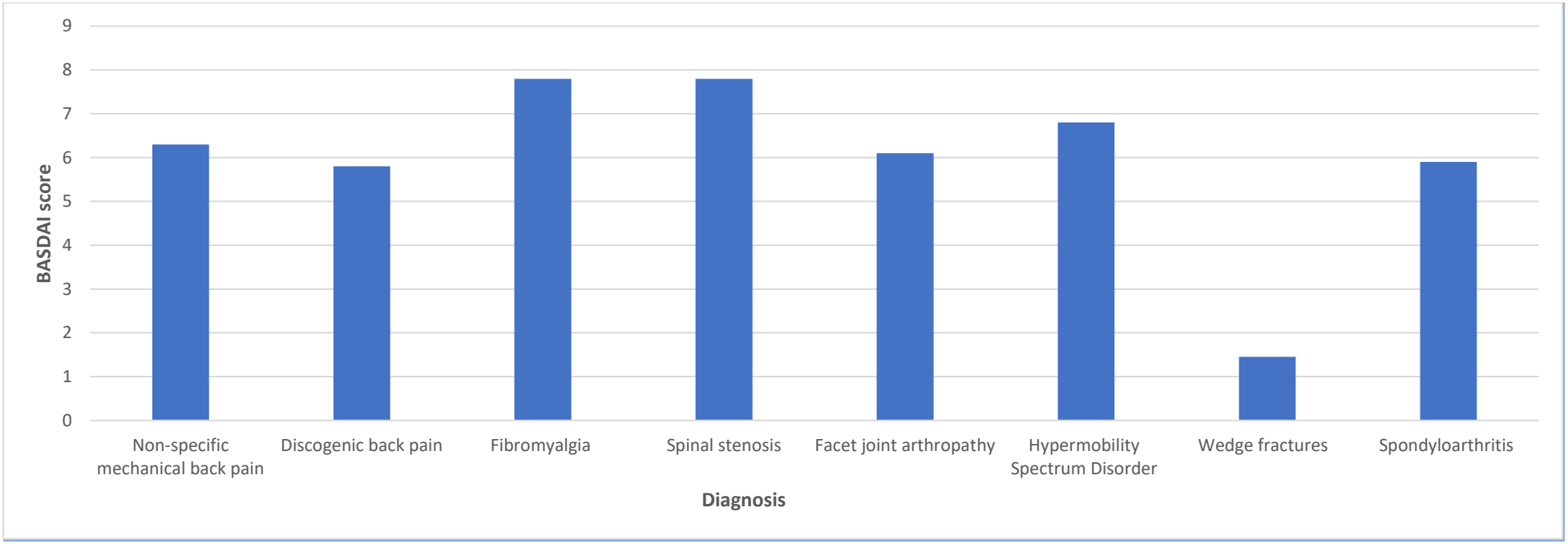
202 patients were include in the study. Baseline characteristics are show in Table 3-1. For each diagnosis, the mean score and standard deviation (SD) for each question in BASDAI (BASDAI 1, 2, 3 etc) and the overall BASDAI score is shown.

Table 3-1 Baseline characteristics and mean (SD) BASDAI results for patients with chronic pain and other spinal pathologies

Spinal disease	Number of patients	F:M:GN	Age	Spinal VAS	BASDAI 1	BASDAI 2	BASDAI 3	BASDAI 4	BASDAI 5	BASDAI 6	Total BASDAI score
Non-specific mechanical back pain	25	12:13	56.1 (14.27)	6.3 (2.51)	6.4 (2.80)	6.8 (2.51)	5.6 (3.16)	6.3 (2.20)	6.4 (3.22)	5.8 (3.10)	6.3 (2.28)
Discogenic back pain	14	7:7	53.9 (14.08)	6.2 (2.04)	6.5 (1.56)	6.2 (2.58)	4.9 (3.51)	5.9 (2.76)	6.5 (2.29)	4.7 (3.07)	5.8 (1.64)
Fibromyalgia	44	41:3	49.7 (12.6)	8.2 (1.32)	8.8 (1.60)	8.4 (1.13)	7.3 (2.02)	8.1 (1.52)	7.1(2.37)	6.4 (2.58)	7.8 (1.43)
Spinal stenosis	2	2:0	70 (15.56)	7.5 (3.54)	9 (1.41)	10 (0)	6 (5.66)	9 (1.41)	5 (7/07)	5 (7.07)	7.8 (3.11)
Facet joint arthropathy	7	5:2	47.3 (10.34)	6.8 (2.63)	5.8(2.63)	7.3 (2.87)	3.8 (3.30)	7 (2.71)	7 (2.16)	6.8 (2.22)	6.1 (2.21)
Hypermobility Spectrum Disorder	108	15:92:1	34.3 (11.86)	6.1 (2.38)	7.7 (1.76)	7.4 (1.92)	6.6 (2.39)	6.2 (2.25)	6.8 (2.50)	5.4 (2.83)	6.8 (1.57)
Wedge fractures	2	1:1	67.5 (14.85)	1.5 (2.12)	2 (2.12)	2 (1.41)	2 (1.41)	2 (1.41)	2 (1.41)	2 (1.41)	1.45 (1.56)
Axial spondyloarthritis	21	6:15	42.7 (10.42)	5.8 (2.06)	5.9 (1.90)	6.2 (2.13)	5.6 (2.25)	5.7 (1.79)	5.4 (2.14)	5.8 (2.67)	5.9 (1.47)

F Female, M Male, GN Gender Neutral, BASDAI Bath Ankylosing Spondylitis Disease Activity Index, VAS visual analogue score. BASDAI (number) denotes the question number in the standard BADSAI questionnaire.

Figure 3-1 BASDAI scores for different spinal pathologies



3.3 Discussion:

BASDAI scores were highest for patients with FM and spinal stenosis. There was no significant difference in total BASDAI scores between patients with axSpA and non-specific back pain ($p = 0.78$), axSpA and discogenic back pain ($p = 0.62$), axSpA and facet joint arthropathy ($p = 0.98$) and axSpA and hypermobility ($p = 0.58$). Patients with FM and spinal stenosis had significantly higher BASDAI scores than patients with active axSpA alone ($p = 0.037$ and $p = 0.041$, respectively). Whilst these p scores are significant, note should be taken of the increased risk of Type I errors in performing multiple paired t tests.

3.4 Conclusion

These results highlight that BASDAI scores are not specific to axSpA and can be affected by a range of degenerative spinal issues and complex pain syndromes.

4 The use of Magnetic Resonance Imaging in the assessment Disease Activity in Axial Spondyloarthritis

4.1 Overview

In this chapter, I will review the role of MRI in the assessment of axSpA, including the characteristic MRI changes associated with axSpA, MRI scoring methods for axSpA and the relationship between imaging scores and clinical disease activity. Finally, I will introduce the potential role for qMRI.

4.2 MRI lesions in axial spondyloarthritis

The recognition that early inflammatory lesions of the spine and SIJ could be demonstrated on MRI without associated radiographic changes has led to significant improvements in the earlier detection and treatment of the disease. Inflammation on MRI is typically seen as areas of increased signal intensity on fluid-sensitive sequences (particularly fat-suppressed, T2-weighted sequences). These areas of increased signal reflect an increase in free water content in the bone marrow (bone marrow oedema), which occurs as a result of inflammation. The existing evidence suggests that bone marrow oedema (BMO) is the most sensitive individual lesion for the diagnosis of axSpA [188–193]. Specificity of this finding can be improved by considering BMO in combination with other structural lesions typically found in axSpA. These include fatty infiltration or fat metaplasia, erosions and ankylosis [189–191,193].

Fatty infiltration is thought to be a post inflammatory process, identified as an area of increased signal on T1-weighted images and low signal on fat suppressed

sequences. Fat infiltration alone shows moderate sensitivity and specificity in the diagnosis of axSpA, but has a greater utility in AS and established disease [189,190,194,195].

Periarticular erosions are visualised as low T1-signal bone defects at joint margin and are important structural lesions in the diagnosis of axSpA. Erosions demonstrate high specificity for axSpA [204–206,] but are more sensitive in AS than nr-axSpA[194,195]. Other lesions including sclerosis, enthesitis, and capsulitis can also be detected on MRI and add further support the diagnosis of axSpA [189,196].

Active sacroiliitis on MRI scanning is identified by the presence of subchondral bone marrow oedema/osteitis. This can be visualised on short T1 inversion recovery (STIR) sequences. In accordance with ASAS guidelines, BMO needs to be present on at least 2 slices or in two separate quadrants on the same slice to be eligible for scoring [197].

Figure 4-1 Active sacroiliitis – bone marrow oedema on STIR images of sacroiliac joints (taken from study participant with consent)

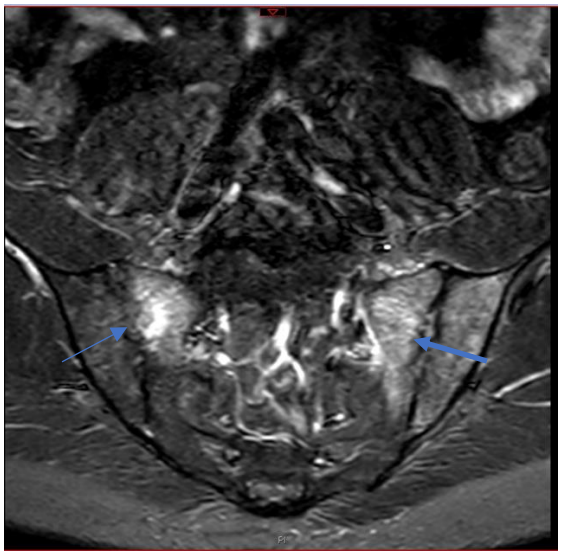
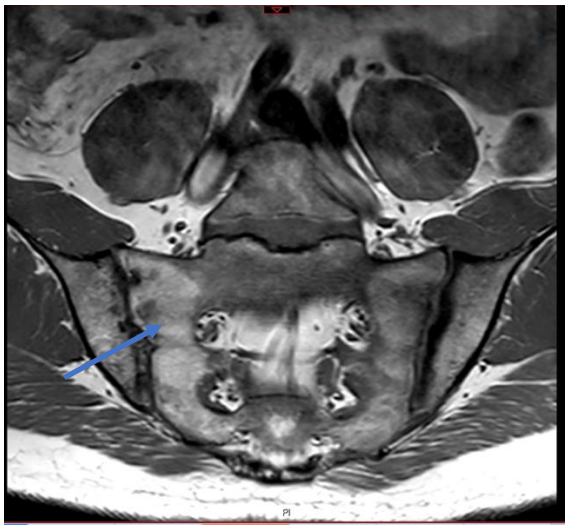


Figure 4-2 Fatty changes of the sacroiliac joints on T1 images (taken from study participant with consent)



Isolated spinal inflammation in the absence of active sacroiliitis has been reported in 24-49% of patients with axSpA[198,199]. Inflammatory lesions can occur anywhere along the spine, but are more prevalent in the thoracic spine. Acute inflammation of spinal enthesis at the anterior vertebral corners produce a "shiny appearance" known as

Romanus lesions. These lesions can also be found at the posterior corners of the vertebral body. Studies have shown that Romanus lesions can be present in patients with degenerative arthritis and healthy volunteers as well[199]. However, when 3 or more Romanus lesions are present, it is highly indicative of SpA[199]. Chronic inflammatory lesions, known as fatty Romanus lesions (FRLs) are seen on fat sensitive scans. A recent study showed that the presence of > 5 FRLs increased the likelihood ratio of the diagnosis of SpA to 12.6 (a highly significant level)[200] .

Figure 4-3 Spinal fatty corner lesions on T1 weighted images (images taken from study participant with consent)

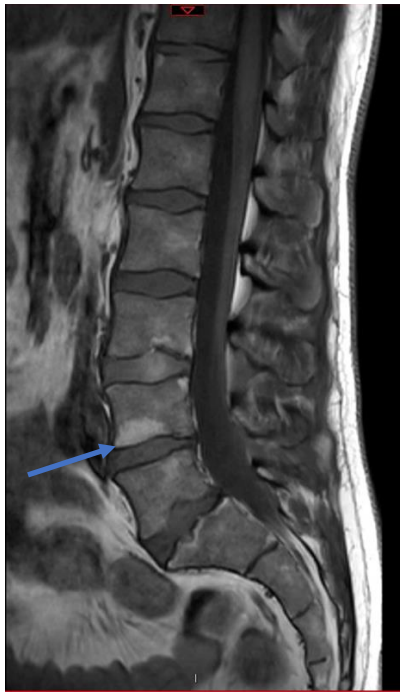
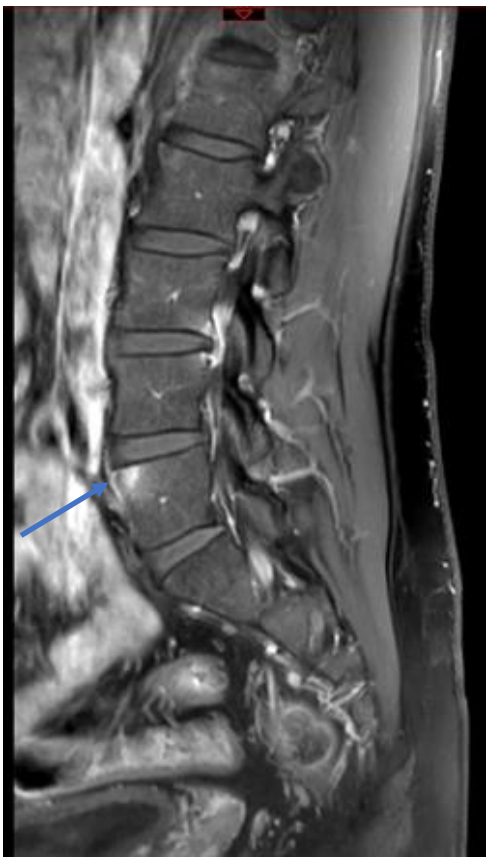


Figure 4-4 Inflammatory spinal corner lesions on post contrast T1 weighted fat saturated image (images taken from study participant with consent)



In some patients, there is BMO on either side of a vertebral end plate with involvement of the intervertebral disc. This is called spondylodiscitis or an Anderson lesion. This can sometimes be associated with vertebral fractures and collapse. Similarly, chronic lesions can involve the entire breadth of the vertebral body leading to calcification of inter-vertebral disc and pseudo-arthrosis of adjacent vertebrae. Other sites of inflammation include the posterior elements - the pedicle, facet and costovertebral joints and spinous processes.

4.3 MRI Scoring systems

A number of scoring systems have been devised to quantify the degree of disease activity on MRI. These scoring systems have been devised to facilitate data collection for clinical trials rather than for clinical purposes. All scoring systems obtain sagittal T1 weighted and STIR sequences of the spine and semi-coronal views of the SIJs. Most systems score both the spine and SIJs, although some systems have been devised for either the spine or sacroiliac joints individually. Most scoring systems score both active lesions (BMO) and structural changes (fatty lesions, ankylosis and erosions) on MRI.

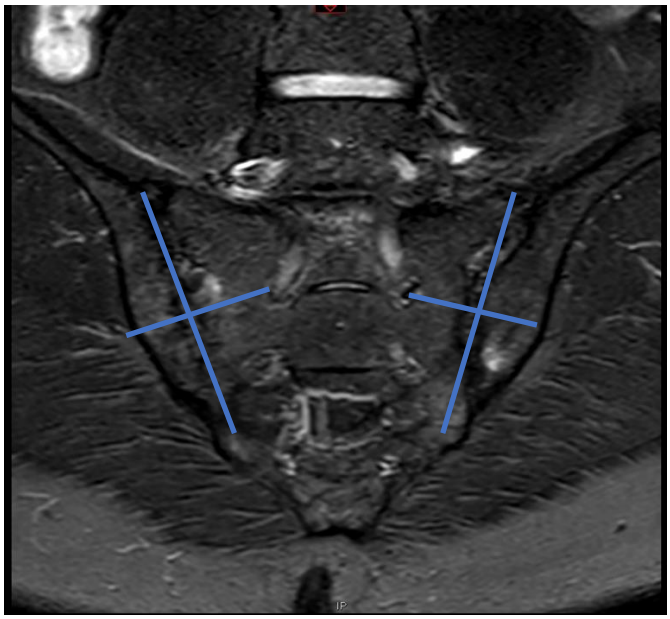
4.3.1 Scoring systems for the sacroiliac joints

Scoring systems for the assessment of disease activity in the SIJs are based on either global scores per quadrant or individual scores in consecutive semi coronal images through the joint. Generally, the presence and extent of BMO in the subchondral portion of the joint is the primary MRI feature that is scored, although some methods also score inflammation in the joint space and/or ligamentous portion of the joint.

The Spondyloarthritis Research Consortium of Canada (SPARCC) is the most widely used score for MRI SIJs[201]. It assesses the subchondral portion of the joint, scoring the presence (score 1) or absence (score 0) of BMO in each SIJ quadrant (defined according to a vertical axis through the joint cavity and a horizontal axis bisecting this line at its midpoint as shown in Figure 4-5) in each of six consecutive semi coronal slices adds points for depth and intensity. An additional score of 1 is added

if the BMO in a quadrant is more than 10mm deep, and another score of 1 is added if the BMO in a quadrant was at least as intense as the cerebrospinal fluid. A total score out of 72 is given. The SPARCC structural score (SPARCC SSS) uses the same six consecutive slices to assess for fat, erosion and ankylosis. The presence/absence of these lesions is evaluated per quadrant (for fat and erosion) and per joint half (ankylosis) providing a total score of 50.

Figure 4-5: Quadrantic approach to SPARCC SIJ score (images taken from study participant)



4.3.2 Scoring systems for the spine

Three scoring methods have been approved by OMERACT: the AS spine MRI score for activity (ASspiMRI-a), the Berlin method (a modification of the ASspiMRI-a), and the SpA Research Consortium of Canada MRI Index for Assessment of Spinal Inflammation in AS (SPARCC). Scoring systems for the spine divide the spine into

disco-vertebral units by drawing an imaginary horizontal line through the centre of each vertebral body. A disco-vertebral unit is, therefore, composed of the lower half of the upper vertebra, the inter-vertebral disc and the upper half of the lower vertebra. This divides the spine into 23 disco-vertebral units extending from the lower border of C2 to the upper border of S1.

The ASspiMRI-a scoring system assesses all 23 DVU. BMO is graded (0-3) for each DVU. Three more grades (4-6) are added if erosions are also visualized, leading to a maximum score of 138 for the entire spine [202]. The Berlin scoring system is a modification of the ASspiMRI-a system, excluding the score for erosions, so that a DVU can score between 0 and 3, bringing the maximum total score to 69 [203]. SPARCC method [204] only takes into account the 6 most affected disco-vertebral units and divides each unit into 4 quadrants. The presence of increased STIR signal in each of these 4 quadrants is given a score of 1 (increased signal) or 0 (normal signal). This is repeated for each of 3 consecutive sagittal slices resulting in a maximum score of 12 per DCV. On each slice, the presence of a lesion exhibiting intense signal in any quadrant was given an additional score of 1. Similarly, the presence of a lesion exhibiting depth >1cm in any quadrant was given an additional score of 1. A maximum additional score of 6 for each specific vertebral unit is therefore given, bringing the total score to 18 per unit.

4.4 Does MRI correlate with other measures of disease activity in axSpA?

The relationship between MRI scores and disease activity is a controversial one with conflicting results from studies. Zhang et al showed a statistically significant

correlation between BASDAI and SPARCC scores in 52 patients with AS[205]. Navarro-Compan et al showed that in male (but not in female) patients, ASDAS scores were longitudinally associated with MRI-SIJ inflammatory lesions [206]. Using the ASspiMR-a score, Konca et al[207] investigated the relationship between spinal MRI disease activity and other clinical outcome measures, including BASDAI, ASDAS, BASFI, BASMI, ASAS and ASQoL. They found that cervical and lumbar spinal scores correlated well with clinical outcome measures but the thoracic spine was the region most related with clinical disease activity scores. Bredella et al[208] showed that increased inflammatory SIJ lesions was associated with greater CRP levels, but not associated with other clinical indices of disease activity. Another study of patients with established AS of >10 years of duration did not find any correlation between MR DAS (spine only) and clinical DAS [209]. Klitx et al[210] found no significant difference in the number of spinal inflammatory lesions between individuals with high and low clinical DAS (using the BASDAI < 4 threshold). Mackay et al[211] showed a weak, non-significant correlation between total SPARCC score and BASDAI, ASDAS ESR and ASDAS CRP. There was no significant difference in the SPARCC score of participants with high and low clinical DAS. Lau et al[212] designed a cross sectional study to assess the correlation between the MRI disease activity scores and clinical DAS in Chinese patients with active axSpA. No statistically significant correlation between the SPARCC scores and clinical disease activity was demonstrated, including ASDAS ESR, ASDAS CRP, ESR, CRP, BASDAI, BASFI, the patients' global assessment and pain score.

There are a number of reasons for the lack of correlation between clinical DAS and MRI DAS. Firstly, clinical DAS may be more reflective of cumulative (chronic) disease activity with MR DAS reflective of the acute disease. Chronic manifestations of axSpA, such as ankyloses and secondary degenerative changes can lead to increased clinical DAS [213] but the relative lack of acute inflammatory lesions would lead to a low MR DAS. In support of this hypothesis are the significant correlations demonstrated between SPARCC scores and inflammatory markers (CRP and ESR) in Mackay et al's study. If clinical and MR DAS are measuring different aspects of axSpA, the lack of correlation should not be surprising.

An alternative explanation is that MRI DAS may offer a more objective overview of disease activity compared with the more subjective nature of clinical DAS. Previous studies have demonstrated weak correlation between patient and physician assessment of disease activity as well as weak correlations between patient assessment of disease activity and other objective markers of disease activity (ESR/CRP)[214]. The objective nature of MR DAS offers a potential advantage in terms of reducing the variability associated with patient-reported measures.

Whilst it may not be associated with clinical DAS, there is evidence to suggest that MRI changes do predict disease progression. Sepriano et al [215] found that the presence of BMO at MRI-SIJ in two large cohorts of axSpA patients was highly predictive of structural progression at 4-5 years. Maksymowych et al[216] showed that fat metaplasia on MRI of the SIJs increases the propensity for disease progression in

the spine of patients with spondyloarthritis. Dougados et al[217] showed that baseline MRI-SIJ inflammation drives 5-year radiographic changes: 40 patients with early inflammatory back pain of < 2 years' duration were followed for a mean of 7.7 years and severe BMO on MRI of the SIJ was together, with HLA B27 positivity, a strong predictor of future AS. Mild or no sacroiliitis, irrespective of HLA B27 status, was a predictor of not developing AS.

4.4.1 Can MRI disease activity scores predict response to treatment?

Cui et al [218] assessed the SPARCC scoring method to compare treatment methods in patients with axSpA. MRI abnormalities in BMO were compared before and after treatment in order to compare the efficacy of anti-TNF and DMARD alone or in combination with treatment for axSpA. After treatment ASDAS and SPARCC scores, ESR and CRP were significantly improved ($p< 0.05$) in the anti-TNF monotherapy and combination groups. Weiß et al [219] used data from 112 patients with axSpA originally enrolled in two RCTs before and after one year of treatment with Etanercept and Adalimumab. They found that change in BASDAI showed a significant correlation with the change in SIJ score in patients with < 4 years of disease. For patients the correlation was poor. Rudwaleit and colleagues scored MRI scans of the spine and SIJs using the Berlin method in patients from two previous RCTs of anti-TNF in AS. They found that patients with a high spinal score (>11) were more likely to achieve a 50% reduction in their BASDAI (BASDAI 50) at 3 months. It is interesting to note, however, that in this study, 33.3% of patient with negative scans had a BASDAI 50 response [220]. Machado et al [221] found that ASDAS

and CRP improvements correlated with MRI improvement. However, stronger correlations were observed for CRP. In the ABILITY-3 trial, consistent and strong baseline predictors of remission following adalimumab therapy included younger age, male sex, HLA-B27 positivity and higher SPARCC MRI sacroiliac joint score[222].

4.4.2 Advantages and disadvantage of qualitative MRI scoring systems

Qualitative MRI is accessible to all healthcare trusts, is relatively fast and sequencies can be standardised between scanners allowing reliable comparison of scans obtained from different scanners. However, there are a number of limitations associated with current MRI scoring systems. Notably, MRI interpretation relies on qualitative assessment of images – that is, the scans are assessed by a radiologist or rheumatologist, who scores the images based on their impression of whether a particular feature is present or not. This is inherently subjective and dependent on the expertise (and opinion) of the radiologist/rheumatologist. Perceptions of inflammation severity may be biased by the nature of the caseload at a given hospital – clinicians who are used to seeing severe cases of axSpA may give systemically lower rating than those who only see the disease rarely. The binary choice for each quadrant does not necessarily reflect the severity of inflammation and very subtle inflammatory changes are allocated the same representation as significant inflammation. Image interpretation also depends on the quality of fat suppression, which is variable and depends on the specific sequence and scanner being used. MR imaging is susceptible to artefacts, and relatively small artefacts can be interpreted as inflammation, particularly by observers who are inexperienced or

unfamiliar to the specific scanner being used. These issues can lead to poor agreement both within and between observers, even in controlled research settings where observers have often undergone calibration exercises prior to participation. Lukas et al [223] performed a multi-reader study examining the inter reader reliability, sensitivity to change and discriminatory ability of 3 different scoring methods. Using 9 experienced readers, they found inter-reader interclass correlation coefficient (ICC) values varied dramatically.

4.5 Quantitative MRI and its potential role in assessing disease activity in axSpA

In the last decade, there has been a rapid expansion in the use of qMRI techniques to measure disease characteristics. These techniques are able to detect tissue attributes such as cellularity, vascularity or fat content, based on the change in signal characteristics over these scans. Each pixel (picture element) has a measurable numerical value that reflects the intrinsic properties of a tissue, rather than arbitrary signal intensity produced by a standard MRI. In this way qMRI images can be viewed as a set of measurements which are analogous to measurements made by laboratory assays. These measurements can be used as quantitative imaging biomarkers (QIB).

Quantitative MRI techniques include diffusion weighted imaging (DWI) and chemical shift encoded (CSE) MRI. DWI measures the mobility of free water in living tissue; areas of active inflammation have increased free water content that results in increased diffusivity. Apparent diffusion coefficient (ADC) values in these regions

are higher than in non-inflamed tissue and have been used to evaluate sacroiliitis and as a biomarker for measuring treatment response.

Chemical shift encoded MRI (CS-MRI) relies on the fact that fat and water protons resonate at slightly different frequencies. Fat fraction, defined as the signal arising from fat protons divided by the sum of the signals from fat and water protons can be calculate from the fat and water images. Like ADC, the proton density fat fraction (PDFF) can be seen as a quantitative image based indicator of biological and pathological processes – an imaging biomarker.

The ADC is an index of diffusivity and can potentially provide additional quantitative information about the intensity of inflammation. Bozgeyik et al [224] showed that the ADCs of SIJs were higher in patients with sacroiliitis than in those with mechanical back pain. In a study of 62 patients with axSpA, Gezmis [225] found a positive correlation between ADC and CRP. These studies mainly focussed on the application of DW imaging on SIJs. Lee et al [226] looked at ADC in discovertebral lesions in a patients who fulfilled ASAS criteria for axSpA. They found that this correlated with disease activity, functional impairment and patient global assessment in axSpA.

Bray et al[227] evaluated PDFF and R2*, that is T2 relaxation values, can be used as potential markers of bone marrow composition and structure in inflamed juxta-articular bone. They created a series of phantoms – compositions containing varying

proportions of fat, water, and trabecular bone and then imaged these in CSE-MRI to assess the relationship between BMO and R2* in the presence of fat and between known FFs and PDFF measurements in the presence of bone. Subsequently, they performed CSE MRI in the SIJs of patients with axSpA and examined whether there were significant differences in PDFF and R2* between areas of active inflammation, fat metaplasia and normal marrow. Their findings showed that PDFF measurements accurately reflect changes in bone marrow composition in areas of oedema and fat metaplasia, which can be viewed as active inflammatory and structural lesions.

Translating this to clinical practice, ADC and PDFF measurements of the SIJs may provide more accurate measures of inflammation then the current scoring systems. Wang et al [228] compared whole lesion ADC histogram analysis with the SPARCC MRI index in evaluating disease activity in axSpA. They found that ADC mean, ADC percentiles and SPARCC MRI index of the active group were significantly higher than the inactive and control groups (all $p < 0.001$). The 90^{th} percentile could differentiate the inactive from the control group and the low disease activity group from the inactive group. The 50^{th} percentile of the high disease activity group was significantly higher than the low group, while the SPARCC MRI index of the very high disease activity group was higher than the high group, demonstrating that whole volume ADC histogram analysis was superior to the SPARCC MRI index in assessing axSpA activity states.

4.5.1 Advantages and disadvantages of quantitative MRI

QIBs have a number of advantages over qualitative scoring systems such as the SPARCC method. Notably, a QIB can eliminate the need for visual interpretation, thus avoiding the bias, inconsistency and operator dependence which are inherent to qualitative scoring. Additionally, QIB measurements can be automated relatively simply, and could be incorporated into scanner software or made available on PACS workstations. This would be mean that objective measurements of disease characteristics would be available to clinicians much more readily and might lower the threshold for introduction into clinical practice. There are limitations associated with qMRI. Notably, QIBs results vary between machines preventing direct comparison of results obtained from difference scanners.

In conclusion, qMRI may provide a more informative assessment of disease activity in axSpA, which removes the subjectivity of expert opinion in qualitative MRI interpretation and could be delivered using a semi-automated tool which is fast and reliable. This will be assessed in a prospective study (Chapter 7).

5 Performance of Magnetic Resonance Imaging in the Diagnosis and Assessment of Axial Spondyloarthritis: A Systematic Literature Review

5.1 Overview

This chapter includes a systematic literature review (SLR) on the use of MRI in the detection and assessment of axSpA. The purpose of this review was to critically appraise all the data on the utility of MRI in axSpA – the evidence for its use, the pitfalls and areas for potential development. This review was used to inform the British Society of Spondyloarthritis (BRITSpA) guidelines on the use of MRI in axSpA[229]. This work was shared equally with Dr Tim Bray, Consultant Radiologist, under the supervision of Professor Pedro Machado, Consultant Rheumatologist.

5.2 Background

Despite the clear utility of MRI in axSpA, there remains inconsistency around its use in clinical practice. A survey of 269 radiologists in acute UK NHS trusts showed substantial variability in the use of contrast, sequence choice and anatomical coverage [230]. This survey found that only 75% of radiologists were aware of the term axSpA, and only 31% and 25% were aware of the ASAS definitions of positive MRI of the SIJ and spine [230]. Despite being widely accepted as a key diagnostic marker, BMO was not used as a potential diagnostic feature of axSpA by 18% of radiologists [230].

The heterogeneity of MRI protocols and image interpretation is likely to cause inconsistency in the way that axSpA is diagnosed and may lead to missed or delays in diagnosis and inadequate or unnecessary treatment for patients. As such, there is a need to standardise the use of MRI and a consensus on how MRI lesions should be interpreted in relation to axSpA. The aim of this SLR is to summarise the available evidence on the diagnostic utility of MRI in axSpA, including the significance of specific lesions, the influence of anatomical coverage and effect of acquisition parameters.

5.3 Materials and Methods

5.3.1 Research Questions

Members of a BRITSpA MRI task force (nine MSK radiologists and nine rheumatologists with an interest in axSpA), proposed clinically relevant research questions (RQs) related to key aspects of the use of MRI in axSpA. Three final research questions (RQ1-3) were formulated and agreed upon by consensus.

Table 5-1 Research questions (RQ) generated by the BRITSpA working group

RQ1	Which lesion, or combination of lesions, is most sensitive and specific for the diagnosis of axSpA?
RQ2	How does the choice of anatomical region influence diagnostic performance?
RQ3	How do MRI acquisition parameters influence diagnostic performance?

These questions were framed according to the Population, Intervention, Comparator, Outcome (PICO) format [231]. For all three questions, the population of interest consisted of adult patients (≥18 years) with suspected and/or established axSpA, and the

reference standard consisted of a clinical diagnosis of axSpA (optimal scenario) or global imaging criteria considered suggestive of axSpA (suboptimal scenario). The outcomes of interest were the sensitivity, specificity and likelihood ratios for the diagnosis of axSpA; for RQ2 and RQ3 additional endpoints including the prevalence of spinal inflammation in groups with and without SIJ inflammation and additional metrics relating to sequence performance.

5.3.2 Study Selection and Data Extraction

The SLR was conducted by two reviewers (AJ and TPJB) under the guidance of the methodologist (PMM). The search strategy from a previous European League Against Rheumatism (EULAR) systematic review, addressing the role of imaging in spondyloarthritis, was adopted [232]. MEDLINE (1946), Embase (1974) and Cochrane (1993) databases were searched without language restrictions. We included all studies performed between January 2013 and March 2017, in addition to relevant studies selected from the previous EULAR SLR, which included all studies from the inception of the databases up to January 2013 [232]. Each reviewer screened titles and abstracts of all citations independently, and potentially relevant articles were reviewed in full text and assessed for risk of bias (RoB). Papers fulfilling the inclusion criteria underwent full data extraction. Both reviewers independently retrieved data using a predefined data extraction sheet. The following data were extracted: main characteristics of study (authors, journal and year of publication), study design, number of included patients (subdivided into axSpA patients and controls), reference standard, features of interest, technical factors relating to the acquisition (magnetic field strength, slice thicknesses,

use of gadolinium, acquisition planes, spine coverage and sequence parameters), and the relevant outcome data. For studies addressing the effect of acquisition parameters (Q3), we also recorded technical performance metrics including the contrast-to-noise ratio.

5.3.3 Search Strategy

The MEDLINE (via Pubmed), EMBASE (via Ovid) and Cochrane databases were searched using the following terms. Note that imaging modalities other than MRI (radiography, CT, PET and US) were included in the search to avoid missing studies of multiple imaging modalities including MRI; studies which did not involve MRI were excluded at the stage of screening by title and abstract.

5.3.3.1 MEDLINE via Pubmed

1. "spondylarthropathies"[MeSH Terms]
2. spondylart*[Text Word]
3. (Reactiv*[TI] AND Arthriti*[TI])
4. (Psoria*[TI] AND Arthriti*[TI])
5. (ankyl*[TI] AND Spondyl*[TI])
6. (((inflam*[TiAB] AND (peripher*[TIAB] OR tendon*[TIAB] or tendinop*[TIAB] OR limb*[TIAB]) AND pain [TIAB]))))
7. spondylo*[TiAB]
8. (((inflam*[TiAB] AND (back[TIAB] OR spin*[TIAB]) AND pain [TIAB])))
9. or/1-8
10. "Tomography"[Mesh]
11. "Magnetic Resonance Imaging"[Mesh]
12. "Ultrasonography"[Mesh]
13. "Tomography, X-Ray Computed"[Mesh]
14. "Positron-Emission Tomography and Computed Tomography"[Mesh]

15. "Positron-Emission Tomography"[Mesh]
16. "Tomography, Emission-Computed, Single-Photon"[Mesh]
17. ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields])
18. "mri"[All Fields]
19. ultrasono*[TIAB]
20. echograph*[TIAB]
21. "CT scan*"[TIAB]
22. tomograph*[TIAB]
23. scintigraph*[TIAB]
24. (PET[Title/Abstract]) AND tomog*[Title/Abstract])
25. (SPECT[Title/Abstract]) AND photon[Title/Abstract])
26. or/10-25
27. 9 and 26
28. (animals[mh] NOT human[mh])
29. 27 not 28
30. (("case report*" [TI]) OR (case reports[Publication Type]))
31. 29 not 30

5.3.3.2 EMBASE via Ovid

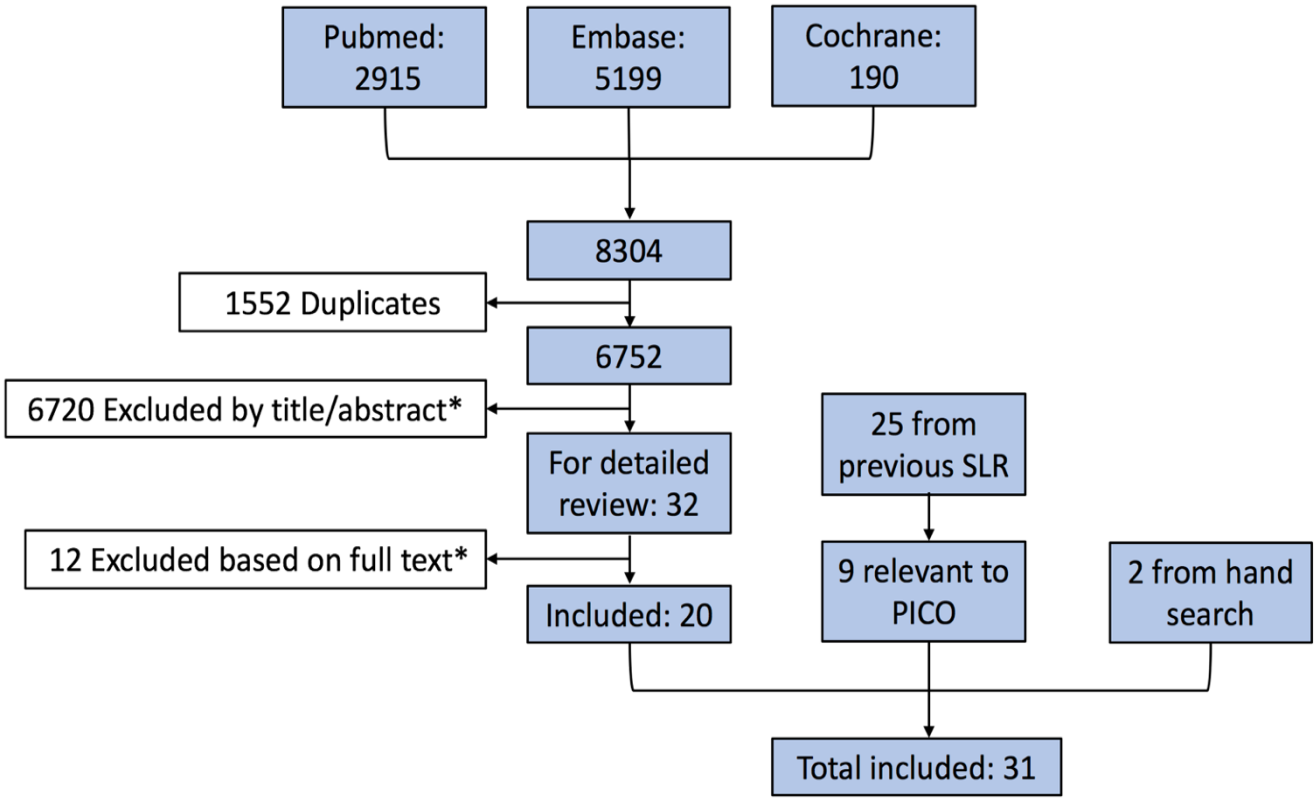
1. (magnetic and resonance and imaging).mp.
2. magnetic resonance imaging.mp.
3. mri.mp.
4. Ultrasonography.mp. or exp echography/
5. magnetic resonance imaging.mp. or exp nuclear magnetic resonance imaging/
6. "ultrasono*".ti,ab.
7. Tomography, X-Ray Computed.mp. or exp computer assisted tomography/
8. "CT scan*".ti,ab.
9. "echograph*".ti,ab.
10. "tomograph*".ti,ab.

11. "scintigraph*".ti,ab.
12. Positron Emission Tomography.mp. or exp positron emission tomography/
13. (PET and tomog*).ti,ab.
14. Tomography, Emission-Computed, Single-Photon.mp. or exp single photon emission computer tomography/
15. (SPECT and photon).ti,ab.
16. or/1-15
17. exp ankylosing spondylitis/
18. exp psoriatic arthritis/
19. exp reactive arthritis/
20. exp spondyloarthropathy/
21. (inflam* and (peripher* or tendon* or tendinop* or limb*) and pain).ti,ab.
22. "spondylo*".ti,ab.
23. (inflam* and (back or spin*) and pain).ti,ab.
24. or/17-23
25. 16 and 24
26. limit 25 to (conference abstract or conference paper or "conference review" or letter or conference proceeding)
27. 25 not 26
28. limit 27 to (animals or animal studies)
29. limit 28 to human
30. 28 not 29
31. 27 not 30
32. "case report*".m_titl.
33. case study.m_titl.
34. case report/
35. or/28-30
36. 31 not 35

5.3.3.3 The Cochrane Library

1. MeSH descriptor: [Spondylitis, Ankylosing] explode all trees
2. MeSH descriptor: [Spondylarthropathies] explode all trees
3. MeSH descriptor: [Arthritis, Reactive] explode all trees
4. MeSH descriptor: [Arthritis, Psoriatic] explode all trees
5. MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
6. MeSH descriptor: [Ultrasonography] explode all trees
7. MeSH descriptor: [Tomography] explode all trees
8. MeSH descriptor: [Radionuclide Imaging] explode all trees
9. MeSH descriptor: [Positron-Emission Tomography] explode all trees
10. MeSH descriptor: [Diagnostic Imaging] explode all trees
11. "ultrasound":ti,ab,kw (Word variations have been searched)
12. "sonograph":ti,ab,kw (Word variations have been searched)
13. "CT":ti,ab,kw (Word variations have been searched)
14. "positron emission tomograph":ti,ab,kw (Word variations have been searched)
15. #1 or #2 or #3 or #4
16. #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
17. #15 and #16

Figure 5-1 Flow chart describing the process of study inclusion



5.3.4 Quality Assessment

Each study was assessed independently for RoB by the same two reviewers who conducted the SLR (AJ and TPJB) using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. This tool involves RoB assessment in four domains (patient selection, index test, reference standard, flow and timing); the first three domains are also assessed for applicability concerns, resulting in seven separate assessments for each study. Each assessment produced a rating of 'low', 'high' or 'unclear' (assigned scores of 0, 1 and 2 respectively). Discrepancies between reviewers regarding study selection, data extraction and RoB assessment were solved by discussion; a third reviewer (PMM) was available in case no consensus could be achieved.

5.4 Results

Of the 8114 articles screened, 31 studies were finally included. Eighteen articles related to the diagnostic accuracy of specific lesions on MRI in the diagnosis of axSpA (RQ1) [189,190,233–242,191–196,199,200], five articles related to the influence of anatomical coverage on diagnostic performance (RQ2), and six related to the influence of acquisition parameters (RQ3).

5.4.1 Diagnostic Accuracy

5.4.1.1 Sacroiliac Joints

Six studies investigated the diagnostic utility of BMO in the sacroiliac joints (SIJ) [188–193]Table 5-3. In general, these studies showed that BMO was the most sensitive individual lesion for the diagnosis of axSpA, although sensitivity (SE) (0.35–0.91) and specificity (SP) (0.75-0.90) estimates varied depending on the patient cohort, definition used for the reference standard, and number of MRI lesions used to categorise the patients [188–193] .

Defining a reference standard for axSpA is challenging. Expert clinical opinion has limitations and is frequently made with knowledge of imaging results, leading to circular interpretation. Imaging standards fail to reflect the full clinical picture of axSpA, and there is a well-known delay from disease onset to radiographic changes. Weber et al [190,191] used clinical examination and plain radiography to identify those patients with axSpA. In their earlier study, Weber et al [193] used a 'global assessment of MRI' to confirm a positive diagnosis of axSpA. Jans et al [189] used the ASAS classification criteria as their reference standard in patients undergoing MRI with inflammatory back pain. Wick et al [192] used a retrospective diagnosis of axSpA from clinical notes – it is unclear whether MRI had been used to make this diagnosis. Marzo-Ortega et al [188] used Calin's criteria for the diagnosis of inflammatory back pain at baseline and one year.

There were subtle differences in the definition of BMO among authors. Jans et al [189] defined a positive MRI SIJ for BMO if there was high T2FS/STIR signal of the ilium or

sacrum typically located periarticularly. If there was only one lesion, this had to be present on at least two consecutive slices. If there was more than one signal on a single slice, this was considered adequate. Weber et al [191,193] used a relatively similar definition using the SPARCC assessment, where the SIJ is represented as a schematic with 4 quadrants. As with the ASAS definition, BMO had to be present in ≥2 SIJs quadrants on the same slice or in the same SIJ quadrant on ≥2 consecutive slices. In an earlier study, Weber et al, 2013 [190] used a cut off of BMO in at least one quadrant. Marzo-Ortega et al [188] used the Leeds scoring system: BMO was defined as low signal on T1 with enhancement after gadolinium administration and/or high or intermediate bone marrow signal with irregular contour on a T2 SPIR image. The presence of BMO was recorded and severity ranked on a semi quantitative scale based on the percentage area covered in each quadrant: 0, absent; grade 1, mild (<25%); grade 2, moderate (25-75%); grade 3, severe (75%). An overall score of inflammatory activity was calculated as the sum of scores of BMO. A positive MRI SIJ was defined as moderate/severe BMO (score ≥2).

Both Jans et al. [189] and Weber et al. [190,191,193] found that the combinations of BMO and/or erosions could increase the sensitivity and specificity of MRI for the diagnosis of axSpA. Sensitivity and specificity were also increased by the combination of BMO and fat infiltration [189,195]. Jans et al. [189] also reported an increase in specificity (but significant decrease in sensitivity) for the presence of BMO concomitantly with enthesitis, capsulitis or ankylosis.

Weber et al. investigated specific lesion-based criteria for defining a global positive sacroiliac joint MRI, and derived estimates of sensitivity and specificity for a number of different lesion cut-offs [191]. It was shown that lesion-based criteria including both BMO and erosions had superior sensitivity compared to criteria including BMO alone; for example the presence of BMO in ≥3 quadrants and erosions in ≥3 quadrants produced SE 0.83 and SP 0.85 for the fulfilment of the global imaging criteria for axSpA [191]. However, estimates of sensitivity and specificity again varied substantially depending on the patient cohort.

Four studies addressed the utility of fat infiltration adjacent to the SIJ [189,190,194,195]. The presence of fat infiltration was found to have low/moderate sensitivity (0.15-0.70) and moderate/high specificity (0.72-0.95) for the diagnosis of axSpA, although estimates varied depending on study design, the specific axSpA population under investigation and lesions' cut-offs [189,190,194,195]. Weber et al. found that fat infiltration was more specific for the diagnosis of AS than for nr-axSpA (SE/SP 0.7/0.72 and 0.46/0.72 respectively) [195]. De Hoodge et al. showed that using a cut off of ≥3 fatty lesions correctly classified 63.6% of AS patients, whilst a combined threshold of ≥5 fatty lesions and/or erosions performed similarly well [194].

Five studies investigated the diagnostic utility of erosions Table 5-4[190–192,194,195]. In general, erosions demonstrated good specificity for the diagnosis of axSpA, but only poor to moderate sensitivity (Table 3). Erosions were more sensitive in AS than in nr-axSpA or axSpA as a whole [194,195], and were more sensitive against a pre-specified MRI

reference standard than against a clinical reference standard [190]. Using both erosions and fat infiltration as a diagnostic criterion increased specificity, but reduced sensitivity, compared to criteria consisting of fat infiltration alone [195].

Three studies addressing other SIJ lesions including high T1 signal in the SIJ, fluid signal in the SIJ, ankylosis, vacuum phenomenon, sclerosis, enthesitis, capsulitis and backfill reported low to moderate diagnostic performance for these features [189,196,233].

5.4.1.2 Spine

Five studies demonstrated moderate sensitivity and specificity of spinal inflammatory lesions in the diagnosis of axSpA Table 5-5[194,199,234,236,238]. In general, these studies demonstrated that lower thresholds for the number of inflammatory lesions resulted in reasonable sensitivity but poor specificity; increasing the threshold improved specificity but worsened sensitivity. Four of the five studies also investigated the diagnostic utility of spinal fatty lesions, and found poor sensitivity and high specificity, shown in Table 4 [194,199,234,236].

5.4.2 Effect of Anatomical Coverage

Five studies evaluated the added value of combined spinal and SIJ MRI over SIJ MRI alone [188,243–246]. Two studies found that combined spinal and SIJ MRI did not add significant value over SIJ MRI alone, either because spinal inflammation was rare in the absence of SIJ inflammation [243] or because combined MRI resulted in a high rate of false positives [244]. However, three studies observed spinal inflammation in up to

half of patients without SIJ inflammation, arguing that combined MRI adds value over SIJ alone [188,245,246].

5.4.3 Effect of Acquisition Parameters on Diagnostic Performance

Six studies specifically investigated the effect of acquisition parameters [247–252]. Of the six studies, three investigated the effect of sequence choice on diagnostic accuracy of axSpA or on the characteristics of the images themselves [247–249]. Boy et al. found that sensitivity and specificity was highest for FS-T2W imaging, and progressively decreased for STIR, diffusion-weighted and dynamic-contrast enhanced images respectively [247]. Dalto et al. showed good levels of agreement between FS-T2W imaging and STIR imaging, with a Lin's concordance correlation coefficient of 0.94 for reader 1 and 0.88 for reader 2 (range 0 to 1) [249]. Ozgen et al. investigated the role of T2-weighted Dixon imaging in the identification of BMO, and found a superior contrast-to-noise ratio compared to FS-T2W imaging [248]. Three studies investigated the role of gadolinium in the SIJs, and overall found minimal or no added value [250–252].

5.5 Discussion

MRI is a key component in the diagnostic pathway for axSpA, however, there is significant heterogeneity in both the acquisition and interpretation of MRI scans across care providers [230]. We systematically reviewed the literature regarding the use of MRI in the diagnosis of axSpA, informing a task force of radiologists and rheumatologists with the aim of standardising the use of MRI in suspected axSpA.

Overall, studies investigating specific SIJ MRI lesions have shown that BMO is the most sensitive and specific individual lesion. Structural lesions including fat infiltration have moderate sensitivity and specificity, whilst erosions demonstrate good specificity but relatively poor sensitivity. An important consideration is that several of these studies use fixed specificity values; it is likely that specificity would be lower, but sensitivity higher, if these values were allowed to vary freely.

Other SIJ lesions including high T1 signal in the SIJ, fluid signal in the SIJ, ankylosis, vacuum phenomenon, sclerosis, enthesitis, capsulitis and backfill have a low to moderate diagnostic utility, and are, therefore, unlikely to be of diagnostic value in isolation. Owing to the heterogeneity of the data, with varying reference standards and patient cohorts across studies, or repeated use of the same cohort (implying an overlap in at least part of the study populations) we have been unable to create an accurate meta-analysis of lesion-based criteria in the diagnosis of axSpA.

A number of studies have assessed combinations of lesions and their diagnostic performance. These studies showed that a combination of BMO and erosions, or BMO and fat infiltration, yielded higher sensitivity and specificity than BMO alone. Pre-defined numbers of lesions or cut-offs have also been analysed and suggest that BMO in ≥3 quadrants and erosions in ≥3 quadrants show high sensitivity and specificity and presence of 3-5 fatty lesions also yield good sensitivity. However, further studies are required to validate these findings.

In the spine, studies investigating the value of spinal inflammatory lesions found moderate sensitivity and specificity, whilst spinal fatty lesions were found to have relatively poor sensitivity and specificity. Although the results suggest that spinal lesions alone are unlikely to have sufficient diagnostic performance for use in axSpA, these lesions might be useful in combination with features identified on SIJ MRI – this is an area that requires further research.

The results of studies investigating the effect of anatomical coverage on diagnosis were mixed: two studies suggested that spinal inflammation is rare in the absence of SIJ inflammation, three found the opposite. Assuming patients seen in clinical practice have variable presentations, imaging the spine would facilitate the diagnosis and management of patients with axial pain. Unfortunately, even amongst studies that have imaged the spine, there has been substantial heterogeneity in anatomical coverage and there is clearly scope for further work to determine the 'optimal' spinal protocol. Importantly, this research will need to consider the trade-off between scan time (and therefore also cost) and diagnostic yield, particularly as pressures on radiology departments continue to increase.

The number of studies assessing the impact of acquisition parameters on diagnostic accuracy was relatively small. The available evidence suggests that contrast adds little value, although no studies have rigorously addressed this question in the spine. Again, there is a need for further research to address this issue.

Of the studies specifically investigating sequence choice, several studies investigated methods of fat suppression other than STIR imaging. FS-T2W was shown to have superior sensitivity and specificity to STIR imaging [247], with assessments of disease severity at the MRI level agreeing closely between the two sequences [249]. Similarly, Ozgen et al. demonstrated superior contrast-to-noise ratios for T2W Dixon imaging compared to STIR, but did not assess diagnostic sensitivity [248]. Overall, these methods are promising alternatives to STIR and may offer improvements in image quality in the future.

There are several limitations of the studies included in this SLR. First, a number of the studies were potentially biased by the inclusion of information from MRI scans in their reference standard. In some studies, a positive MRI scan was used as an inclusion criterion; other studies selected patients based on previous MRI scans. Even those studies that did not explicitly use MRI-based reference standards, it is unclear whether MRI had been used in the patients' prior diagnostic work-up or referral.

A true assessment of the diagnostic utility of MRI would omit any MRI imaging from the reference standard. However, in the absence of a robust biomarker for the disease, finding an accurate and reliable reference standard poses a challenge. Some studies incorporated a purely clinical reference standard with a diagnosis of axSpA made by a panel of expert physicians. An alternative approach might be to use reference standards based on follow-up and assessment at multiple time-points, to ensure high level of confidence in the diagnosis of axSpA.

The use of control groups by the included studies was suboptimal, resulting in 'unclear' or 'high' RoB for a number of studies when assessed using the QUADAS-2 tool. Healthy controls can artificially inflate the sensitivity and specificity statistics, since it is typically easier to distinguish axSpA from healthy patients than from patients with other axial problems, namely chronic non-specific low back pain.

On a similar note, there remains uncertainty about the frequency of MRI lesions in the general population. Marzo-Ortega et al [188] reported a high prevalence of BMO in up to 6/22 (27%) in a control sample of healthy volunteers and patients with mechanical back pain. A similar proportion of MRI lesions suggestive of axSpA were recorded in MRI assessment of the spine. An evaluation of SIJ MRI in athletes showed BMO compatible with ASAS standards as concordantly reported by at least two of three trained readers in 30%–35% of hobby runners and 41% of elite ice-hockey players, respectively [253]. In patients with chronic low back pain recruited from primary care without previous rheumatological assessment, 21% met the MRI classification criteria based on SIJ BMO alone, but 42% of these lesions were small and of questionable clinical relevance as they showed no association with clinical SpA features [254]. A further limitation of this SLR is that the numbers of studies included under each of the research questions (RQs) was relatively small. The number of studies was particularly small for RQ2 and RQ3, and further work is needed to answer these questions more definitively.

Future research into the use of MRI in axSpA should assess MRI scans longitudinally in a cohort of patients with suspected axSpA, correlating lesions with symptoms, response to treatment and rate of radiographic progression. This cohort should cover the entire spectrum of axial disease. Separate studies on healthy controls should aim to assess the background noise of SIJ and spinal lesions associated with mechanical causes in a normal population, providing guidelines on minimum requirements or 'cut-offs' for lesions to determine an abnormal scan. Further advances in quantitative imaging may help in this regard by creating a score of inflammation that is not dependent on binary assessment of lesions [255]. To conclude, the results of this SLR have informed the recommendations of a consensus group aiming to standardise practice around the use of MRI scan in the UK and can inform similar exercises in other countries or at the international level. A summary of these recommendations can be found in Table 5-2 Recommendations for Acquisition and Considerations for Interpretation of MRI of the Spine and Sacroiliac Joints in the Investigation of Axial Spondyloarthritis in the UK.

Table 5-2 Recommendations for Acquisition and Considerations for Interpretation of MRI of the Spine and Sacroiliac Joints in the Investigation of Axial Spondyloarthritis in the UK

Overarching principles (OP) and recommendations (Rec)		*LoE*	LoA
OP1	The diagnosis of axSpA is based on clinical, laboratory and imaging features.	-	9.7 (0.7) 100% ≥8
OP2	Some patients with axSpA have isolated inflammation of the SIJs or spine.	-	9.8 (0.4) 100% ≥8
Rec1	When requesting an MRI for suspected axSpA, imaging of both the SIJs and the spine is recommended.	3	9.1 (1.4) 88% ≥8
Rec2	T1-weighted and fat-suppressed, fluid sensitive sequences (including STIR, fat-saturated T2 or Dixon methods) are recommended when requesting an MRI for suspected axSpA.	2/3/5	9.5 (0.8) 100% ≥8
Rec3	The minimum protocol when requesting an MRI for suspected axSpA should include sagittal images of the spine with extended lateral coverage and images of the SIJs which are coronal to the joint.	5	8.8 (1.7) 88% ≥8
Rec4	In the SIJs, the presence of bone marrow oedema, fatty infiltration or erosion is suggestive of the diagnosis of axSpA. The presence of more than one of these features increases the diagnostic confidence of axSpA.	2	9.2 (1.2) 82% ≥8
Rec5	In the spine, the presence of multiple corner inflammatory lesions and/or multiple corner fatty lesions increases the diagnostic confidence of axSpA.	2	9.2 (0.8) 100% ≥8
Rec6	In the SIJs and/or spine the presence of characteristic new bone formation increases the diagnostic confidence of axSpA.	2	8.8 (1.1) 94% ≥8
Rec7	The full range and combination of active and structural lesions of the SIJs and spine should be taken into account when deciding if the MRI scan is suggestive of axSpA or not.	5	9.5 (0.6) 100% ≥8

LoE; levels of evidence LoA levels of agreement. Numbers in column 'LoA' indicate the mean, SD (in parenthesis) and the percentage of task force members giving an agreement level ≥8 from a numeric rating scale, ranging from 0 (do not agree) to 10 (fully agree). Note that the overarching principles are general statements and have therefore not been assigned with LoE.

Table 5-3 Sensitivity and specificity of criteria using bone marrow oedema (BMO) and combinations in the sacroiliac joints.

Feature	Study	Criterion	n	Reference standard	Sensitivity	Specificity	LR+	LR-
BMO	Jans et al. [189]	BMO	517	Clinical diagnosis SpA	0.65	0.75	2.60	0.47
	Weber et al. [190]	BMO ≥ 2 quadrants	177	Global MRI score	0.91/0.83 *	0.90/0.90 */**	9.10/8.30 *	0.10/0.19 *
				Clinical diagnosis SpA	0.73/0.39 *	0.90/0.90 */**	7.30/3.90 *	0.30/0.68 *
	Weber et al. [191]	BMO ≥ 2 quadrants (ASAS definition)	157	Clinical diagnosis SpA	0.8/0.42*	0.76/0.73 *	3.37/1.54 *	0.26/0.80 *
	Wick et al. [192]	BMO	179	Clinical diagnosis SpA	0.35	0.78	1.59	0.83
	Weber et al. [193]	BMO ≥ 2 quadrants (ASAS definition)	187	Clinical diagnosis SpA	0.9	0.97	30.0	0.10
	Marzo-Ortega et al. [188]	BMO > 0 (Leeds scoring)	76	Clinical diagnosis SpA	0.82	0.42	1.41	0.43
BMO and erosions	Jans et al. [189]	BMO and erosion	517	Clinical diagnosis SpA	0.77	0.81	4.05	0.28
	Weber et al. [190]	BMO and/or erosion ≥ 1 quadrant	177	Global MRI score	0.98/0.96 *	0.90/0.90 */**	9.80/9.60 *	0.02/0.04 *
				Clinical diagnosis SpA	0.82/0.51 *	0.90/0.90 */**	8.20/5.10 *	0.20/0.54 *
	Weber et al. [191]	BMO ≥ 2 quadrants and ≥ 1 erosion (MORPHO definition)	157	Clinical diagnosis SpA	0.88	0.72	3.14	0.17

	Weber et al. [193]	BMO and erosion	187	Clinical diagnosis SpA	0.9	0.97	30.0	0.10
BMO and fat infiltration	Jans et al. [189]	BMO and fat	517	Clinical diagnosis SpA	0.68	0.76	2.83	0.42
	Weber et al. [195]	BMO and fat	157	Clinical diagnosis (NR axSpA)	0.39	0.91	4.33	0.67
				Clinical diagnosis (AS)	0.58	0.91	6.44	0.46

***Values for two separate cohorts. **Pre-determined specificity.**

BMO, Bone marrow oedema; LR, likelihood ratio.

Table 5-4 Sensitivity and specificity of criteria using fat infiltration and erosions in the SIJs

Feature	Study	Criterion	n	Reference standard	Sensitivity	Specificity	LR+	LR-
Fat infiltration	de Hooge et al. [194]	Fat in ≥3 quadrants	287	Diagnosis AS (mNY)	0.46	0.95**	9.20	0.57
				Diagnosis nr-axSpA	0.15	0.95**	3.00	0.89
				Clinical diagnosis SpA (clinical arm)	0.15	0.95**	3.00	0.89
	Weber et al. [195]	Fat in ≥2 quadrants	157	Diagnosis AS	0.70	0.73	2.59	0.41
				Diagnosis nr-axSpA	0.44	0.73	1.63	0.77
	Jans et al. [189]	Presence of any fat	517	Clinical diagnosis SpA	0.55	0.84	3.44	0.54
	Weber et al. [190]	Lesion-based criteria for fat infiltration	177	Pre-specified positive MRI	0.34/0.74 *	0.90/0.90 *	3.40/7.40 *	0.73/0.29 *
				Clinical diagnosis	0.30/0.49 *	0.90/0.90 *	3.00/4.90	0.78/0.57
Erosions	de Hooge et al. [194]	≥3 erosions	287	Diagnosis AS (mNY)	0.64	0.95**	12.80	0.38
				Diagnosis nr-axSpA	0.47	0.95**	9.40	0.56
				Clinical diagnosis SpA (clinical arm)	0.13	0.95**	2.60	0.92
	Weber et al. [191]	≥2 erosions	157	Clinical diagnosis SpA	0.98/0.77	0.97/0.90	32.7/7.7	0.02/0.26
	Weber et al. [190]	Lesion-based erosion criteria	177	Pre-specified positive MRI	1/1*	0.90/0.90 */**	10	0

				Clinical diagnosis	0.77/0.54 *	0.90/0.90 */**	7.70/5.40	0.26/0.51
	Wick et al. [192]	Presence of any erosion	179	Clinical diagnosis	0.11	0.93	1.57	0.96
Fat infiltration and erosions	Weber et al. [195]	Fat infiltration with erosion	157	Diagnosis AS	0.68	0.98	34.00	0.33
				Diagnosis nr-axSpA	0.34	0.98	17.00	0.67

***Values for two separate cohorts. **Pre-determined specificity.**

LR, Likelihood ratio; mNY, modified New York criteria.

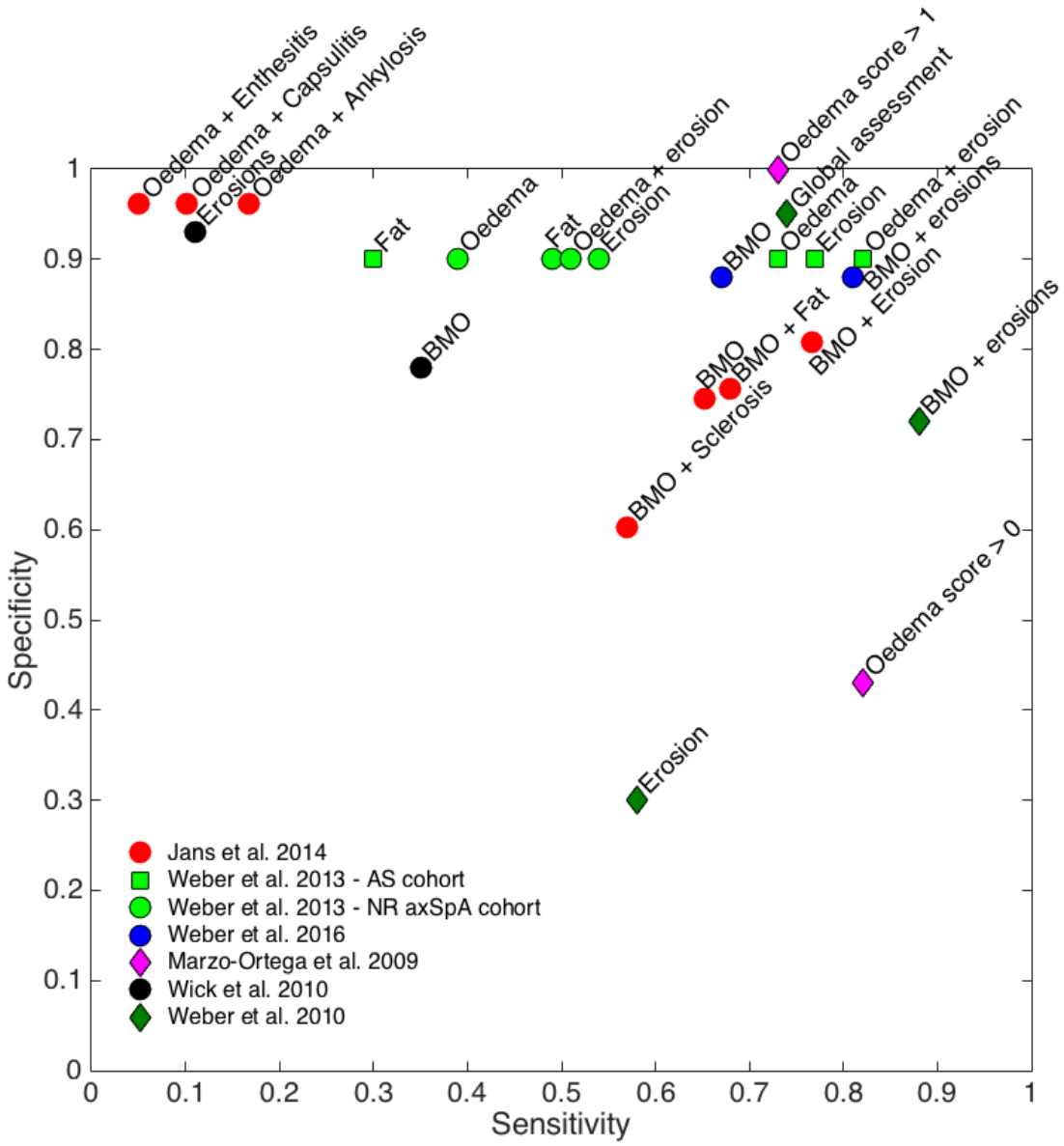
Table 5-5 Sensitivity and specificity of criteria using inflammatory lesions and fatty lesions in the spine

Feature	Study	Criterion	n	Reference standard	Sensitivity	Specificity	LR+	LR-
Spinal inflammatory lesions	Weber et al. [236]	≥ 2 CILs	130	Clinical diagnosis	0.53/0.55 *	0.64/0.74 *	1.47/2.12*	0.73/0.61 *
		≥ 3 CILs			0.43/0.25 *	0.75/0.89 *	1.72/2.27*	0.76/0.84 *
	Weber et al. [238]	≥ 2 CILs	95	Clinical diagnosis	0.69	0.94	11.50	0.33
	de Hoodge et al. [194]	Presence of spinal inflammatory lesions	287	Diagnosis AS (mNY)	0.27	0.95**	5.40	0.77
				Diagnosis nr-axSpA	0.14	0.95**	2.80	0.91
				Clinical diagnosis axSpA (clinical arm)	0.05	0.95**	1.00	1.00
	Hu et al. [234]	≥ 1 CIL	400	Diagnosis AS (mNY)	0.52	0.55	1.16	0.87
		≥ 6 CILs			0.45	0.66	1.32	0.83
		≥ 11 CILs			0.04	0.78	0.18	1.23
	Bennett et al. [199]	≥ 1 inflammatory lesion†	185	Clinical diagnosis	0.67	0.56	1.52	0.59
		>3 inflammatory lesion			0.45	0.81	2.37	0.68
		>3 inflammatory lesions and age <50			0.33	0.97	11.00	0.69
Spinal fatty lesions	Weber et al. [236]	≥ 6 spinal fatty lesions	130	Clinical diagnosis	0.26/0.40 *	0.82/0.81 *	1.44/2.11*	0.90/0.74 *

de Hoodge et al. [194]	Presence of spinal fatty lesions	287	Diagnosis AS (mNY)	0.18	0.95**	3.60	0.86
			Diagnosis nr-axSpA	0.22	0.95**	4.40	0.82
			Clinical diagnosis axSpA (clinical arm)	0.02	0.95**	0.40	1.03
Hu et al. [234]	≥ 1 spinal fatty lesion	400	Diagnosis AS (mNY)	0.13	0.94	2.17	0.93
	≥ 2 spinal fatty lesions			0.09	0.99	9.00	0.92
Bennett et al. [199]	≥ 1 spinal fatty lesion†	185	Clinical diagnosis	0.33	0.93	4.71	0.72
	>5 spinal fatty lesions†			0.22	0.98	12.56	0.80

*Values for two separate cohorts. **Pre-determined specificity. †These lesions were referred to as Romanus lesions and fatty Romanus lesions in [199].
CIL Corner Inflammatory Lesions; LR Likelihood ratio; mNY modified New York;

Figure 5-2 Diagnostic performance of BMO and combinations in MRI SIJs. Sensitivity and specificity values are shown on a scatterplot for all relevant studies; performance for other features include in those studies (e.g. erosions alone)



6 What do patients want?

6.1 Overview

A principle of OMERACT is bringing together multiple stakeholders in collaborative research. One the most important stakeholder groups is the patients themselves. In this chapter, I summarise the findings of my public and patient involvement (PPI) work; the aims of which were to understand patient perspectives and priorities for the assessment and monitoring of axSpA. Organisation and chairing of the PPI meetings was done by myself. Ellie Hawkins, rheumatology research nurse, took minutes for each meeting. This work received ethical approval from the London Riverside Ethics Committee (IRAS 208355).

6.2 A Patient Participation and Involvement Meeting

Two focussed patient group meetings were organised. The first consisted of patients attending the National Ankylosing Spondyloarthritis Society (NASS) physiotherapy and hydrotherapy session at UCLH and took place on the 19th February 2019. Patients were emailed by the chair of the NASS group ahead of the meeting to see if they were willing to take part in the discussion, which occurred after their group physiotherapy session. 7 patients took part in this meeting. The second PPI meeting comprised patients recruited from the axSpA clinic at UCLH. Patients were asked during their clinical appointment if they would be interested in joining a panel group to discuss axSpA and their care. Patients were selected at random and at any stage of their disease from mild to severe. Patients did not need to be on biologic

therapy to be included Information was provided and an email to contact, if they were interested. 10 patients took part in the meeting which occurred at the Rayne Institute, UCL on 17th July 2019.

Both patient cohorts included equal numbers of men and women, across a range of ages (24 to 67 years), with a wide variation in disease severity, duration and treatment. Both meetings were chaired by myself. The second meeting was attended by Dr Madhura Castellino, Consultant Rheumatologist, at UCLH and Miss Ellie Hawkins, Rheumatology Research Nurse (UCLH). Dr Madhura Castellino was present to observe the PPI session and to ensure any risk of bias was mitigated. This included reviewing the questions asked in the meeting. General questions regarding patient views on disease management and assessment of disease activity were asked, however, the agenda (Box 1) was kept flexible to encourage patient dialogue. Verbal and written consent to take notes (non-identifiable) and photography (17th July) was provided by all patients.

Figure 6-1 Axial Spondylarthritis patient focus group meeting

Figure 6-2 Agenda for PPI meeting 17th July 2019

1. **Background and understanding of disease activity**

- Do you feel confident in your understanding of axial spondyloarthritis?
- What has helped you understand your condition?

2. **Disease assessment**

- Do you feel confident assessing when your axSpA is more active?
- What do you rely on for this assessment?
- What would improve your ability to assess your disease?
- When you see you physician – what information do you really want to know?

3. **Disease monitoring**

- Do you feel that your condition is being accurately monitored by the clinical team?
- How would you like your condition be monitored?
- What do you think of the BASDAI/patient reported outcomes?

4. **MRI**

- What do you think of MRI scans as a component of measuring disease activity?
- Pros/Cons of MRI

6.2.1 Background and understanding of disease activity in axSpA

To open the meeting, the group was asked to describe their journey to the diagnosis of axSpA. The responses highlighted the delays in diagnosis and the significant personal impact of the diagnosis. For some individuals, a substantial amount of time and money had been invested to make the diagnosis and facilitate their care.

"I am 20 years into this disease and it wasn't until this last flare, a few years ago, that I finally got the diagnosis. My first symptoms were in 1993. The first people I saw didn't explain anything and it was put down to stress of being a young woman. I felt it was all in my head"

"I spent months visiting my GP, going round in circles, being told to do stretches and take more pain killers"

"They thought I had a bad back/ slipped disc until I couldn't walk. I ended up having a private MRI and blood test which showed I had the gene"

"The diagnosis was not a relief. I went down a dark hole, which was quite scary. I thought I might end up in a wheel chair or it might disappear completely, I had no way of knowing"

"I was pleased that someone believed me"

"Hour to hour, I would go from OK to agony so I was pleased it was something, although only I was only offered pain relief"

"I have spent tens of thousands of pounds on private care to manage symptoms (back pain). This hadn't got me anywhere. It was coming to UCLH that I got the diagnosis"

Assessment of disease activity in axSpA relies on the patient's ability to decipher which symptoms relate to their disease. It is, therefore, important to assess the level of understanding patients had about their disease and the sources of information they used to acquire this knowledge. Patients were not forthcoming with their answers to this question and did not appear confident describing the basic concepts of the disease aetiology. One patient explained that he still wasn't sure what was causing the disease and exactly what was going on in his spine. Most patients used this opportunity to highlight the lack of information and support they received after being diagnosed with axSpA. In some cases, patients appeared to have been misinformed by their clinical team.

"I think I do understand (axSpA) but very little was explained by my doctor"

"I was told I would end up in a wheelchair"

"I was told I would not get better, and that there was no cure"

"I feel I do understand my disease but it has taken considerable effort on my part and a lot of time. It sometimes feels like a part time job"

Summary:

- **Patients report a lack of information regarding their disease**
- **Patients feel that the onus of information gathering regarding their disease is on them**

6.2.2 Patients' assessment of disease activity

When asked how confident the group felt at assessing their disease, feedback was mixed. One patient explained that she had suffered with the disease for such a long time, that she felt very confident knowing when her disease was active. Patients agreed that pain and fatigue were their most troublesome symptoms and felt these were good measures of disease activity. However, a number of patients also expressed how vague these symptoms were and how difficult it was to gauge what was to be expected from the disease and what could be a variant of normal life.

"I have had this (axSpA) for *so long that I know when things aren't right and when there is something wrong"*

"How do I know when my fatigue is due to the disease or I am just tired from a hard week at work"

When asked what they want to know when they attend clinic, a common theme was the severity of disease and prognosis:

"I want to know, am I going to get worse? Are my symptoms to be expected or something to worry about?

"How bad is my disease compared to others?"

Interestingly, two patients agreed that they could manage their symptoms of pain and stiffness if they had more knowledge over what impact this was having on their spine and sacroiliac joints.

Summary:

- **Patients struggle to interpret their symptoms**
- **Patients are keen to know how active their disease relative to others and if it is going to get worse**

6.2.3 Patient feedback on disease monitoring

Patients were unsure whether their disease was being accurately monitored. One patient explained that he had moved hospital as he did not feel his axSpA was being monitored appropriately by his rheumatology team. One patient felt that a lot of responsibility was placed on the patient to explain and describe their symptoms. When asked what information would increase their confidence regarding disease monitoring, there was a firm bias towards facts and robust measures of disease activity.

"I just want to be told the facts"

"We need proper measurements on us"

"An inflammation marker would be really useful"

"I would like some kind of measurement"

"I would like a graph of my inflammatory scores"

"I would like reports of my MRI scan"

One patient explained how management of axSpA was reactionary and that monitoring should enable the clinical team to pre-empt flares of disease and prevent them.

"I would like the doctors to be ahead of the game instead of waiting for my pain to be unbearable or to be in a crisis in order to get treatment"

Each member of the PPI group was provided with a reference pack, including common patient report outcome measures (PROMS) such as the BASDAI, BASFI and FACIT. Patients were given some time to re familiarise themselves with the questionnaires.

On the whole, feedback on the questionnaires was negative. Patients explained how they found the PROMs difficult to answer. They were unsure how to grade their symptoms and how to use the scale. A number of patients commented that the questionnaires failed to reflect the variability in their disease symptoms. It was also apparent that, in answering the questions, patients were mindful of the ramifications of their responses with regards to their ongoing care and treatment. Some patients were very honest about the fact that they had manipulated their scores to escalate or maintain their treatment.

"I find this (BASDAI) really hard to complete. My symptoms are different day to day. There is no average"

"I find a 1 to 10 scale difficult. What does it mean?"

"Is my 6 the same as your 6? Pain is relative".

"If I have a good week, I won't put 0 as you'll think I'm OK, and it will affect my ongoing treatment"

"If I put down a low score, I'll get bumped down to 1 appointment per year"

Summary:

- **Patients prefer objective measures of disease activity**
- **Patients find scales of fatigue and pain difficult to use**

6.2.4 What do patients think about MRI?

On the whole, patients were keen to have imaging. They found imaging reassuring and also liked the idea that any damage to the spine could be accurately visualised. When asked how patients would feel when the MRI did not match their symptoms, one patient responded with, *"It would"*. One patient reported that he would need to be sedated to have an MRI and it is quite an ordeal owing to claustrophobia. Others explained that they did not find it an issue and were unbothered by the duration of the scan. A number of patients agreed that if the scan was normal in the presence of persistent pain, it would not disappoint them. Three patients liked the reassurance that there was no structural damage on the MRI. A number of patients did express their frustration that their scan was not discussed with them in detail and they did not have access to the report.

"I like the fact an MRI is objective and not relying on me having to accurately describe how I felt"

"It's not just about the MRI per se, it's the fact that it is an accurate measure"

"I am interested in seeing my MRI, I would like to how my axSpA is developing"

Summary:

- **Patients are in favour MRI as an assessment of their disease**

In conclusion, this PPI work highlighted patient's frustrations with current disease monitoring. Whilst patients agree that symptoms of pain and fatigue are important measures of disease activity, they struggled to relay this information using PROMs. In particular, they found scales of pain and fatigue difficult to utilise. Patients admitted that completion of the PROM was influenced by how their score may affect their ongoing care. Patients were keen to have clear, robust measures of disease activity. Whilst patients liked MRI, it was apparent that it is the use of a particular investigation into their disease, providing objectivity to their symptoms which they found reassuring.

7 Measurement of response to treatment in axial spondyloarthritis using quantitative imaging biomarkers: A pilot study

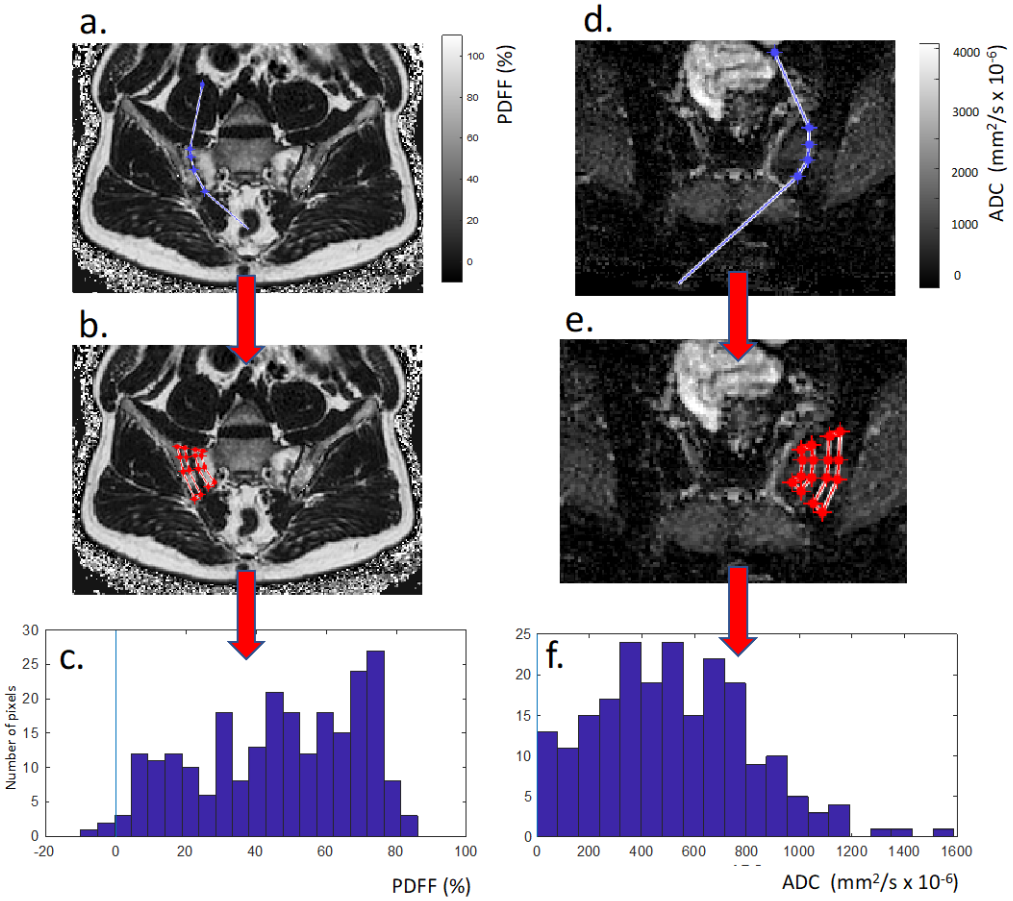
7.1 Introduction

The potential role and promise of QIBs in the assessment of disease activity in spondyloarthritis was discussed in Chapter 4. Increased ADC values in the SIJs of both adult axSpA and adolescents with enthesitis related arthritis have been reported and show response to treatment[227]. Fat metaplasia in the SIJ has been shown to predict spinal radiographic progression in axSpA[216] and could reflect overall structural burden.

At present, assessment of ADC and fat metaplasia requires a skilled reader to manually plot regions of interest (ROIs). This is a time consuming, specialised skill which demonstrates variability amongst reporters. To address this, Bray and colleagues have developed the BEACH tool for ADC and PDFF measurement in subchondral bone marrow[187]. The BEACH tool incorporates two main elements: (1) partially-automated ROIs and (2) analysis of pixel values within the ROI using histographic analysis. The assessor is prompted to define the line of the SIJ using a single series of connected straight lines (an open polygon). Anchor lines are used to define the angle made by the joint, enabling the shape of the polygonal ROIs to be tailored to the precise geometry of the subchondral bone in each patient. The software then automatically generates a pair of polygonal ROIs in the subchondral bone, to a depth of 10 mm, on either side of the joint. The procedure is repeated for

both the left and right sacroiliac joints, on each slice, until the subchondral bone included in the imaging volume had been fully sampled.

Figure 7-1 Partially-automated image analysis using the BEACH tool



The observer is prompted to define the line of the sacroiliac joint (a,d), using anchor lines to define the angle between the joint and bone cortex. The software automatically propagates polygonal ROIs onto subchondral bone (b,e) and histograms are generated from the defined ROI (c,f).

Histogram analysis generated from the BEACH tool, provides the reader with the number of pixels with 0%, 25%, 50% (median), 75% and 100% fat (PDFF) or water (ADC) respectively.

In this study, we aimed to test the hypothesis that ADC and PDFF scores derived from the BEACH tool are valid and responsive markers of response to biologic therapy, based on MRI and clinical assessments at baseline and at 12-16 weeks in a cohort of 30 patients with axSpA undergoing biologic therapy. Responsiveness was assessed in terms of standardised response means (SRMs) for the various QIBs and was compared against the SRM for visual SPARCC scoring. Validity was assessed by the correlation of QIBs with conventional MRI and clinical activity scores. We also assessed whether QIBs at baseline were able to predict clinical response determined by linear regression.

The design of this study, patient recruitment and consent, data collection and analysis were completed by myself. Professor Margaret Hall Craggs and Dr Tim Bray were blinded SPARCC scorers and Dr Tim Bray and Dr Naomi Saiki were blinded QIB scorers.

7.2 Methods

This study received ethical approval from the London Riverside Ethics Committee (IRAS 208355).

7.2.1 Subjects

Subjects were recruited prospectively from UCLH between April 2018 and July 2019. Patients aged >18 years with a diagnosis of axSpA according to 2009 ASAS criteria[25] and active disease according to NICE guidelines (NG65) criteria were approached to take part. Suitable patients were identified from medical records and approached by a member of the research team (not their attending clinician) with both verbal and written information regarding the study (patient information leaflet). Patients were invited to contact the research team if interested in taking part in the study. Verbal and written consent was obtained for all patients in the study. Exclusion criteria included contraindications to MRI such as metallic implants, pacemaker, severe claustrophobia, pregnancy, body weight > 150kg. Previous treatment with an oral, intra-articular or intra-muscular glucocorticoid within 4 weeks prior to inclusion was not allowed. Patients continued in the study if their MRI fulfilled ASAS criteria for sacroiliitis – this included evidence of BMO of the SIJs on two consecutive slides or BMO on one slide covering two quadrants [197]. Patients had to be eligible for their first biologic drug (biologic naive) or a change biologic therapy (switchers) in accordance with best practice (NICE guidelines NG65). A repeat scan was performed after 12 weeks (+/- 2 weeks) of continuous anti-TNF treatment or 16 weeks (+/- 2 weeks) of anti-IL 17 treatment. Patients were withdrawn from the study if biologic therapy was declined, contraindicated or stopped owing to adverse events.

Table 7-1 Primary and secondary outcomes

Primary outcomes	**Change in ADC and PDFF 12-16 weeks after biologic treatment**
Secondary outcomes	**Change in BASDAI 12-16 weeks after biologic treatment**
	Change in spinal VAS 12-16 weeks after biologic treatment
	Change in CRP and ESR 12-16 weeks after biologic treatment
	Change in ASDAS 12-16 weeks after biologic treatment
	Change in SPARCC BMO and SPARCC SSS 12-16 weeks after biologic treatment
	Number of patients achieving BASDAI 50, ASDAS CII, ASDAS DI 12-16 weeks after biologic treatment

ADC, apparent diffusion coefficient; ASDAS ankylosing spondyloarthritis disease activity index; BASDAI, Bath ankylosing disease activity index; CCI, clinically important improvement; CRP, c reactive protein PDFF proton density fat fraction; SPARCC, Spondyloarthritis Research Consortium of Canada; BMO, bone marrow oedema; SD, standard deviation, SSS, sacroiliac joint structural score; VAS, visual analogue score

7.2.2 Clinical Assessments

Information regarding patient demographics (age, sex and ethnicity), disease duration, history of peripheral arthritis and enthesitis, extra articular manifestations, HLA B27 status, drug history and smoking history were recorded at baseline. In addition, patients were assessed for FM/CWP in accordance with ACR criteria[256]. Clinical examination including tender and swollen joint count and assessment of peripheral enthesitis at baseline and after 12-16 weeks of treatment. BASDAI and ASDAS scores as well as CRP and ESR were recorded at baseline and after 12-16 weeks of continuous treatment. A clinical response was assessed on the basis of a BASDAI improvement of ≥ 1.2 and an improvement in spinal VAS of ≥ 1. This criterion is in accordance with NICE criteria to reflect real life clinical practice. Other

clinical response measures included a reduction in BASDAI by 50% (BASDAI 50), a clinical important improvement in ASDAS (CII ASDAS) defined as a change in ASDAS >1.1 and inactive disease defined as an ASDAS of < 1.3 (ASDAS ID).

7.2.3 MRI Acquisition

All quantitative and conventional MRI scans of the SIJs and lumbar spine were performed on a 3.0T Ingenia scanner (Philips, Amsterdam, Netherlands), in a single attendance. Quantitative imaging consisted of chemical shift-encoded MRI (CSE-MRI), also known as Dixon MRI, PDFF maps and DWI, producing ADC maps. The images were acquired using a multi echo gradient echo acquisition with bipolar readouts (first echo time 1.17 ms, echo spacing 1.6 ms, flip angle 3°, repetition time 25ms, matrix size 320x320, pixel spacing 1.76 x 1.76mm); fat water separation was performed inline using an investigational version of the Philips mDixon Quant software, assuming 10-peak model of human adipose tissue and a single R_2* decay term for the bone marrow. DWI was performed with b-values of 0, 50 and 600 s/mm^2 using a standard Stejskal-Tanner sequence with spectrally-attenuated inversion recovery (SPAIR) fat suppression and echo-planar readout. The DWI acquisition was optimised to minimise fat-ghosting artifacts. Conventional MRI consisted of T2-weighted short tau inversion recovery (STIR), T1-weighted turbo spin echo and fat-suppressed T1-weighted turbo spin echo post-contrast imaging. All conventional MRI images of the SIJs were acquired in both angled coronal (parallel to the sacrum) and angled transverse (perpendicular to the sacrum) planes. Post-contrast scans were also acquired through the thoracolumbar spine.

7.2.4 Quantitative Image Analysis

Quantitative measurements were obtained from the PDFF and ADC maps using the BEACH tool as described previously. The software for this tool is publicly available at https://github.com/TJPBray/BEACH. In the case of ADC maps, we included all slices where the synovial joint was visible, whereas alternate slices were used for the PDFF maps due to the much thinner slices (2mm) available from CSE-MRI. To be consistent with the visual scoring systems used for comparison in this work, only the subchondral bone corresponding to the synovial part of the joint was defined (the bone corresponding to the ligamentous part of the joint was excluded). For each patient, pixel values from the total volume of defined subchondral bone (i.e. from all ROIs) were analysed histographically. The ROIs for the BEACH tool were generated by two radiology registrars (NS and TB) with four and six years of experience in MSK MRI respectively and experience of using this tool in previous studies. For both ADC and PDFF, the 25th, 50th, 75th and 90th percentiles of the distribution were measured, referred to as ADC_{25}, ADC_{median} ADC_{75} and ADC_{90} and $PDFF_{25}$, $PDFF_{median}$, $PDFF_{75}$ and $PDFF_{90}$ for ADC and PDFF respectively. Mean ADC and mean PDFF were also recorded.

7.2.5 Qualitative Image Scoring

Each set of conventional MR images (including STIR, T1-weighted and contrast enhanced images) were assessed by two radiologists with over 6 and 25 years of experience in musculoskeletal radiology, who scored the images independently

using the SPARCC system. Images were read on a dedicated research workstation where the reader was blinded to clinical diagnosis, treatment and quantitative measurements. The presence of BMO was evaluated in six consecutive slices based on SIJs divided into eight quadrants. Each quadrant was scored for the presence/absence of BMO (1 or 0). An additional score of 1 was added if the BMO in a quadrant was more than 10mm deep, and another score of 1 was added if the BMO in a quadrant was at least as intense as the cerebrospinal fluid. A total score out of 72 was reached for SPARCC BMO. In addition, the presence of fatty change was assessed using the SPARCC SIJ structural score (SPARCC SSS). The presence/absence of fatty lesions per quadrant was calculated. A total score out of 50 was obtained.

7.2.6 Statistical analysis

The mean SPARCC and QIB scores between two readers was calculated. The Shapiro Wilk test was used assess normality of distribution. For data which were normally distributed, a paired t test was performed. If not normally distributed, a non-parametric test was applied (Mann Whitney or Wilxocoxon test). A p-value of <0.05 was considered statistically significant.

Responsiveness was reported using standardized response mean (SRM), calculated as the mean change score for each BEACH parameter divided by the standard deviation of the corresponding change score. The SRM values were defined as small (0.2-0.5), moderate (0.5-0.8) or large (>0.8).

The relationship between ADC and PDFF QIBs, SPARCC scores and clinical scores was assessed using Pearson's r correlation coefficient for data which was normally distributed. A Spearman's correlation coefficient was used for data that was not normally distributed.

Binary logistic regression was used to investigate the association between clinical outcomes (dependent variables) and baseline ADC and change in ADC scores (independent variables).

Inter-reader reliability of the ADC and PDFF maps was assessed using Bland-Altman limits of agreement analysis and the intraclass correlation coefficient.

7.3 Results

48 patients were found to be eligible for the study and approached to take part. 17 patients were excluded: 6 patients decided not to start biologic treatment. 2 patients had been given oral steroids. 4 patients' MRI scans did not meet NICE criteria for sacroiliitis and 5 patients were not able to take part in the study. 31 patients consented to take part in the study. One patient was withdrawn owing to side effects of the treatment (n=30). The ratio of females to males was 16:14. The mean age was 42.7 years. 13 patients were diagnosed with AS and 17 patient with nr-axSpA. Average disease duration was 7.5 years. 26.7% of patients had peripheral arthritis and 16.7% peripheral enthesitis. 60% of patients were HLA B27 positive. 9 patients (30%) were diagnosed with concomitant FM. Biologic treatment initiated included

Humira, Benepali (Enbrel biosimilar), Secukinumab and Golimumab (figure 5). 25 patients were biologic naive and 5 patients were switched to either a 2nd (n = 4) or 3rd (n = 1) biologic therapy owing to primary or secondary failure. Baseline characteristics of the participants can be found in Table 7-2. The data were collected prospectively. Unfortunately, one piece of data was erroneous and removed from the collection making the data set 29.

Figure 7-2 Flow chart of participant recruitment to study

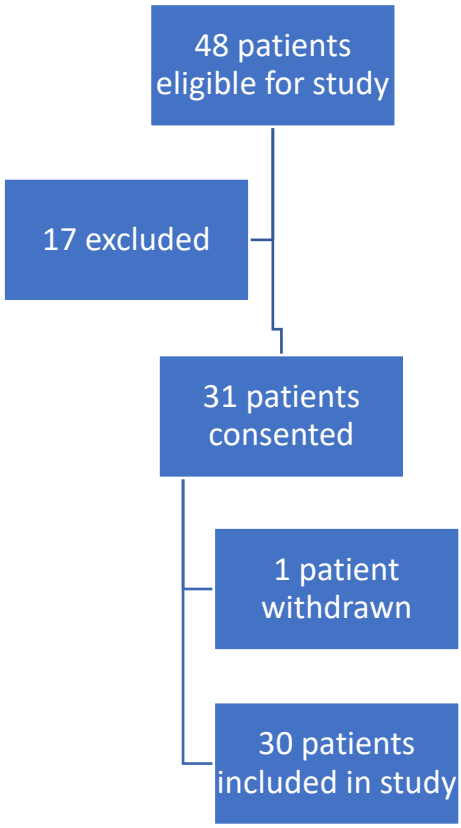


Table 7-2 Baseline characteristic of study participants

Baseline characteristics	Number/percentage
Patient number	30
Age (mean years)	42.7 (22-67)
Females: Males	16:14
Ankylosing spondylitis: non-radiographic axSpA	13:17
Mean duration from symptom onset to diagnosis (years)	7.5 (SD 5.1)
Mean duration of symptoms (years)	14.3 (SD 11.1)
Peripheral arthritis	8 (26.7%)
Peripheral enthesitis	5 (16.7%)
HLA B27	18 (60.0%)
Fibromyalgia	9 (30.0%)
Biologic naive	25 (83.3%)
2nd biologic therapy	4 (13.3%)
3rd biologic therapy	1 (3.3%)
Baseline SPARCC (BMO)	15.3 (SD 15.2)
Baselines SPARCC SSS (fat)	17.7 (SD 8.1)
Baseline SPARCC SSS (erosion)	25.3 (SD 4.3)
Baseline SPARCC SSS (ankylosis)	2 (SD 0.4)

HLA, Human leucocyte antigen; SPARCC, Spondyloarthritis Research Consortium of Canada; BMO, bone marrow oedema; SD, standard deviation, SSS, sacroiliac joint structural score.

Figure 7-3 Biologics initiated in patient cohort

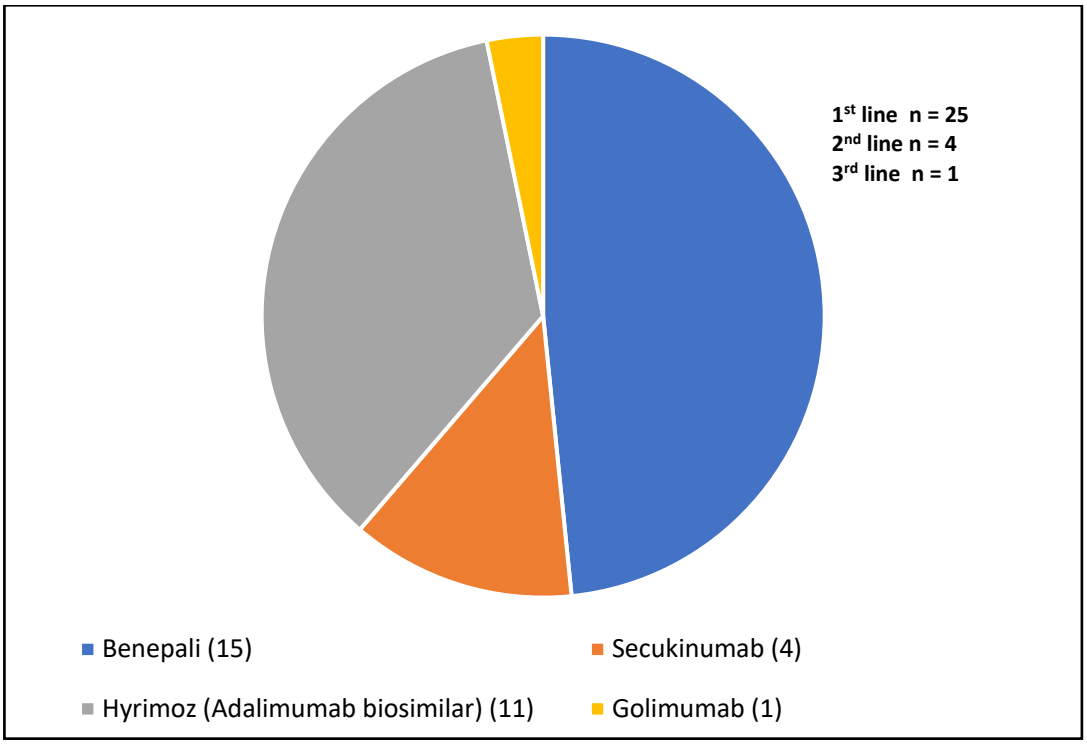
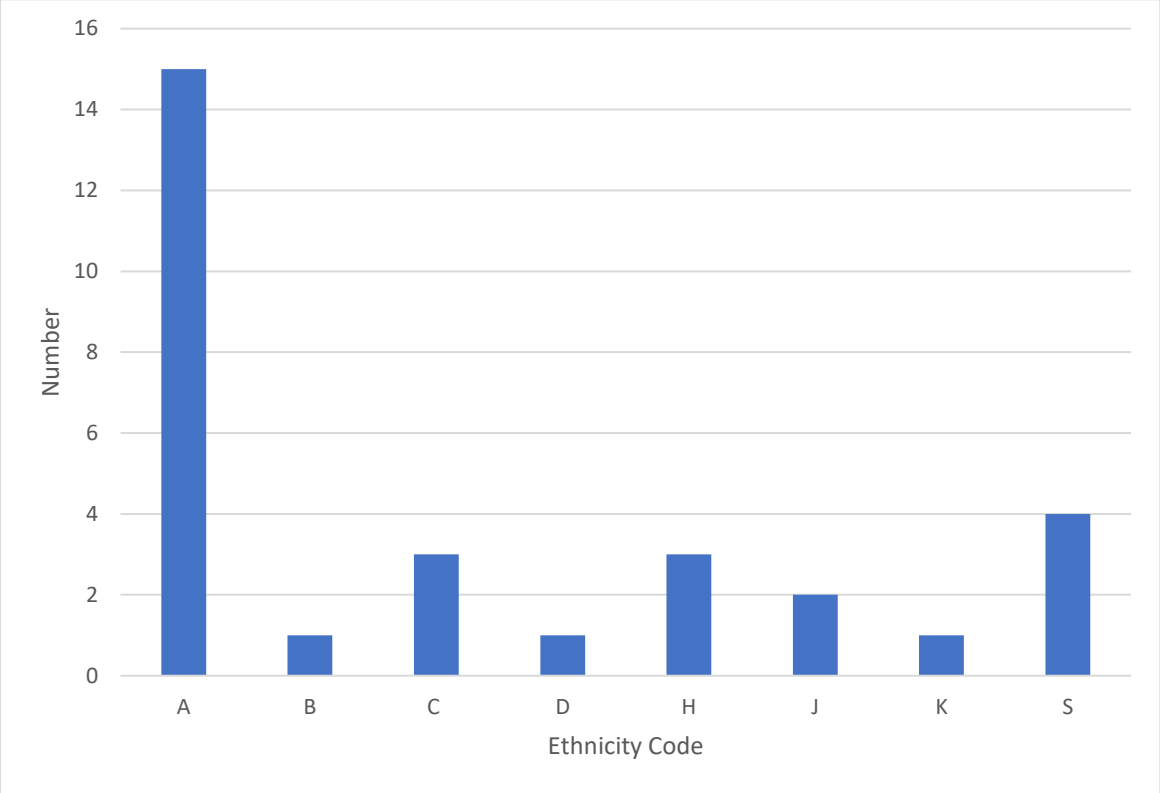


Figure 7-4 Ethnicity of patient cohort



Ethnicity	Code
White - British	A
White - Irish	B
White - Any other white background	C
Mixed - White and Black Caribbean	D
Asian or Asian British - Indian	H
Asian or Asian British - Pakistani	J
Asian or Asian British - Bangladeshi	K
Other Ethnic groups	S

Pairwise comparisons showed significant reductions after treatment for both ADC median ($p = 0.01$) and SPARCC BMO scores ($p = 0.01$) before and after biologic treatment. There was no significant difference in ADC mean, ADC25, ADC 75, ADC90 and PDFF parameters before and after treatment Table 7-3.

There were significant reductions in clinical parameters before and after biologic therapy including BASDAI (p = <0.001), spinal VAS (p = <0.001), ASDAS CRP (p = <0.001) and ASDAS ESR (p = <0.001). CRP (but not ESR) also demonstrated a significant difference before and after treatment (p = 0.02).

7.3.1 Responsiveness

Both ADC median and SPARCC BMO showed moderate responsiveness following biologic therapy (SRM 0.52 and 0.50 respectively). PDFF-based QIBSs showed small responsiveness to biologic therapy.

Figure 7-5 ADC median before and after biologic therapy

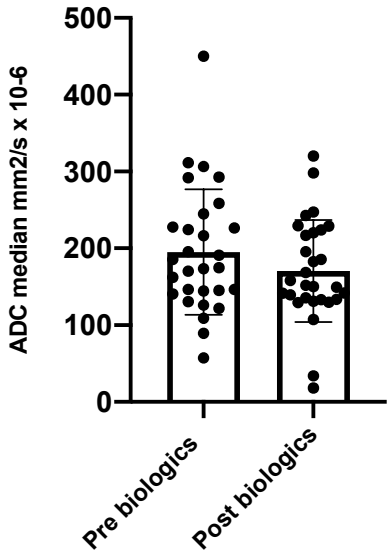


Figure 7-6 SPARCC BMO before and after biologic therapy

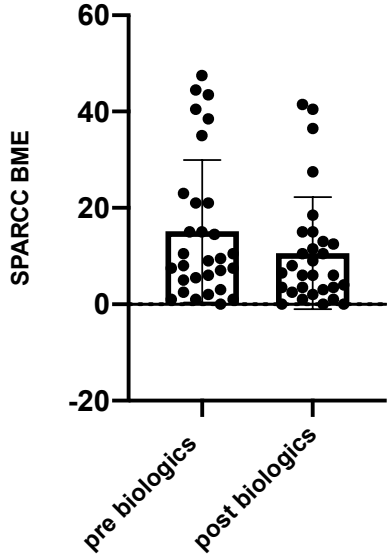


Figure 7-7 Changes in histograms before and after treatment Pre- treatment (a) and post-treatment (c) images and corresponding histograms (b, d) are shown. In this subject the histogram has two peaks (denoted * and **) which may correspond to oedema and normal marrow/fat metaplasia respectively. On the post-treatment scan, there is a rightward shift in the histogram with both peaks moving upwards in terms of PDFF, although the lower 'oedema' peak remains present.

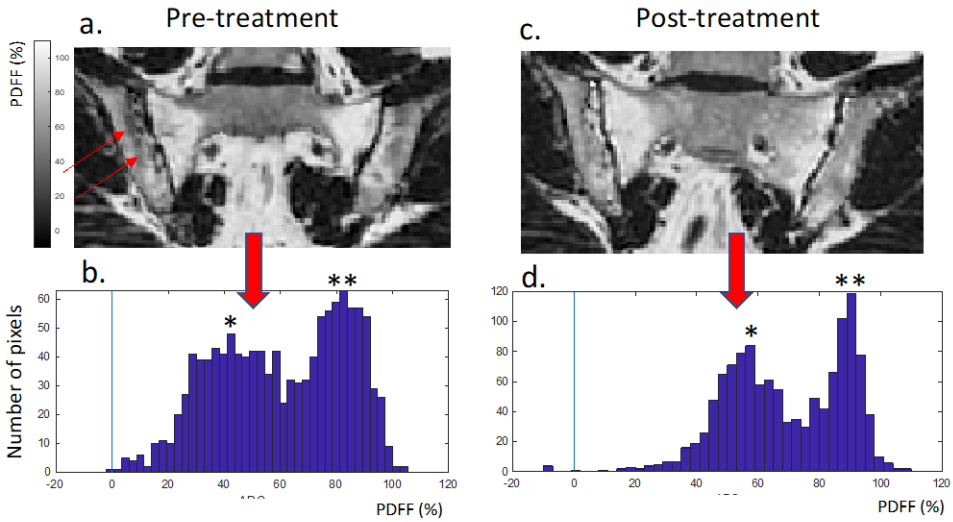


Table 7-3 Clinical outcomes, SPARCC and QIBs before and after biologic therapy

	Pre-biologics (mean)	Post-biologics (mean)	p value	Confidence interval (CI)	Standardised response mean
BASDAI	6.88	4.91	<0.001*	-2.97 - 1.15	0.89
Spinal VAS	6.90	4.76	<0.001*	-3.07 - 1.19	0.85
ASDAS CRP	3.32	2.4	<0.001*	-1.32- -0.53	0.88
ASDAS ESR	3.19	2.29	<0.001*	-1.24 -–0.56	0.98
CRP	5.35	1.99	0.02*	-6.13 to -0.58	0.45
SPARCC BMO	15.18	10.6	0.01*	-7.85 to -1.31	0.52
SPARCC SSS (fat)	17.73	19.63	0.16	-0.80 to 4.60	0.26
ADC mean	291.22	277.16	0.06	-28.49 - 0.37	0.37
ADC median	195.21	170.52	0.01*	-43.53 - 5.83	0.50
ADC 25	8.59	4.09	0.16	-10.83-1.87	0.27
ADC 75	476.4	457.2	0.08	-40.62 - 2.35	0.34
ADC 90	585.3	573.9	0.17	-46.31 - 8.56	0.26
PDFF mean	57.39	59.54	0.10	-0.426 - 4.73	0.31
PDFF median	56.79	58.76	0.16	-0.83 - 4.78	0.27
PDFF 25	47.84	50.26	0.13	-0.73 - 5.57	0.29
PDFF 75	66.84	68.92	0.10	-0.43 - 4.57	0.31
PDFF 90	51.21	50.53	0.13	-0.54 - 3.90	0.28

*****denotes p value < 0.05. Shaded boxes represent standardised response means > 0.40*

BASDAI, Bath ankylosing Spondylitis Disease Activity Index; VAS, visual analogue score; ASDAS Assessment of Spondyloarthritis Disease Activity score; CRP, c reactive protein; SPARCC, Spondyloarthritis Research Consortium of Canada; BMO, Bone marrow oedema; SSS, sacroiliac joint structural score; ADC, apparent diffusion coefficient; PDFF, proton density fat fraction

7.3.2 Correlation. between qualitative and quantitative MRI scores

Correlations between ADC and PDFF parameters with SPARCC BMO and SPARCC SSS (fat) scores at baseline are shown in Table 7-4. ADC values demonstrated a linear relationship with SPARCC BMO with strongest correlation between ADC 75 and SPARCC BMO (r = 0.70). Likewise PDFF parameters correlated well with qualitative fat scores. However, change in ADC and PDFF before and after biologic did not correlate with change in SPARCC BMO of fat scores before and after biologics.

Table 7-4 Correlation between quantitative and qualitative MRI scores

QIB	SPARCC-BMO	SPARCC SSS (fat)
ADC mean	0.67	0.11
ADC median	0.57	0.13
ADC 25	0.32	0.21
ADC 75	0.70	0.06
ADC 90	0.68	0.08
PDFF mean	-0.27	0.52
PDFF median	-0.17	0.50
PDFF 25	-0.37	0.42
PDFF 75	-0.06	0.59
PDFF 90	-0.09	0.52

Shaded boxes represent r > 0.50 ADC, apparent diffusion coefficient,; BMO; Bone marrow oedema; PDFF, proton density fat fraction SPARCC, Spondyloarthritis Research Consortium of Canada;; SSS, sacroiliac joint structural score;

Figure 7-8 Relationship between SPARCC BMO and ADC

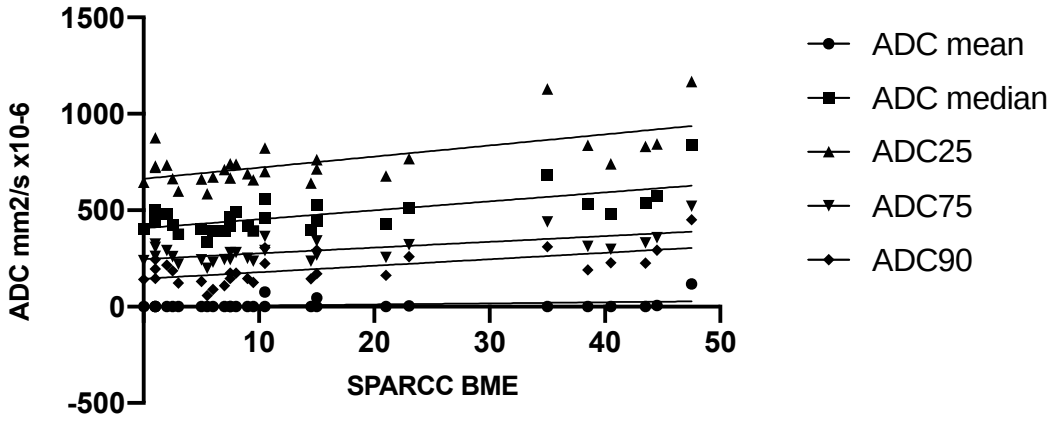
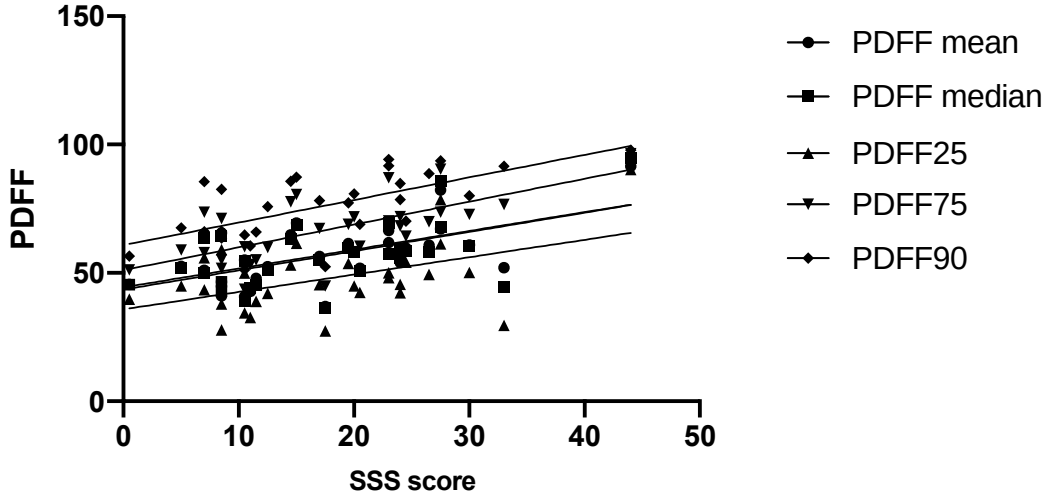


Figure 7-9 Relationship between SSS score and PDFF



7.3.3 Correlation between quantitative MRI scores and clinical disease activity scores.

ADC and PDFF values did not correlate with BASDAI, spinal VAS, ASDAS ESR, ASDAS CRP or laboratory variables (CRP or ESR).

7.3.4 Association between QIB and clinical scores. Do QIBs predict clinical response?

There was no significant difference between clinical responders and non-responders with regards to SPARCC and QIB scores. Neither baseline ADC, change in ADC (ΔADC), PDFF and change in PDFF (ΔPDFF) were able to predict BASDAI 50, ASDAS CII or ASDAS ID after 12-16 weeks post biologic treatment. This finding was did not change after removing those patients with concomitant pain. Table 7-5 shows outcome predictions based on ADC and changes of ADC from baseline.

Table 7-5 Outcome predictions based on the apparent diffusion coefficients (ADC) and changes of ADC from baseline. No statistically significant predictions were identified (p>0.05)

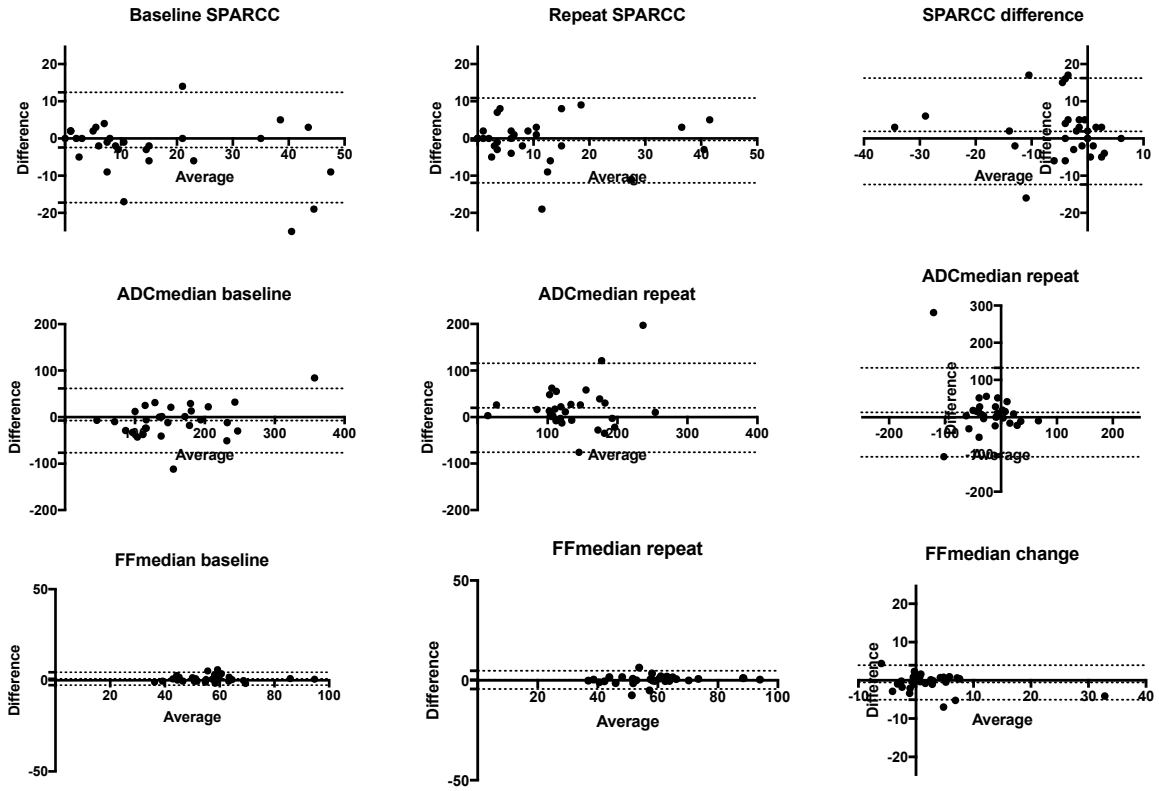
	BASDI 50	ASDAS CII	ASDAS ID
ADC mean	0.99 (0.98-1.01)	1.00 (0.98-1.01)	1.01 (0.99-1.04)
ΔADCmean	1.01 (0.97-1.00)	1.00 (0.98-1.03)	0.99 (0.96-1.02)
ADCmedian	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.02)
ΔADCmedian	0.97 (0.94-1.00)	0.98 (0.96-1.00)	1.00 (0.98-1.02)
ADC25	0.97 (0.92 – 1.00)	0.98 (0.92 – 1.01)	Not convergent
ΔADC25	0.98 (0.91 -1.03)	0.98 (0.92-1.03)	Not convergent
ADC75	0.99 (0.98-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.01)
ΔADC75	0.98 (0.95-1.00)	0.99 (0.97-1.01)	1.00 (0.99-1.03)
ADC90	0.00 (0.98-1.00)	0.99 (0.98-1.00)	1.01 (1.00-1.02)
ΔADC90	0.97 (0.94-0.99)	0.99 (0.98-1.00)	1.00 (0.99-1.02)

Results are expressed as odds ratios (95% confidence intervals). ADC, apparent diffusion coefficient; BASDAI 50, change in BASDAI by 50%; CII ASDAS, a clinical important improvement in ASDAS defined as a change in ASDAS >1.1; ASDAS ID, inactive disease defined as an ASDAS of < 1.3.

7.3.5 The inter-rater reliability of the BEACH tool.

Bland-Altman plots for inter-reader reliability are shown in Figure 7-9 Bland-Altman plots for interobserver variability. Bias (LoA) was: -2.43 (-17.3 to 12.4) for baseline SPARCC, -0.53 (-11.9 to 10.9) for repeat SPARCC, 1.9 (-12.4 to 16.2) for SPARCC change, -7.7 (-77 to 61) for baseline ADC median, 19.8 (-76 to 115) for repeat ADC median, 13 (-107 to 133) for ADC median change, 0.85% (-2.7 to 4.4) for FF median baseline, 0.24% (-43 to 4.8) for FF median repeat and -0.55% (-5.1 to 4.0) for PDFF median change.

Figure 7-9 Bland-Altman plots for interobserver variability



Patients with chronic pain and axial spondyloarthritis

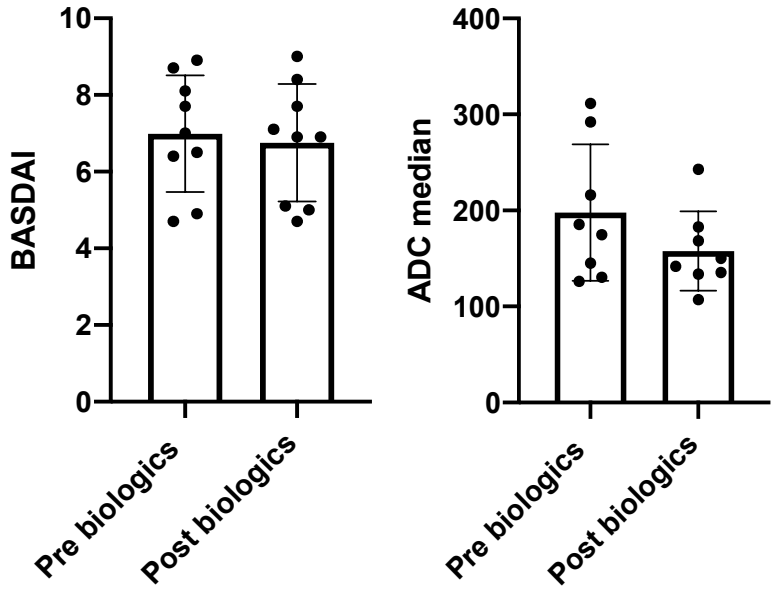
9 patients included in the study fulfilled ACR criteria for FM. These patients were predominately female (8:1) with an average age of 48.8 years. 2 patients were diagnosed with AS and 7 patients with nr-axSpA. 3 patients were HLA B27 positive and 6 were HLA 27 negative. 1 patient demonstrated peripheral enthesitis whilst there was no concomitant peripheral synovitis in any of the patients. All patients were biologic naïve. These patients did not respond well to biologic therapy and there were no significant difference in their clinical outcomes (BASDAI, Spinal VAS, ASDAS CRP and ASDAS ESR) before and after treatment. Interestingly, there were significant changes in ADC median and ADC 75 (Table 7-6) suggesting that changes in inflammation could be occurring in the absence of symptomatic improvement.

Table 7-6 Results for patients with axial spondyloarthritis and fibromyalgia before and after biologic treatment (n=9)

	Pre-biologics (mean)	Post-biologics (mean)	p value	Confidence interval (CI)
BASDAI	6.99	6.76	0.40	-0.84 to 0.38
Spinal VAS	6.78	6.56	0.75	-1.75 to 1.30
ASDAS CRP	3.26	3.03	0.40	-0.79 to 0.35
ASDAS ESR	3.04	2.77	0.40	-0.96 to 0.42
CRP	3.83	3.62	0.89	-3.53 to 3.11
SPARCC BMO	11.22	10.56	0.63	-3.74 to 2.41
SPARCC SSS (fat)	15.63	16.00	0.80	-3.026 to 3.776
ADC mean	293.91	264.26	0.06	-61.32 to 2.01
ADC median	197.72	157.83	0.05	-79.68 to -0.10
ADC 25	5.68	0	0.35	-19.10 to 7.746
ADC 75	480.44	439.12	0.05	-82.73 to 0.11
ADC 90	750.05	707.33	0.12	-120.0 to 16.54
PDFF mean	56.02	57.43	0.38	-2.15 to 5.05
PDFF median	55.54	56.52	0.45	-2.03 to 4.14
PDFF 25	46.97	48.40	0.44	-2.76 to 5.73
PDFF 75	65.15	66.21	0.42	-2.07 to 4.45
PDFF 90	73.69	75.09	0.35	-1.98 to 4.95

Shaded boxes represent p value < 0.05. BASDAI, Bath ankylosing Spondylitis Disease Activity Index; VAS, visual analogue score; ASDAS Assessment of Spondyloarthritis Disease Activity score; CRP, c reactive protein; SPARCC, Spondyloarthritis Research Consortium of Canada; BMO, Bone marrow oedema; SSS, sacroiliac joint structural score; ADC, apparent diffusion coefficient; PDFF, proton density fat fraction

Figure 7-10 BASDAI and ADC median before and after biologic therapy in patients with fibromyalgia



7.3.6 Is there any difference between patients with peripheral disease versus purely axial

There was no significant difference in in BASDAI response in patients with peripheral versus axial disease. However, there was a significantly greater change in SPARCC BMO and ADC medians scores before and after biologic treatment in patients with purely axial disease versus those with concomitant peripheral disease.

7.3.7 Relationship between QIBS and other clinical parameters

There was no significant difference in ADC and PDFF scores in those patients who were HLA B27 positive versus those that were negative. Only a weak association (R = 0.37 – 0.39) between disease duration and PDFF values. There was no association

between ADC and disease duration. There was no significant difference between diagnosis (axSpA versus AS), disease duration, HLA B27 positivity and QIB scores before and after treatment between diseases. Interestingly, there was also no difference in incidence of chronic pain.

7.4 Discussion

ADC values and SPARCC BMO scores of the SIJs demonstrate significant reductions following biologic treatment in patients with axSpA. The ADC median of the SIJ joints was particularly sensitive to change following biologic therapy and demonstrated a superior response compared with SPARCC BMO.

PDFF values and SPARCC SSS (fat) scores did not show significant change before and after treatment with biologic therapy and demonstrated non-significant SRMs. Other studies have shown similar results for quantitative structural scores[257]. One explanation could be that structural changes in bone marrow take longer than 12 – 16 weeks to present on MRI. PDFF scores correlated well with SPARCC SSS (fat) scores at baseline, arguing for their validity as a tool for measuring of fat fraction.

There was no significant difference in QIB scores between clinical responders and non-responders and QIBS could not predict those patients who reached BASDAI 50, CII ASDAS or ASDAS ID. There may be a number of factors that could have contributed to this finding. Firstly this study assessed inflammation in the SIJs only, excluding any contribution from spinal inflammation, peripheral joint, entheseal pain and fatigue captured in clinical scores. Fatigue, in particular, is a complex

symptom which does not always parallel objective reductions in inflammation in rheumatic disease [258]. We deliberately included patients with concomitant fibromyalgia and those patients switching biologic therapy following primary or secondary failure to reflect real life clinical practice. We have shown that these patients with chronic pain/fibromyalgia did not demonstrate a clinical response to biologic therapy despite there being a change in ADC parameters. This shows the possible disconnect between symptomatic changes and MRI changes. The heterogeneity of our study group resulted in only 27% of our patients achieving a BASDAI 50 response at 12 weeks compared with 50-60% of biologic naïve patients typically reported in clinical trials[259].

This study was designed as a pilot study and this included relatively few patients (n=30) with a shorter follow up than other studies of axial SpA. It would have been useful to look at 6 and 12 month changes. It should also be noted that much of the statistical analysis involved multiple pairwise t testing leading to an increase probability of type I errors.

A significant advantage of our study was its single centre prospective design. All patients were imaged using the same MRI system and the same protocol defined at predefined time points. Variations in scanner, sequences and timings were, therefore, minimized. Few prospective studies have used ADC measurements to assess responses to biologic treatment in axSpA and in these studies ROIs were used[226]. This study validates the use of the BEACH tool as a semi-automated

method of calculating QIBS which is faster and requires less expertise that using ROIs. The BEACH tool also demonstrates high inter-rater reliability.

7.5 Conclusion

Quantitative imaging biomarkers are sensitive to changes in inflammation following biologic therapy. In this cohort, ADC-median showed moderate responsiveness, whilst responsiveness was low for the qualitative SPARCC method.

8 Discussion

The purpose of this work was to critically appraise the way in which we currently assess disease activity and response to treatment in axSpA and to examine the potential role of qMRI to meet this clinical need.

Patient reported outcome measures remain the gold standard for assessing disease activity in axSpA. Whilst they address important disease characteristics, such as pain, stiffness and fatigue, their interpretation is limited in patients with concomitant chronic fatigue, FM and mechanical spinal pain – which represent a significant proportion of patients with axSpA. In these patients, symptoms may not be driven by active inflammation but aberrant pain processing or degenerative changes in the spine, which require a focus on physical therapies and/or holistic pain management programs rather than biologic treatment. Selecting the most appropriate treatment for an individual patient at the right time underpins the concept of precision medicine, and has significant implications for individualisation of patient care as well as health economics.

This work has addressed the use of QIBs in the assessment of disease activity in axSpA, and shows promise for the use of ADC as a potential biomarker for disease. This biomarker could be used in conjunction with clinical and biochemical parameters (ESR and CRP) to provide a more accurate assessments of disease activity.

The major issue encountered by research in axSpA is the lack of gold standard for disease. In my study, I have tried to overcome this by looking at the response of clinical and imaging parameters to treatment, however, not all patients with active disease will respond to treatment and those that do, may respond with the varying effect. A stronger study design would correlate these biomarkers with an established pathological or histological process associated with the disease.

The study was designed as a pilot study and, as such, has a small study population (n=30). Furthermore, the study population was heterogenous to reflect real life clinical practice. Patients with peripheral arthritis and FM were included in the study as well those patients switching to a second and third biologic, owing to primary or secondary failure. Whilst, this provided some interesting findings, the combination of a small and heterogenous population group will have underpowered the study. Further work should include a larger, prospective study in biologic naive patients with axial disease only and no concomitant FM or CWP to assess the true correlation of QIBs with inflammatory symptoms associated with axSpA.

An interesting finding of this study was the lack of correlation between clinical and imaging parameters of disease activity. It would be interesting to look at individual components of the BASDAI and ASDAS and correlate these with imaging scores to see if certain symptoms (i.e. morning stiffness) correlate better than others with imaging biomarkers of disease activity. The BASDAI and ASDAS assume that fatigue, pain and stiffness are all driven by the same process in axSpA, however, this

may be too simplistic. We know, for example, that following biologic therapy, patients' symptoms of fatigue may persist even when pain and stiffness has improved. Perhaps different symptoms represent different pathological pathways within the disease process.

One of the benefits of including a heterogenous cohort of patients was some further insights into the role of chronic pain. We found that in those patients with chronic pain, there was no significant improvement in their clinical outcomes measures following biologic therapy. However, there were significant changes in qMRI scores, notably ADC median and ADC75 suggesting that improvements in inflammation may not manifest in symptomatic improvement in these patients. This also adds weight to the proposition that clinical scores are limited in this cohort of patients.

In the study, we focussed on the sacroiliac joints only, however, axSpA affects the entire axial skeleton and isolated spinal inflammation can occur in the absence of active sacroiliitis in up to 24-49% of patients with axSpA[198,199]. Future research should look at the relative contribution of the spine: assessing ADC and PDFF histograms in each discovertebral unit in addition to the scores of the SIJs. This may provide a more accurate assessment of inflammatory burden.

In this study, qualitative and quantitative MRI scores were recorded after 12-16 weeks of biologic therapy to reflect current recommendations on assessment of clinical response to biologic therapy. It would have been interesting, however, to

assess qMRI scores after 6 and 12 months of treatment to see if changes lag behind a clinical response. Long term prospective studies could also look at how ADC and PDFF values may be related to radiographic progression of the disease. Studies have shown that fatty changes at vertebral end plates predict formation of syndesmophyte in patients with axSpA[260]. It would be interesting to see whether PDFF and ADC scores are associated with the development of sclerosis, fusion or ankylosis in patients over time.

In this study, we used an automated tool to populate qMRI values. The BEACH tool devised by Bray et al is a much faster method of providing QIBs than standard ROI plots and has demonstrated excellent interrater reliability. This tool adds to the growing body of work on artificial intelligence (AI) in clinical medicine. As technology continues to advance, AI will arguably play a greater role in clinical medicine, serving to improve the accuracy and speed of clinical assessments and remove cognitive biases associated with clinical interpretation[261].

Whilst the focus of this work has been on the assessment of disease activity, there could be scope to use qMRI in a diagnostic capacity. A number of studies have demonstrated the appearance of sacroiliitis (subchondral bone marrow oedema and fatty change) on MRI SIJ of patients with mechanical back pain, athletes and post-partum women[262] . If patients were to also present with some features of inflammatory back pain, such as morning stiffness, an incorrect diagnosis of axSpA could be made. Quantitative MRI could be used to assess the degree of bone marrow

oedema and fatty change using ADC and PDFF in these patients. One could hypothesise that ADC and PDFF scores might be lower in patients with mechanically driven sacroiliitis compared to those with true inflammatory sacroiliitis found in axial spondyloarthritis. If this were the case, ADC and PDFF values could more accurately determine those patients with inflammatory axSpA versus those with non-specific and mechanical changes.

Whilst it is a legitimate argument that MRI is too expensive to be used for routine assessment of disease activity, it is important to consider the cost of initiating or continuing expensive biologic treatment in inappropriate patients. Furthermore, qMRI is only likely to be used in a select group of patients, where reported outcome measures prove difficult to interpret. This includes patients with FM, CWP, long term mechanical damage from AS or degenerative spinal changes.

Assessment of disease activity and response to treatment remains an area of unmet clinical need in the management of axSpA. With burgeoning development of biologic therapies over the past ten years, the need to adopt precision medicine into rheumatology practice has never been more critical. Quantitative MRI offers a potential solution to this problem. Further work will be needed to refine its role and accessibility to clinicians.

Following this pilot study, the next step would be to carry out a large prospective study on patients with purely axial disease and no concomitant widespread pain or

fibromyalgia. This may provide a more reliable correlation between clinical and imaging disease activity. MRI scans taken at baseline and then 3, 6 and 12 months after biologic therapy will provide more information regarding both inflammatory and structural changes on SIJs over time.

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