

**Exploring Pathogenesis and Treatment
Response in Different Disease Phenotypes in
Spondyloarthritis**

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Intellectual property and publication statements

The candidate confirms that the work submitted is his own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter 2 is based on works from jointly authored publications by Dubash S, De Marco G, Bridgewood C, McGonagle D, Marzo-Ortega H.

Dr Sayam Dubash performed the literature review, critically appraised the scientific evidence of relevant topics and led the writing of the manuscripts. All other senior authors above revised the manuscripts for important intellectual content and final approval of the manuscript (first two publications below).

Dr Sayam Dubash performed the literature review, critically appraised the scientific evidence and led the writing of the manuscript which included introduction, tendon pathologies, dactylitis, limitations of ultrasound (US), comparison of US with clinical examination and composite clinical scores, unmet needs in US imaging in psoriatic dactylitis, figure of characteristic ultrasound appearances, composite US scores in joints and entheses, guided interventions and conclusions. Dr Gabriele De Marco performed the literature review and writing of the manuscript for methods, synovitis and subclinical synovitis, enthesal pathology, unmet needs in US imaging in psoriatic oligo/polyarthritis, management and prognosis. Both authors contributed equally to writing of the manuscript. All other senior authors above revised the manuscripts for important intellectual content and final approval of the manuscript (third publication below).

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Dubash S, Bridgewood C, McGonagle D, Marzo-Ortega H. The advent of IL-17A blockade in ankylosing spondylitis: secukinumab, ixekizumab and beyond. *Expert Rev Clin Immunol*. 2019 Feb;15(2):123-134.

Dubash S*, De Marco G*, Wakefield RJ, Tan AL, McGonagle D, Marzo-Ortega H. Ultrasound imaging in Psoriatic arthritis: What have we learnt in the last five years? *Front. Med*. 7:487. (*denotes joint first author)

Chapter 4 is based on works presented in jointly authored publications by Dubash S, Pease C, Aslam A, Coady D, Marianayagam T, Tinazzi I, Al-Araimi T, Pagnoux C, Weizman AV, Richette P, Tran Minh M-L, Allez M, Singh A, Ciccica F, Hamlin J, Tan AL, McGonagle D, Marzo-Ortega H.

Dr Sayam Dubash conducted these two case series evaluations, led the collection of data, management and analysis of data, review of literature, critically appraised scientific evidence of the relevant topics and led the writing of the manuscripts. All other senior authors above revised the manuscripts for important intellectual content and final approval of the manuscript.

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Dubash S, Marianayagam T, Tinazzi I, Al-Araimi T, Pagnoux C, Weizman AV, Richette P, Tran Minh M-L, Allez M, Singh A, Ciccica F, Hamlin J, Tan AL, Marzo-Ortega H, McGonagle D. Emergence of Severe Spondyloarthropathy Related Enteseal Pathology Following Successful Vedolizumab Therapy for Inflammatory Bowel Disease. *Rheumatology (Oxford)*, 2019 Jun 1;58(6):963-968.

Dubash S, Marzo-Ortega H, McGonagle D. Comment on: Emergence of severe spondyloarthropathy-related enteseal pathology following successful vedolizumab therapy for inflammatory bowel disease: reply. *Rheumatology (Oxford)*. 2019 Jun 1;58(6):1115-1117.

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“If anyone travels on a road in search of knowledge, Allah will cause him to travel on one of the roads of Paradise”

Prophet Muhammad (pbuh)

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Dubash S, Marianayagam T, Tinazzi I, Al-Araimi T, Pagnoux C, Weizman AV, Richette P, Tran Minh M-L, Allez M, Singh A, Ciccio F, Hamlin J, Tan AL, Marzo-Ortega H, McGonagle D. Emergence of Severe Spondyloarthropathy Related Enteseal Pathology Following Successful Vedolizumab Therapy for Inflammatory Bowel Disease. *Rheumatology (Oxford)*, 2019 Jun 1;58(6):963-968.

Dubash S, Marzo-Ortega H, McGonagle D. Comment on: Emergence of severe spondyloarthropathy-related enteseal pathology following successful vedolizumab therapy for inflammatory bowel disease: reply. *Rheumatology (Oxford)*. 2019 Jun 1;58(6):1115-1117.

Dubash S, McGonagle D, Marzo-Ortega H. New advances in the understanding and treatment of axial spondyloarthritis: from chance to choice. *Ther Adv Chronic Dis* 2017; 9: 77–87.

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Dubash S*, De Marco G*, Wakefield RJ, Tan AL, McGonagle D, Marzo-Ortega H. Ultrasound imaging in Psoriatic arthritis: What have we learnt in the last five years? *Front. Med.* 7:487.

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- b. *North-west and York meeting 2018*

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Abstract

Background: The pathogenesis of spondyloarthritis (SpA) is thought to be driven by enthesitis, yet there remain gaps in the understanding of these diseases. Different SpA phenotypes characterised by inflammatory enthesal/joint pathology may result in structural/functional damage. Despite therapeutic advances, challenges in measuring treatment responses persist.

Objectives: To explore the: (i) pathogenesis of severe SpA in different phenotypes; (ii) clinical/ultrasound (US) characteristics of early PsA; (iii) significance of dactylitis and disease severity in early PsA; (iv) mechanisms of measuring treatment response in infliximab (IFX) treated SpA.

Methods: (i) Two separate clinical case series evaluations were conducted in patients with severe SpA phenotypes. (ii/iii) A prospective observational clinical/ultrasound (US) study was conducted to examine characteristics of DMARD-naive early PsA, and significance of dactylitis. A prospective clinical evaluation was performed to assess IFX drug trough levels (DLs), anti-drug antibodies (ADAs), and treatment responses (iv).

Results: (i) Severe enthesitis was found in a phenotype mimicking appearances of infection. De novo severe SpA and enthesitis manifested following successful vedolizumab (VDZ) treated inflammatory bowel disease (IBD). (ii) Swollen joints were more likely to have US synovitis than tender joints in early PsA. (iii) The presence of dactylitis was found to be significantly associated with greater SJC, CRP, US synovitis and US erosions in early PsA. (iv) Measuring DLs/ADAs in IFX treated SpA enabled rationalisation of treatment responses.

Conclusion: Severe enthesitis was identified in extreme SpA phenotypes likely to resemble ReA, and paradoxical reactions to VDZ. Swollen joints were the better proxy for US synovitis than tender joints, and dactylitis represented a marker for a phenotype of greater disease severity in early PsA. Use of DL/ADAs to IFX treated SpA may support rationalisation of treatment responses. These findings add to the knowledge and understanding of disease in SpA, and contribute towards improving the care of patients.

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Abbreviations

ACPA	Anti-citrullinated protein antibody
ADA	Anti-drug antibody
ADM	Adalimumab
ANA	Anti-nuclear antibody
AS	Ankylosing spondylitis
ASAS	Assessment of spondyloarthritis international society
ASQoL	Ankylosing spondylitis quality of life index
AS-WIS	Ankylosing spondylitis work instability scale
ATI	Antibodies to infliximab
axSpA	Axial Spondyloarthritis
$\alpha 4\beta 7$	Alpha 4 beta 7 integrin
$\alpha 4\beta 1$	Alpha 4 beta 1 integrin
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
bDMARDs	Biologic disease modifying anti-rheumatic drugs
BMI	Body mass index
BMO	Bone marrow oedema
CASPAR	Classification criteria for psoriatic arthritis
CD	Crohn's disease
csDMARDs	Conventional synthetic disease modifying anti-rheumatic drugs
CT	Computed tomography
CT-P13	Biosimilar of the reference drug infliximab
CRF	Case report form
CRP	C- reactive protein
DLQI	Dermatology life quality index

DL	Drug trough level
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology (formerly European League against Rheumatism)
GUESS	Glasgow Ultrasound Enthesitis Scoring System
HAQ-DI	Health assessment questionnaire disability index
HLA-B27	Human leucocyte antigen-B27
HCQ	Hydroxychloroquine
IBD	Inflammatory bowel disease
IBP	Inflammatory back pain
IFX	Infliximab
IMIDs	Immune mediated inflammatory diseases
IQR	Interquartile range
IRL	Inflammatory Romanus lesion
LEI	Leeds enthesitis index
LOR	Loss of response
LTHT	Leeds teaching hospitals trust
MADCAM-1	Mucosal addressin cell adhesion molecule-1
MASES	Maastricht ankylosing spondylitis enthesitis score
MCP	Metacarpophalangeal joint
MDA	Minimal disease activity
MHC1	Major histocompatibility complex class 1
MTX	Methotrexate
mNAPSI	Modified nail psoriasis severity index
mGUESS	Modified Glasgow Ultrasound Enthesitis Scoring System
mNY	Modified New York criteria
MRI	Magnetic resonance imaging

MSK	Musculoskeletal
MTP	Metatarsophalangeal joint
NHS	National health service
nr-axSpA	Non-radiographic axial spondyloarthritis
NSAIDs	Non-steroidal anti-inflammatory drugs
NTZ	Natalizumab
OMERACT	Outcome Measures in Rheumatology
PAMPs	Pathogen-associated molecular patterns
PASI	Psoriasis area severity index
PIP	Proximal interphalangeal joint
PsA	Psoriatic arthritis
PsAQoL	Psoriatic arthritis quality of life index
pSpA	Peripheral SpA
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
ReA	Reactive arthritis
RF	Rheumatoid factor
SIJ	Sacroiliac joint
SNPs	Single nucleotide polymorphisms
SpA	Spondyloarthritis/spondyloarthropathy/spondyloarthritides
SpARRO	The Leeds SpA register for research and observation
SPARCC	Spondyloarthritis research consortium of Canada
STIR	Short tau inversion recovery
TDM	Therapeutic drug monitoring
TNF α	Tumour necrosis factor α
TNFi	Tumour necrosis factor inhibitor (anti-TNF)
tsDMARDs	Targeted synthetic disease modifying anti-rheumatic drugs

UC	Ulcerative colitis
US	Ultrasound scan
VCAM-1	Vascular cell adhesion molecule-1
VDZ	Vedolizumab
VLDA	Very low disease activity

Chapter 1. Introduction

Musculoskeletal (MSK) disorders including arthritis affect an estimated 18.8 million people in the United Kingdom, being one of the leading causes of work disability (Versus arthritis, 2021). In fact MSK disorders represent more than one fifth of all health morbidity across all ages having a significant impact on quality of life (Institute for health metrics and evaluation, 2018). Arthritis accounts for a substantial proportion of the MSK burden, not only causing significant impairment to the individual, but also the attached socio-economic impact.

Spondyloarthritis (SpA) is one of the main disorders that along with rheumatoid arthritis (RA), form the two prime categories of idiopathic inflammatory arthritis. Indeed they share similarities such as in prevalence, including that either can cause articular and extra-articular clinical manifestations. However, SpA encompasses a group of inflammatory disorders with a heterogeneous phenotype that also share underlying common aetiopathogenesis.

People with SpA often have peripheral and/or axial disease and may be classed within one of the several disease groups, either with a diagnosis of psoriatic arthritis (PsA), axial SpA (axSpA) which includes non-radiographic axSpA (nr-axSpA) and ankylosing spondylitis (AS), or the less commonly associated inflammatory bowel disease (IBD) related arthritis (enteropathic arthritis), or reactive arthritis which may occur post-infection. Occasionally, some patients may not satisfy a diagnosis or criteria for SpA, but may progress to do so at a later date and are therefore termed “undifferentiated SpA”.

Some SpA phenotypes may be more severe than others, which is not well understood and the diagnosis in some patients may not be easily discernible due to lack of biomarkers. Identifying clinical features and patterns may hold weight in improving early recognition for prompt intervention.

In Leeds, the late Professor Verna Wright reported on observed associations identified with other of diseases of the SpA family, including AS, ReA, and IBD related arthropathy (Moll et al., 1974). The SpA disorders are underpinned by a shared association with the major histocompatibility complex class 1 (MHC-

1) alleles linked to disease immunopathogenesis, which differs from RA (Moll et al., 1974).

Evolution of inflammation transitioning from enthesitis to synovitis is a unique feature of the disease in SpA. Although radiographs can play a role in identification of more chronic disease, these pathologies can be identified earlier using sensitive imaging techniques such as ultrasound (US) or magnetic resonance imaging (MRI).

Enthesitis is one of the distinct pathological processes of disease onset in SpA and may precede the onset of synovitis (Kaeley, 2020). Both pathologies are identifiable by imaging techniques such as US which is sensitive in the assessment of joints and entheses of the peripheral skeleton. Conversely, clinical examination is less sensitive than US for the identification of enthesitis or synovitis.

Current literature suggests enthesitis is a pivotal feature of SpA onset that leads to the development of further pathologies such as synovitis or bone oedema. Persistent inflammation can lead to significant damage including bone erosions. Synovitis or enthesitis are linked to the development of erosions which can lead to structural and functional impairment. A high frequency of enthesopathy and synovitis in skin PsO was reported in individuals asymptomatic for musculoskeletal symptoms (Naredo et al., 2011). Identification of its presence may be suggestive of a biomarker of disease. Other prospective cohorts of PsA have reported that polyarticular onset of disease predicted erosive deforming disease progression over time (Zabotti, Piga, et al., 2018). Small patient numbers have been a limitation in several studies, and data from larger patient cohorts is required for increased reliability and accurate results.

Adopted strategies in RA have shown that early treatment with regular review of therapy in relation to the treatment goal, can result in significantly better outcomes (Coates et al., 2015). Various composite measures have been produced to define the treatment targets including minimal disease activity (MDA) criteria and very low disease activity (VLDA) criteria in PsA (van Mens et al., 2018). Nevertheless over the last two decades, beyond csDMARDs which are generally less effective, biologic DMARDs (bDMARDs) have

revolutionised the treatment of SpA and despite a large proportion of patients that respond to therapy successfully, up to 50% of individuals do not (Costa et al., 2017). As a result some may fail to respond to successive biologic therapies. In these cases clarification of the diagnosis, in addition to further investigations, may be more helpful than a blanket next in line therapy approach.

In routine practice, there are still no validated biomarkers specific to a diagnosis of PsA. The lack of serological biomarkers for PsA translates to the dependence of clinicians on conducting a thorough clinical examination to identify the key clinical features in particular the presence of skin PsO.

Loss of response (LOR) to therapy is a significant problem affecting 50% of bDMARD treated SpA patients (Bendtzen, 2015). Despite complex underlying mechanisms, it is known that a significant proportion of these are associated with the drug (bDMARD) itself, its bioavailability and immunogenicity caused by the formation of anti-drug antibodies (ADAs). One method for maximising treatment response is to adopt the use of therapeutic diagnostics (“theranostics”) to improve treatment success and identify LOR. This approach may also reduce the financial burden attached to drug therapies. Therefore measuring serum drug trough levels (DLs) and ADAs to the relevant tumour necrosis factor inhibitor (TNFi) may be useful markers for the monitoring and assessment of treatment response to bDMARDs.

Rather than a “one size fits all” approach, measurement of DLs and ADAs links to the drive for a proactive and tailored approach towards management of the individual. Importantly, in an era of increasing bDMARD therapies, there is anticipation on greater ability to monitor and assess response to therapy with a view to personalising treatment regimens, a step further towards achieving “personalised medicine”.

The purpose of this programme of research is to explore underlying disease pathogenesis and treatment response in different disease phenotypes in SpA. This will be achieved via addressing the two main hypotheses and the aims and objectives as detailed in chapter 3.

Chapter 2. Review of the literature

2.1 Spondyloarthritis (SpA): a spectrum of disorders

The term spondyloarthritis (SpA) refers to a group of heterogeneous disorders that share common aetiopathogenic and clinical manifestations and are underpinned by a complex genotype. Chronic inflammation may occur at MSK sites such as synovium and entheses, and extra-articular targets such as in the gut, uvea and the aortic valve root.

These disorders primarily comprise of psoriatic arthritis (PsA), axial spondyloarthritis (axSpA) of which ankylosing spondylitis (AS) is the prototype, inflammatory bowel disease (IBD) associated arthritis (enteropathic arthritis), reactive arthritis (ReA) which occurs post-infection, and juvenile SpA. Phenotypes of patients with SpA may be evolving at the early stages of disease or do not conform to a specific disease and are therefore nosologically defined as undifferentiated SpA (uSpA). Finally, less common syndromes are also considered to sit within the spectrum of SpA such as the synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO syndrome) which is testament to the heterogeneity of these diseases. Alternatively, SpA can be defined by the predominant symptomatic burden, with either axial (axSpA) or peripheral arthritis (pSpA)(Rudwaleit et al., 2011).

There is considerable overlap between clinical features in SpA conditions. However, even though SpA occurs as commonly as rheumatoid arthritis (RA), these disorders have intrinsic differences from RA. Considered to be the first to describe the SpA diseases as a separate entity, the late Wright and Moll linked their observations of these diseases and their common articular and extra-articular features to a unifying concept, that of the “seronegative spondyloarthropathies” (Wright and Moll, 1976). These conditions were termed seronegative due to their absence of rheumatoid factor (RF).

Unlike in RA, where presence of RF or anti-citrullinated protein (ACPA) can provide a clue to diagnosis, in SpA, no association with antibodies and the fact that inflammatory markers are normal in the majority of cases can make the diagnosis more difficult to confirm. Nonetheless human leucocyte antigen B27 (HLA-B27) may be useful in the diagnosis of axial spondyloarthropathy

(axSpA), present in up to 96% of AS and less than 10% of the healthy population, although its use is limited for peripheral disease and has no role for the monitoring of treatment (McHugh and Bowness, 2012). Imaging modalities such as X-ray, US and MRI, play an increasing role for confirming diagnosis and disease activity.

Enthesitis is an important pathological feature of SpA and can be identified using sensitively imaging techniques such as US or MRI. Though less is known about the significance of enthesitis and whether it can be used meaningfully as a biomarker for disease progression in SpA, it is not a recognised feature of RA, and therefore its presence has discriminatory value in differentiation of SpA from RA. Other forms of SpA may run an acute severe form which can mimic other diseases, posing challenges to diagnosis and treatment.

Although some phenotypes of PsA may seem mild, literature on MSK burden in PsA for example, appears to be comparable to RA, with joint related damage, functional impairment and reduced quality of life over time (Gladman et al., 2005). At the molecular level, understanding of SpA disease pathogenesis remains incomplete, though there is growing research in this field.

2.2 Axial SpA

2.2.1 Ankylosing spondylitis and non-radiographic axial SpA

The earliest discovery of this disease comes from palaeopathological study of the pharaohs of ancient Egypt and their mummified skeletons, found to have ankylosed spines, and radiographs of their skeletons confirmed sacroiliac joint fusion and ossification of the paraspinal ligaments, features almost certainly indicative of ankylosing spondylitis (AS) (Feldtkeller et al., 2003). The disease also affected father (Ramses II) and son (Merenptah) consistent with the known familial association.

Axial spondyloarthritis (axSpA) has a broad phenotype which includes both AS, the prototype spondyloarthropathy, also known as radiographic axSpA, with an extreme phenotypic manifestation characterised by sacroiliac joint (SIJ) and spinal damage which may vary from mild erosive disease to new bone formation and joint fusion, and the non-radiographic spectrum of the disease (nr-axSpA) that may represent either early or mild phenotypes of disease with the potential to progress into AS. The recent literature recognises these disorders as two ends of a spectrum indicative of one unified disease entity (Baraliakos and Braun, 2015).

2.2.2 Epidemiology

Axial SpA commonly starts in the second to third decade of life with a male to female ratio of approximately 2-3:1. Disease onset is about 5 years sooner in HLA-B27 positive individuals compared with those who are HLA-B27 negative (Sieper and Poddubnyy, 2017). The majority of epidemiological studies performed to date have been in ankylosing spondylitis, which has an estimated prevalence of 0.5-1% (Braun et al., 1998). The overall prevalence of axSpA is variable with estimates between 0.32% and 1.4% depending upon geographical region and ethnicity (Sieper and Poddubnyy, 2017). The average age of symptom onset in axSpA is slightly later in women than men with a lower prevalence of HLA-B27 in women which may account for slightly longer diagnostic delay (Ciurea et al., 2014).

2.2.3 Clinical and pathology disease burden

The typical presentation of AS, the epitome of axial SpA, is axial spinal vertebral disease manifesting as lower back and buttock pain usually with an insidious onset. The burden of long-term disease resulting from post inflammation new bone formation and specifically spinal ossification, causes permanent functional limitation. Peripheral joint disease, enthesitis and extra-articular manifestations such as uveitis, aortic valve regurgitation (aortic valve root dilatation) and underlying IBD, the latter often subclinical, are well described and shared amongst the clinical spectrum of diseases within SpA. Peripheral arthritis occurs in 30% of individuals with axSpA, usually with asymmetrical large joint oligoarticular involvement of the lower limb joints such as knees, ankles, and hips, or involvement of the shoulders or dactylitis may be present (Van Der Horst Bruinsma and Nurmohamed, 2012). Reportedly dactylitis occurs in nearly 14% of early axSpA, and may precede the onset of axial symptoms in over 40% of cases (Wendling et al., 2020).

Axial SpA is a chronic inflammatory disease with a varied clinical phenotype which in its severe advanced stage (AS), can be identified by a combination of clinical symptoms and established radiographic changes at the SIJs which can be graded according to the definitions given in the 1984 modified New York criteria (mNY) (Linden et al., 1984) as shown in Table 2:1. It is important to distinguish the fact that these classification criteria are developed to facilitate the inclusion of patients into clinical trials and that these should not be used for the purposes of diagnosis. Furthermore, the fact that the mNY criteria refer to radiographic imaging is currently considered too insensitive for the detection of early axial inflammation which can be captured via MRI.

all, as radiographic progression is not universal. However, in addition to HLA-B27 in AS, smoking has also been shown to predict poor prognosis including radiographic structural progression over time (Poddubnyy et al., 2013).

The most recent classification criteria for axSpA, developed by the assessment of spondyloarthritis international Society (ASAS), incorporates both radiographic and non-radiographic disease stages, and include a combination of features such as sacroiliitis on either radiography or magnetic resonance imaging (MRI), HLA-B27, C-reactive protein (CRP), and other associated clinical characteristics (Sieper et al., 2009). These classification criteria capture the broad spectrum of features accountable towards identifying axSpA for clinical trials research (Figure 2:1). There have been several other criteria for SpA classification, such as the European spondyloarthropathy study group (ESSG), Calin, Berlin, and Amor criteria, however these are exclusive of MRI findings. These ASAS criteria specifically include radiographic or MRI sacroiliitis as one of the key SpA features for axSpA classification and are now widely accepted.

Figure 2:1. ASAS classification criteria for axial SpA in patients with back pain for at least 3 months, and less than 45 years of age.

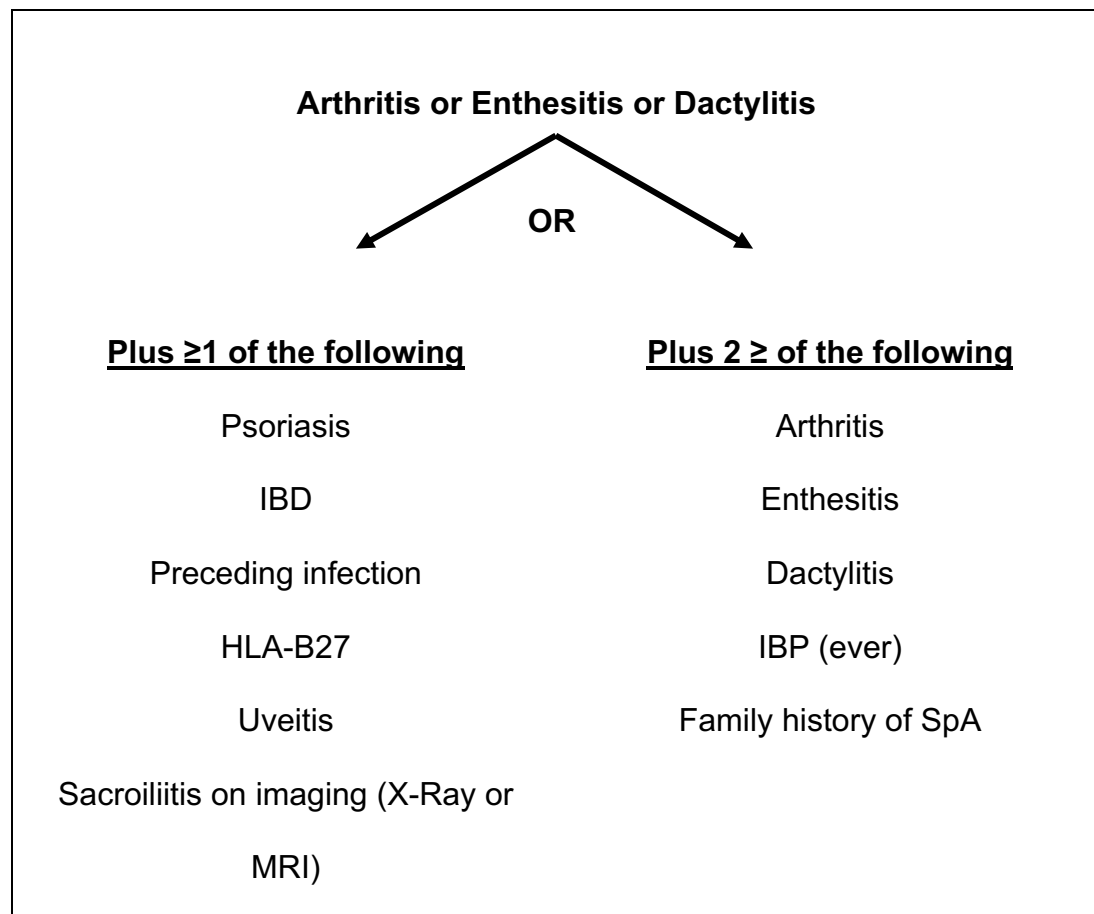
<p>Sacroiliitis on imaging*</p> <p>plus</p> <p>at least x1 SpA feature</p>	<p>HLA-B27 positive</p> <p>plus</p> <p>at least x2 SpA features</p>
<p>Any of the following SpA features:</p> <p>Inflammatory back pain</p> <p>Dactylitis</p> <p>Arthritis</p> <p>Psoriasis</p> <p>Crohn's and ulcerative colitis</p> <p>Enthesitis (heel)</p> <p>A good response to NSAIDs</p> <p>Uveitis</p> <p>Family history of SpA</p> <p>HLA-B27 positive</p> <p>Elevated CRP</p>	

*Sacroiliitis is defined by definite radiographic evidence by modified New York criteria or on MRI by ASAS consensus definition [adapted: (Rudwaleit et al., 2009)].

2.3 Peripheral SpA

The classification criteria designed for inclusion for clinical trials can often guide clinicians towards a diagnosis. The ASAS peripheral SpA (pSpA) criteria provide some guidance of the features considered to be indicative towards its classification. Although such axial and peripheral criteria may be useful for the classification in clinical trials, they do not include the natural history of the underlying disease which is attached to diseases that make up the umbrella term of SpA. This may be true for ReA where the presentation may be more acute and not conform to chronic history of symptoms. On the other hand, pSpA encompasses the whole spectrum of diseases within SpA and therefore are inclusive for research purposes. The ASAS peripheral SpA criteria (adapted) are outlined in Figure 2:2 (Rudwaleit et al., 2011).

Figure 2:2. ASAS classification criteria for peripheral SpA.



2.4 Psoriatic arthritis

Psoriasis and arthritis were observed at least as far back as 1818 (Alibert, 1818). However, it was not until 1956, in Leeds, when the late professor Verna Wright first described the connection between psoriasis and arthritis (PsA) in greater detail (Wright, 1956). Together with his late colleague John Moll, they first described the five clinical subtypes of PsA as distinct clinical entities within the spectrum of PsA recognised as different from rheumatoid arthritis (RA) (Moll and Wright, 1973).

2.4.1 Epidemiology

PsA varies in prevalence between 0.06% and 0.25% of the general population (Ogdie and Weiss, 2015). It occurs more frequently in individuals with skin psoriasis (PsO) in an estimated 6-42% (Gladman et al., 2005). The prevalence of skin PsO occurs in 2-4% of the United States population with higher rates reported in up to 8.4% in Norway (Stern et al., 2004; Langley et al., 2005). The approximate incidence rate for the development of PsA in the presence of PsO is almost 2% per year (Eder et al., 2011). The development of PsA tends to occur approximately 10 years following the development of PsO in the majority of cases (Merola et al., 2018). It is estimated that up to 20% of patients present with signs and symptoms of PsA without any skin PsO thus termed PsA *sine* PsO, and may later proceed to develop PsO (Olivieri et al., 2009).

2.4.2 Clinical features extra-articular features and comorbidities

Psoriatic arthritis (PsA) is a heterogeneous disease characterised by joint, tendon and enthesal inflammation in both the peripheral and axial skeleton. At these sites, inflammation gives rise to pain, tenderness and swelling which is either localised around a joint or more diffuse (e.g. along a whole digit) known as dactylitis. This feature presents frequently in SpA/PsA and does not occur in RA. As well as cutaneous PsO which is highly prevalent in the majority of cases, family history of a first or second degree relative is also significant in individuals with PsA where a genetic association is present.

Psoriatic nail dystrophy is more prevalent in PsA than PsO, which may be linked to the intimate association between the nail and nearby entheses in proximity of the DIP joint (Tan et al., 2007).

It is this diversity in clinical phenotype that has hindered research in SpA and PsA and led to the somehow artificial divide of axial versus peripheral SpA. In reality, individuals with a predominant axial disease may develop peripheral joint involvement, much the same as individuals with typical peripheral psoriatic arthritis can develop axial involvement sometimes indistinguishable from those with AS (Lambert and Wright, 1977). In PsA there is an association with the same extra-articular manifestations associated with SpA disorders particularly inflammatory bowel disease and uveitis. Although the diagnosis is made on a clinical basis, the CASPAR classification criteria, for clinical trials are often used as a diagnostic guide given their high sensitivity (91.4%) and specificity (98.7%) which have been shown for PsA (Taylor et al., 2006). These criteria include five domains including current, past history or family history of psoriasis, dactylitis, presence of RF, psoriatic nail dystrophy, and radiographic new bone formation as shown in Table 2:2.

The musculoskeletal burden is comparable to RA, with joint related damage, functional impairment and reduced quality of life over time (Gladman et al., 2005). It is known that there are several poor prognostic factors such as erosive joint damage which occurs in nearly half of all patients at 2 years (Kane et al., 2003). Further risk factors for radiographic progression include increased disease severity at presentation and elevated CRP (Gladman et al., 2005; Gladman et al., 2010). These PsA patients frequently have multiple comorbidities including obesity, fatty liver, hypertension, type 2 diabetes mellitus, cardiovascular disease, depression and osteoporosis. Indeed criteria for metabolic syndrome is fulfilled in up to 40% of PsA patients (Haroon et al., 2014). Similar to that in axSpA/AS, the association with subclinical gut barrier dysfunction and intestinal dysbiosis may explain the propensity for the development of IBD. Uveitis, affecting anterior or posterior poles of the eye occur in approximately 7% of PsA and is a sight threatening manifestation (Lambert and Wright, 1976). In a cohort study of nearly 150,000 people with PsO, people with PsA or severe PsO were reported to have the greatest risk (odds ratio 2.4) of developing uveitis (Chi et al., 2017).

Table 2:2. The CASPAR classification criteria

Classification Criteria for Psoriatic Arthritis (CASPAR)		
The patient should have joint, enthesal or spinal disease and score 3 or more (out of 5 in total) in the following domains:		
Domains	Description	Points
Current PsO OR Personal history PsO OR Family history PsO	Current skin or scalp PsO as judged by a dermatologist or rheumatologist History of psoriasis according to the patient or GP, dermatologist, or rheumatologist History of psoriasis in a first or second degree relative according to the patient	2 or 1 or 1
Psoriatic nail dystrophy	Typical psoriatic nail dystrophy (e.g., onycholysis, pitting, or hyperkeratosis) according to observation during current physical examination	1
Negative test for RF	Based on reference range at local laboratory (any testing method except latex, with preference for ELISA or nephelometry)	1
Current dactylitis OR History of dactylitis	Swelling to entire digit on examination According to a rheumatologist	1
Radiographic evidence of juxta-articular new bone formation	Ill-defined ossification near joint margins (excluding osteophyte formation) on plain radiographs of hand or foot	1

PsA phenotypes

Five clinical subtypes of PsA were detailed by the late Moll and Wright (Moll and Wright, 1973) as below:

- Oligoarticular: <5 joints involved
- Polyarticular: ≥5 joints involved
- Distal interphalangeal (DIP) joint: >50% DIP involved
- Spondylitic (axial): predominant axial symptoms
- Arthritis mutilans: severe destructive form (rare)

The oligoarticular subtype is associated with asymmetrical joint involvement often typically involving large joints, such as the knee. In early PsA, oligoarthritis may evolve into a pattern of polyarthritis with time. The prevalence of oligoarthritis and polyarthritis subtypes varies between cohorts at 14-70% and 15%-78% respectively with longer disease duration suggesting a greater polyarticular prevalence (Eder et al, 2013). Previously the symmetrical polyarthritis was thought to resemble the characteristics observed in RA, but it is increasingly recognised that in PsA, polyarthritis and oligoarthritis have less in common with RA (Helliwell et al., 2007). The polyarticular phenotype has been shown to predict erosive and deforming disease (Queiro-Silva et al., 2003).

Although any DIP involvement is common occurring in up to 46% of PsA, it is the predominant phenotype (>50% DIP involvement) in an estimated 16% (Veale et al, 1994). The DIP subset may be confused with osteoarthritis due to the similarities in its clinical presentation and that both are associated with new bone formation at these joints (McGonagle et al., 2015). However, periosteal new bone formation in PsA is often a late sign and therefore modern modalities such as US have been embraced for identification of early pathology such as enthesitis and synovitis. The most destructive of phenotypes is arthritis mutilans which occurs rarely (<5%) and results in erosive bony destruction and osteolysis of peripheral joints typically with telescoping of digits, and is associated with marked impairment (Gladman et al., 2005).

Although the majority of PsA patients present with peripheral involvement, axial disease is not uncommon either ranging from 25-70 % in various studies (Gladman, 2007). Whether axSpA with PsO is the same as axPsA is not entirely clear, however evidence from studies suggest distinct differences. In axPsA there is greater peripheral arthritic involvement and less back pain, whereas in axSpA with or without PsO, there is a phenotype closer to that of AS, associated with younger age, male preponderance, predominant back pain features, worse radiographic sacroiliitis and positive HLA-B27 (Feld et al., 2020). These features should also inform clinicians towards applying appropriate labelling of diseases within SpA.

Beyond these phenotypes, there are other features that may be determine the overall phenotype of PsA. In PsA, early onset PsO (type 1) was associated with a greater probability of extensive skin PsO involvement (Alonso et al., 2016). Along with the presence of PsO, dactylitis is another common clinical feature recorded in both of these subtypes, occurring in up to 57% of polyarticular and 45% of oligoarticular phenotypes, but is not a recognised manifestation of RA (Helliwell et al., 2007). The significance of this lesion is not entirely clear in early PsA, where it is often an inaugural feature, but in chronic disease longitudinal studies suggest it is associated with radiological damage in dactylitis affected digits (Brockbank et al., 2005).

Lack of biomarkers in PsA

The challenges of diagnosis in early PsA are not just confined to the heterogeneity of disease. There are no reliable biomarkers in contrast to RA. Proteins such as ACPA or RF are absent in at least 95% of PsA and unlike axial SpA, HLA-B27 is less frequently found in only 25% (Ritchlin et al., 2017). Therefore diagnosis is dependent upon identification of clinical features such as psoriasis, dactylitis, and inflammatory joint or enthesal disease. In addition, elevation of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or both, occur in only 40% of patients despite active disease so are of limited value (Ritchlin et al., 2017). Lastly, the absence of PsO in the presence of arthritis may lead to a label of undifferentiated SpA which include PsA *sine* PsO some of which may develop PsO later in life. Reflecting these

shortcomings, imaging has been increasingly utilised for PsA evaluation and therapy assessment. The absence of biomarkers might account towards the reported underdiagnosis of PsA as described in some studies (van de Kerkhof et al., 2015). In fact screening studies have reported significant delays to diagnosis in up to 50% that present with already established disease (Coates et al., 2016).

Other interesting PsA (SpA) phenotypes

These syndromes should be considered as less common phenotypes within the spectrum of PsA and SpA.

The synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome (SAPHO)

The synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome (SAPHO) was first coined by a group of researchers recognising that osteoarticular manifestations such as aseptic osteitis and synovitis were occurring in affected individuals with palmoplantar pustulosis (PPP), pustular PsO, hidradenitis suppurativa, and severe acne. Subsequently they found that in all cases the unified pathology accounted to inflammatory osteitis and hyperostosis regardless of whether the cutaneous manifestations were present (Benhamou et al., 1988). Following these findings, several nosological terms have been used to describe these disorders including pustulotic arthro-osteitis, sternocostoclavicular hyperostosis, acne-associated SpA, acquired hyperostosis syndrome, or chronic recurrent multifocal osteomyelitis (CRMO). There is also an association with IBD and pyoderma gangrenosum. Bone pain is the most common symptom, and the disease tends to run a relapsing and remitting course. The most common paediatric form CRMO, represents the chronic asymmetrical type that often involves the metaphyses of tubular bones, whereas in the adult form, SAPHO affects the anterior chest wall, commonly the sternoclavicular joint, and then the thoracic followed by the lumbar spine (Nguyen et al., 2012). Sacroiliitis has been reported in 52% which is usually unilateral with sclerosis and hyperostosis greater on the iliac

side of the SIJ (Depasquale et al., 2012). Bacterial cultures are usually negative but previous studies have cultured *Propionibacterium acnes* (*P. acnes*) from deep bone biopsy. Prolonged courses of antibiotics have been empirically administered with reportedly good outcomes, but bisphosphonates or TNFi may provide longer term efficacy (Matzaroglou et al., 2009; Nguyen et al., 2012).

Psoriatic onycho-pachydermo-periostitis (POPP) and acrodermatitis continua of Hallopeau (ACH)

The psoriatic onycho-pachydermo-periostitis (POPP) syndrome is a rare subtype of psoriatic arthritis characterised by extreme onychodystrophy, psoriasis, and a drumstick appearance of the terminal phalanx. Original reports spared the distal interphalangeal (DIP) joint but some reports show this can be affected (Fournié et al., 1989; Boisseau-Garsaud et al., 1996). The majority involve the great toe but reports are present of involvement in fingers or toes (Bethapudi et al., 2014). The description of this syndrome is very similar, even considered a spectrum of the same disorder that rarely presents within dermatology clinics called acrodermatitis continua of Hallopeau (ACH), recognised by sterile pustular eruption of at least one digit, tender pustules, and underlying erythema of the tip of the finger or toe. In extreme cases, the appearance of dactylitis has been reported (Smith et al., 2019). These extreme phenotypes can lead to osteitis and osteolysis of the distal phalangeal tuft.

Recognition of ACH/POPP is important not to confuse with other mimics particularly infection, that can mistakenly result in surgical amputation if not appropriately recognised. The use of MRI may be helpful in determining between infection/osteomyelitis where there is greater extent of soft tissue oedema, and joint and bone involvement (Bethapudi et al., 2014). Successful treatment of this phenotype has been reported with TNFi and IL-17A blockade (Bongartz et al., 2005; Balestri et al., 2018; Miller et al., 2021).

Despite unconfirmed triggers including trauma or post-infectious aetiology, genetic associations associated with loss of function mutations in the IL-36 receptor antagonist have been identified in pustular psoriasis. Mutations to its

gene are associated with the familial generalised pustular psoriasis (GPP) and inherited forms of this disease are known as “deficiency of interleukin thirty-six receptor antagonist” (DITRA). Proinflammatory cytokine signalling (normally inhibited by the IL-36 receptor antagonist) is the resultant effect via binding to the IL-36 receptor in the skin recruiting T cells, neutrophils and dendritic cells (Smith et al., 2019). Indeed ACH can evolve into GPP and the life threatening von Zumbusch type (Kim et al., 2016). It has been suggested that several genetic mutations are reportedly linked to ACH and other pustular psoriatic phenotypes (Marrakchi et al., 2011).

2.5 Reactive arthritis

Reactive arthritis (ReA) is a sterile arthritis typically occurring following a bacterial infection. Classically arthritic symptoms may present from between 1-6 weeks of either a gastrointestinal or genitourinary tract infection. *Chlamydia trachomatis* is the most common cause of genitourinary infection, whilst the enteric form is commonly caused by *Salmonella*, *Shigella*, *Campylobacter* or *Yersinia* infection. Although in the majority ReA resolves spontaneously or with initial treatment, it is estimated that in up to 50% arthritis becomes chronic. The trafficking of organisms has been demonstrated in the synovium of affected individuals and bacterial antigens may persist in synovial tissue or fluid leading to chronic arthritis (Zeng et al., 2020). Only 30-50% of affected individuals are HLA-B27 positive which is thought to predispose to disease severity rather than susceptibility (Carter and Hudson, 2009). Several pathogenic theories have been postulated including molecular mimicry, when foreign antigens share a sequence or match structural features with self-antigens. In ReA antibodies are produced against foreign bacterial antigens and cross react with HLA-B27, which binds arthritogenic peptides and presents them to T cells (Cusick et al., 2012).

An acute onset asymmetrical oligoarthritis is the typical phenotype, usually affecting the weight bearing joints in the lower limbs, and also the sacroiliac joints and lumbar spine. Enthesitis is a common feature of ReA in at least 30% affected with plantar fasciitis or Achilles tendinitis (Cheeti and Ramphul, 2019). The most common chronic joint problem in ReA is sacroiliitis which is more

prevalent in HLA-B27 positive individuals and increases the risk of ReA recurrence. In another study of Chlamydia induced ReA demonstrated that 88% had asymmetric unilateral sacroiliitis of grades 2-3 (Carter et al., 2009). Peripheral features may also include dactylitis (“sausage digit”), which is associated with underlying enthesitis, tendinitis and synovitis, the pathologies that underpin SpA.

Characteristically the symptoms relating to the urogenital tract include the triad of arthritis, urethritis, and conjunctivitis, however not all patients experience these symptoms. Aside from these features, several extra-articular manifestations may occur including keratoderma blenorrhagica, circinate balanitis, ocular complications (such as uveitis, episcleritis, keratitis, corneal ulceration), and pyoderma gangrenosum and painless oral ulcerations have been reported. In severe cases, post urogenital infection, glomerulonephritis and IgA nephropathy have been described including ascending aortitis and aortic regurgitation (Cheeti and Ramphul, 2019).

Prolonged courses of antibiotics have been trialled in several studies with mixed results, showing benefit in the treatment of post chlamydial ReA with dual agents, with the aim of eradicating the underlying organism (Barber et al., 2013). However, despite the fact NSAIDs and corticosteroids can be effective to treat ongoing inflammation, there have been lack of specific studies in ReA, only sulphasalazine which has been specifically trialled with little effect (Clegg et al., 1996). DMARDs and TNFi have been used with some effect but there is paucity of evidence for these therapies where the treatment of SpA has largely been extrapolated to ReA (Carter, 2010). Anecdotal case series have confirmed the efficacy of TNFi in ReA and more recently trials of non-psoriatic peripheral SpA have reported success with TNFi therapy (adalimumab) and included mixed SpA subtypes including individuals with ReA (Wechalekar et al., 2010; Mease et al., 2015).

2.6 Inflammatory bowel disease (IBD) related SpA

Inflammatory bowel disease (IBD) refers to a group of chronic relapsing and remitting inflammatory disorders including Crohn's disease (CD) and ulcerative colitis (UC). The most common associated extra intestinal manifestation of IBD is SpA occurring in up to 22- 39% of individuals (De Vlam et al., 2000; Palm et al., 2002).

Equally there is high prevalence of subclinical gut inflammation in SpA (60%), and capsule endoscopy studies have reported 42% with small bowel CD including 32% with large bowel inflammation (Ciccia et al., 2016; Kopylov et al., 2018). In SpA the prevalence of symptomatic IBD is reported to be in the range of 10-20% for CD and 5-10% for UC (Orchard et al., 1998). It is known that HLA-B27 in IBD is associated with a greater risk of developing AS, and although less prevalent than in AS, in IBD related SpA an estimated 53-73% may have the HLA-B27 allele (Brewerton and James, 1975). Several studies have suggested pathogenic mechanisms between the gut and the joint, including the activation of T-cells in the gut, followed by homing towards the entheses and joints (Salmi et al., 1997; Jacques and Elewaut, 2008).

In IBD associated SpA, peripheral arthritis occurs in up to 35% of affected individuals (Peluso et al., 2013). Previously classifications of peripheral arthropathy had been given to characterise clinical features into two entities: type 1 (oligoarticular) affecting typically affecting mainly large joints, or the frequently symmetrical type 2 (polyarticular) subset, the former being linked to IBD disease activity (Orchard et al., 1998). Further, type 1 is associated with HLA-B27, whereas type 2 has been shown to have HLA-B44 (Orchard et al., 2000).

The most characteristic feature of IBD related SpA includes sacroiliitis which has subclinical presence of 32% in IBD (Arvikar and Fisher, 2011). Indeed inflammatory back pain is common reported in 46% with IBD (Kopylov et al., 2018). In the same study of 162 IBD patients, none had any history of dactylitis or grade 4 sacroiliitis (Kopylov et al., 2018).

There are several commonly used drugs effective for both IBD and SpA such as corticosteroids and sulphasalazine, but mononclonal TNFi therapy appears to be highly effective in inducing remission for IBD and SpA. This negates the

need for two separate biologic DMARDs (bDMARDs) in concomitant SpA and IBD, particularly important in severe IBD and related manifestations including fistulating CD (Present et al., 1999). Moreover, the monoclonal TNFi approach (infliximab or adalimumab) for the treatment of both diseases simultaneously (IBD/SpA) is crucially also effective for uveitis (Fragoulis et al., 2019). Whereas both etanercept and IL-17 blockers have been associated with exacerbation of IBD, several new therapies have emerged including inhibitors of integrins and Janus kinases (JAK) that may prove useful in IBD associated SpA. However, further “real-world” data is needed to inform clinicians on the efficacy of these agents in IBD related SpA.

2.7 Undifferentiated SpA (uSpA)

Whether these group of patients represent a distinct clinical entity or early features of an evolving disease is an unmet need in clinical research. One study found at 2-year follow up that 75% were still classified as uSpA, 13% went into disease remission, 10% were relabelled as AS and 2% as PsA (Sampaio-Barros et al., 2001). A longer term follow up study found that HLA-B27 and buttock pain were significant predictors of progression to AS which occurred in 24% of the cohort (Sampaio-Barros et al., 2010). This SpA entity appears to be researched much less however longitudinal cohorts may contribute to further understanding of this SpA subset.

2.8 Pathogenesis of SpA

2.8.1 Anatomy of the enthesis

A distinctive pathological feature of SpA that differentiates this disease from other arthropathies, in particular RA, is the presence of inflammation at the enthesis or “enthesitis”. The enthesis is the point of attachment or insertion of a “sinew”, tough fibrous tissue which unite muscle to bone, usually a tendon or ligament. This is the primary site of joint disease in SpA which differs from RA where the primary site of disease is the synovium (Benjamin and McGonagle, 2001).

The enthesis organ comprises of a cluster of tissues responsible for resisting mechanical stress and providing tissue anchorage. These tissues include fibrocartilage, fat pad, bursae, adjacent trabecula bone networks, deep fascia, and the enthesis itself. The fibrocartilage lining the enthesis organ has a synovial lining that provides oxygen and nutrients hence why inflammation at the enthesis can manifest as swelling to the synovium and this region is known as synovio-entheseal complex (Benjamin and McGonagle, 2001).

2.8.2 The synovio-entheseal complex

In some enthesis organs the synovio-entheseal complex, a highly specific anatomical region, possesses a fibrocartilaginous section lined by synovial tissue which provides necessary exchange of nutrients and waste products to the enthesis to maintain homeostasis (McGonagle, 2015). The fibrocartilages that line tendons and ligaments at their insertion into bone (enthesis) can tolerate high levels of mechanical stress and it is disruption to this system that leads to inflammation resulting in enthesitis and synovitis (McGonagle et al., 2007).

2.8.3 Pathophysiology of SpA (including AS and PsA)

Axial and peripheral SpA

Axial SpA is characterised by a polyenthesitis, which at the molecular level results in an osteitis and secondary synovitis (McGonagle et al., 1998). The common denominator between enthesitis and subchondral osteitis that characterises early sacroiliac joint disease, is disease localisation to sub-fibrocartilaginous bone that is a site of high physical stress (McGonagle et al., 1999). The current understanding is that bone repair leads to excessive bone formation by syndesmophyte formation and subsequent ankylosis typical of AS, but which can mark the evolution of the disease process from axSpA into AS.

In peripheral SpA, experimental models first revealed that the disease process is initiated at the enthesis. Pathological examination of these mice revealed dactylitis, onychoperiostitis and spontaneous arthritis, with diffuse neutrophil infiltration of their paws, which draws parallels with the human form of PsA (Lories et al., 2004). The MRI evidence in humans suggests that enthesitis is the primary lesion in SpA, which was indicated by the detection of prominent enthesal abnormalities (enthesal bone oedema and joint effusion,) not a typical features of RA, but fully congruent with the clinical presentation of new onset synovitis in SpA (McGonagle, Gibbon, O'Connor, et al., 1998).

Similarly, the current understanding of disease pathogenesis in pSpA mimics that for axial SpA, where enthesitis leads to a secondary synovitis and new bone formation at peripheral sites. Perhaps a hallmark lesion in SpA, dactylitis epitomises the enthesopathic process, encompassing several related pathologies including microanatomical enthesitis, tendinitis, soft tissue oedema and osteitis, yet this lesion is not a feature of RA (McGonagle et al., 2019). In fact high resolution MRI studies have further confirmed bone marrow enhancement at enthesal insertions of involved digits with diffuse bone marrow oedema supporting the hypothesis of a primary enthesal pathological process (Tan et al., 2015). Findings are important for the understanding and management of SpA.

The pathogenic role of HLA-B27

There are several mechanisms implicated in the pathogenesis of disease including HLA-B27, a class 1 surface antigen encoded by the B locus of the major histocompatibility complex (MHC). The basis for the association between HLA-B27 and AS remains unexplained but there are two major theories. Firstly, the fact that AS has, at the population level been associated with other MHC class-1 antigens and is genetically linked to single nucleotide polymorphisms involved in peptide loading to T cells, invokes a CD8 T cell driven disease, although a putative antigen has not been defined (McGonagle, Aydin, et al., 2015). The second theory holds that there is abnormal function of antigen presenting cells and a tendency of HLA-B27 to misfold, triggering the production of IL-17 and IL-23 (Taurog et al., 2016). T-cell mediated mechanisms have been described for CD4+ and CD8+ T cells resulting in further release of cytokines including tumor necrosis factor α (TNF- α), IL-22, IL-17 associated with bony destruction, osteoproliferation, and synovitis. IL-23 regulates the expression of IL-22 downstream which is associated with osteogenesis. Structural bony damage causes stimulation of repair mechanisms that also involve osteoproliferation associated with the development of syndesmophyte formation and leads to bony ankylosis, the hallmark of AS and main cause for loss of functional ability.

The two major non-HLA-B27 loci specifically associated with AS are the endoplasmic reticulum aminopeptidase (ERAP) and the IL-23 receptor (Pimentel-Santos et al., 2009). The ERAP gene is specific to HLA-B27 positive subjects and is involved in the processing of proteins, including those presented by HLA-B27, for the MHC class 1 presentation to immune effector cells (McGonagle, Aydin, et al., 2015). The IL-23 receptor activates pro-inflammatory cells including the T-helper cells leading to the secretion of IL-17.

The gut microbiome

The intestinal microbiome is also thought to play a pertinent role in the pathogenesis of disease that is not yet fully understood. Dysbiosis in the gut flora may drive pro-inflammatory cytokines resulting in intestinal inflammation (Taurog et al., 2016). Barrier dysfunction in axSpA is associated with exposure

of the immune system to micro-organisms. *Ruminococcus gnavus* has recently been shown to be specific to the gut in SpA and is associated with disease activity (Breban et al., 2017). This contributes towards damage to dermal and mucosal surfaces by chronic inflammation leading to the subsequent development of skin psoriasis and clinical or subclinical intestinal inflammation (Joachim Sieper, Braun, Dougados, et al., 2015).

Although the microbiome has been posited to be central to most common diseases, the fact that AS subjects often have abnormal mucosal permeability and that subclinical gut lesions correlate with MRI determined sacroiliitis, suggests a very strong connection between the gut environment and clinical disease in AS and SpA (Brakenhoff et al., 2010). More recently, the presence of group 3 innate lymphoid cells, which form an essential part of the gut and skin barrier in SpA, were also identified in enthesal soft tissue and adjacent peri-enthesal bone suggesting a role in the pathogenesis of axSpA (Richard J. Cuthbert et al., 2017). Despite the improved understanding of AS and SpA, the pathogenic insights are yet to show significant therapy advances. Indeed the greatest advances have come from empirical studies utilizing cytokine pathway blockade, resulting in some spectacular success, representative of the pivotal role of TNF and IL-17A thus far.

There is a sizeable body of evidence connecting the gut microbiome with intestinal inflammation, and both the IL-17/23 axis and HLA-B27 have been implicated as key factors in the pathogenesis of AS and axSpA. Interestingly, IL-17A serves a protective function in maintaining the integrity of the intestinal barrier and is involved in gut epithelial cell proliferation and healing (Whibley and Gaffen, 2015). But unlike antibodies to IL-23 which have shown improvement in signs and symptoms of inflammatory bowel disease, neutralization of IL-17 causes disruption to the intestinal barrier and atypical macrophage subpopulations causing exacerbation of colitis (Nishikawa et al., 2014; Lee et al., 2015). This may be explained by the direct effect of IL-17 blockade at tight junctions in the intestine cell wall where IL-17 producing resident $\gamma\delta$ T cells are present to maintain homeostasis (Lee et al., 2015)

The role of IL-17 in SpA

IL-17 is an inflammatory cytokine involved in defence against bacterial and fungal infections. However, it also contributes to chronic inflammation and appears to have a pivotal role in SpA, particularly AS, PsO, and PsA (Qu et al., 2013). First thought to be secreted by CD4⁺ T cells, it is now known that IL-17 is also produced by lymphocytes of both the adaptive and innate immune system, including T helper-17 cells (Th17), IL-17-producing CD8⁺T cells (Tc17), $\gamma\delta$ T cells and type 3 innate lymphoid cells (ILC3) (Aggarwal et al., 2003; Papotto et al., 2017) as shown in Figure 2:3. These cells can also release several other cytokines including IL-21, IL-22, IL-23, TNF α , and IL-17F, depending upon the stimulus (Raphael et al., 2015).

Such IL-17 mediated inflammation has been strongly conceptualised in terms of the upstream cytokine IL-23, with the resultant IL-23/IL-17 axis driving disease (Figure 2:4). IL-23 is primarily produced by antigen presenting cells such as macrophages and dendritic cells and along with other cytokines including IL-1 and IL-6, it promotes the polarization to IL-17 expressing cells. There are single nucleotide polymorphisms (SNPs) in the *IL-23R* gene which are strongly implicated in the IL-23/IL-17 axis in AS (Vidal-Castiñeira et al., 2016). These genetic polymorphisms to the IL-23 receptor have been shown to correlate with susceptibility for the development of AS and could potentially play a significant role in the induction of Th17 cells (Sherlock et al., 2014). Furthermore, it was found that the *IL23R R381Q* gene variant is protective against IL-23 induced tissue pathologies (Di Meglio et al., 2011). This gene selectively attenuates IL-23 induced Th17 cell effector function, without any intrusion on Th17 cell differentiation. Genetic variations of genes in the IL-23 signalling pathway and their influence on Th17 cell effector function in patients with AS and SpA have also been described in other studies (Coffre et al., 2013). AS patients also have more IL-23⁺ cells in the subchondral bone marrow when compared to controls (Appel et al., 2013). However, no correlation is seen between IL-23R polymorphism and serum IL-17 levels in AS patients (Nossent et al., 2017).

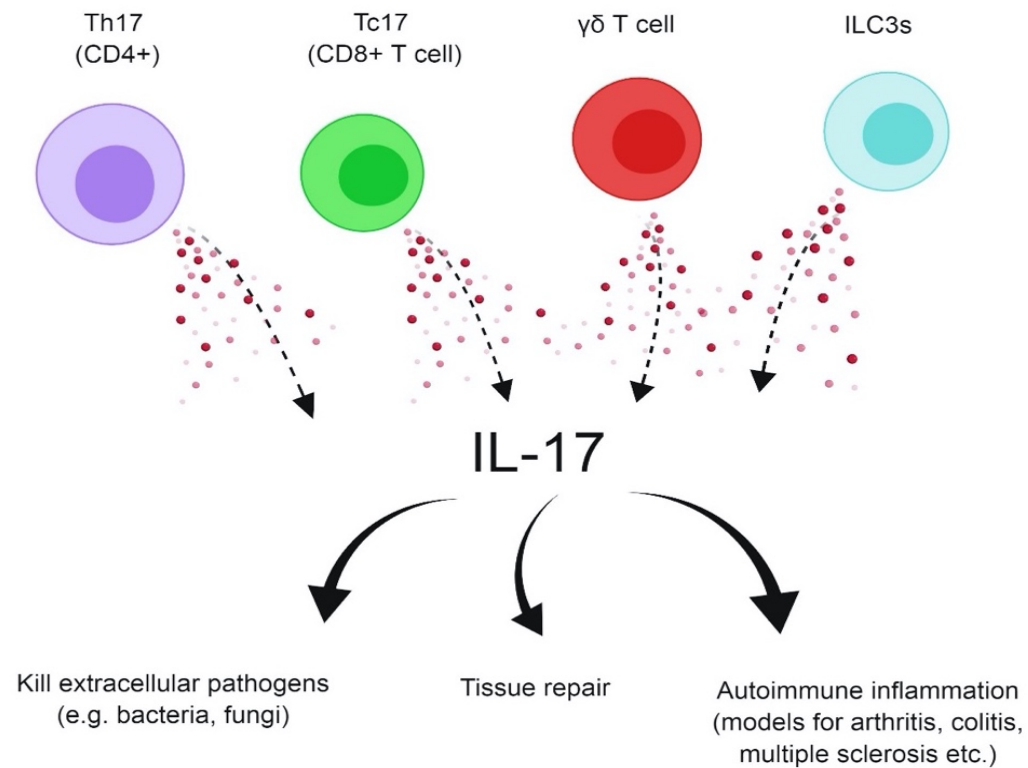


Figure 2:3 The role of T17 cells

The term “T17” cells includes populations of different cells that are involved in the production of IL-17 mainly for host defence against extracellular pathogens such as fungi and bacteria, and for tissue repair. These cells are also the predominant producers of IL-17 in immune mediated inflammatory disease. Figure created with Biorender.com

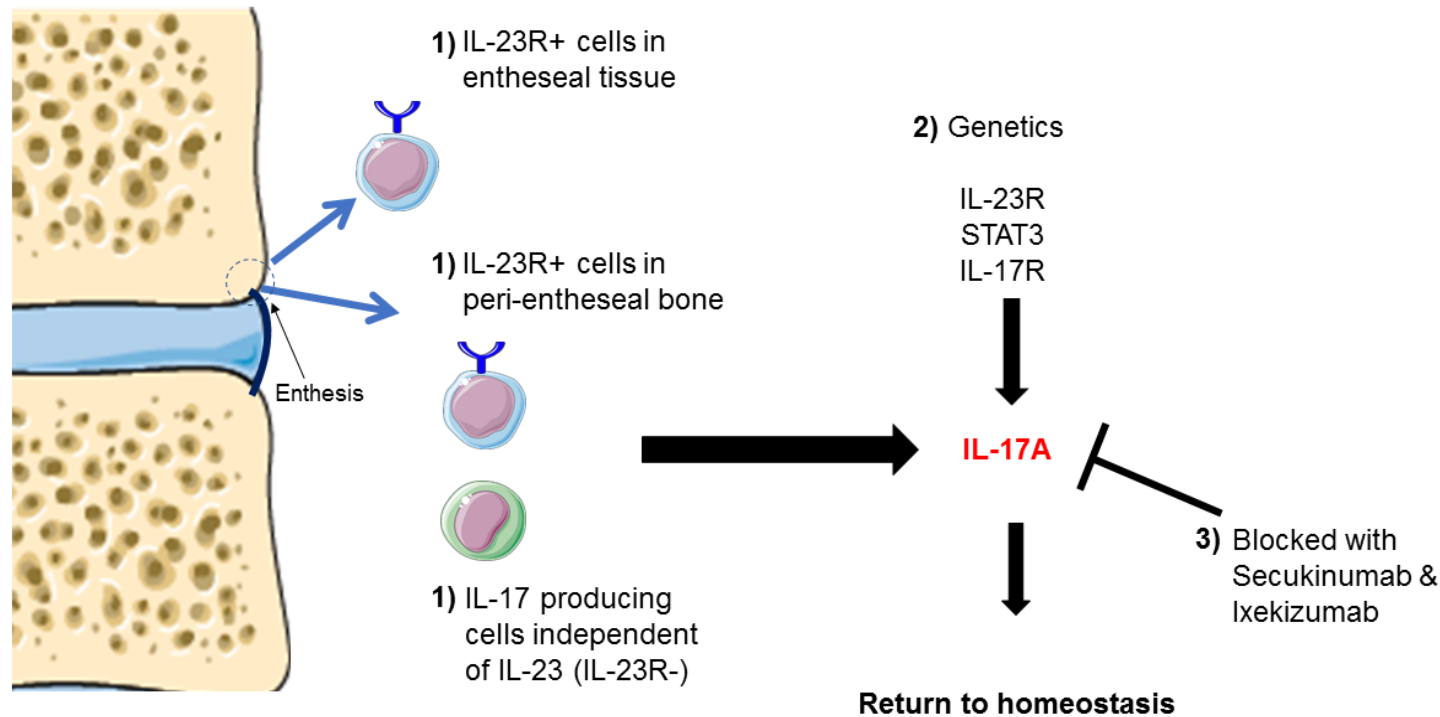


Figure 2:4. The immunological basis for IL-17 efficacy in SpA

There are several populations of IL-17A producing lymphocytes at enthesal tissue and perienthesal bone. 1) These IL-23R positive (+) cells are the predominant producers of IL-17A but some are independent of IL-23, i.e. IL-23R negative (-). 2) Genetic polymorphisms in AS are likely associated with increased IL-17A production. 3) The efficacy of IL-17A inhibitors in AS validates the immunological concept of a pivotal role for this immune pathway for AS pathogenesis. The spinal image is partially reproduced from <https://smart.servier.com> (Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License) and was changed in terms of shape and size (Dubash et al., 2019).

Genome wide association studies have identified *TRAF3IP2* SNPs on chromosome 6q21 as a susceptibility locus for PsA and PsO with this gene coding for the ACT1 protein that is involved in IL-17 receptor A (IL-17RA) signalling (Lee J. S. et al., 2015). Whole exome sequencing and refining of SNPs has located *rs4819554* at the G minor allele of the IL-17RA promotor region of AS patients which is associated with functional severity (BASFI) and may be a good biomarker of disease severity (Vidal-Castiñeira et al., 2016). At the tissue and cellular level, current knowledge in disease mechanisms in AS relates to poly-enthesitis, including adjacent spinal vertebral osteitis at the human axial skeleton, with a secondary synovitis at the synovio-entheseal complex or diseased peripheral joints (McGonagle, Gibbon and Emery, 1998). The strong HLA-B27 association with AS incriminates the major histocompatibility class I (MHC-I) pathway in disease pathogenesis (Evans et al., 2011). Such MHC-I molecules expressed on virtually all cells and most notably permit T lymphocyte screening and detection of foreign proteins, in turn allow the removal of infected or transformed cells by cytotoxic CD8 T cells (Campbell et al., 2012). The epistatic interaction between HLA-B27 and the ERAP-1 gene which trims peptides prior to HLA class 1 presentation certainly supports the idea that peptide presentation to CD8 T cells is important in disease pathogenesis (Evans et al., 2011). Such primed CD8 T cells are capable of the production of IL-17A and are termed “Tc17 cells” (McGonagle, Aydin, et al., 2015).

Experimental animal models or human data have thus far failed to firmly incriminate CD8+ T cells as the key pathogenic drivers in AS but the genetic evidence for CD8 T cell involvement is growing (Cortes et al., 2013). It is known that HLA-B27 alone is not enough to cause disease and alternative models have been considered including the presence of HLA-B27 homodimers on the cell surface resulting in misfolding and the formation of these HLA-B27 homodimers at the cell surface to trigger IL-23 and IL-17 production (Jethwa and Bowness, 2016). Macrophages from HLA-B27 positive AS patients may secrete increased IL-23, which is thought to be independent of protein misfolding associated stress (Ambarus et al., 2018).

In HLA-B27 transgenic rats there is upregulation of IL-17 after Th17 cell development (DeLay et al., 2009). It is also known that overexpression of IL-23 in a murine model can reproduce a SpA like disease with enthesitis and new bone formation (Sherlock et al., 2012). In this model, disease was dependent on IL-23 inducing IL-17 in resident population of $\gamma\delta$ T cells (Nossent et al., 2017). These $\gamma\delta$ T cells have also been recently described in the healthy human enthesis (R J Cuthbert et al., 2017). Another murine model showed that during local inflammation, $\gamma\delta$ T cells expressing IL-17 accumulate at the enthesis, aortic valve, and ciliary body (Reinhardt et al., 2016). The ciliary body is particularly relevant given propensity of AS for uveitis. There is much less data on the human enthesis but a recent study has shown that the normal spinal enthesis soft tissue and bone contains a population of resident type 3 innate lymphoid cells that are capable of IL-17 production (Richard J. Cuthbert et al., 2017). Furthermore, the expansion of type 3 innate lymphoid cells (ILC3s), producing IL-17 and IL-22, has also been shown at the bone marrow, synovial fluid and peripheral blood of patients with AS (Ciccina et al., 2015).

Knowledge from recent animal models has provided a greater insight into the pathogenic link between IL-23, IL-22, IL-17 and early enthesal disease including periosteal bone formation. At the enthesis, specific types of IL-23 receptor positive T cells have been identified [retinoic acid receptor-related orphan nuclear receptor γ t positive CD3+CD4-CD8- (ROR- γ T)] that produce IL-22 and IL-17 in response to IL-23 (Breban et al., 2014). Following the in-vivo stimulation of enthesal cells by IL-23, expression of IL-22 and IL-17 downstream caused enthesitis in addition to enthesal new bone formation and occurred without any synovitis (Sherlock et al., 2012). Given the improved understanding of animal SpA, it is yet to be determined whether this knowledge can be extrapolated to human SpA, although these current developments remain very promising (Breban et al., 2014).

Once secreted, IL-17 triggers the stimulation of macrophages, fibroblasts, epithelial and endothelial cells initiating the release of pro-inflammatory chemokines and cytokines such and $\text{TNF}\alpha$, IL-6 and IL-1 (Jethwa and Bowness, 2016). More specific for AS is the fact that IL-17A facilitates osteoblastic differentiation and proliferation therefore promoting bone

formation and regeneration (Ono et al., 2016). Therefore, the inhibition of IL-17A, is anticipated to have effects on halting radiographic progression in AS (Uluçkan et al., 2016). Further, understanding on the role of IL-17 to promote angiogenesis is lacking but appears to be important in both inflammatory joint disease (Pickens et al., 2010; Raychaudhuri and Raychaudhuri, 2017). Figure 2:5 illustrates the pathogenic basis for IL-17 in disease pathogenesis in SpA/PsA.

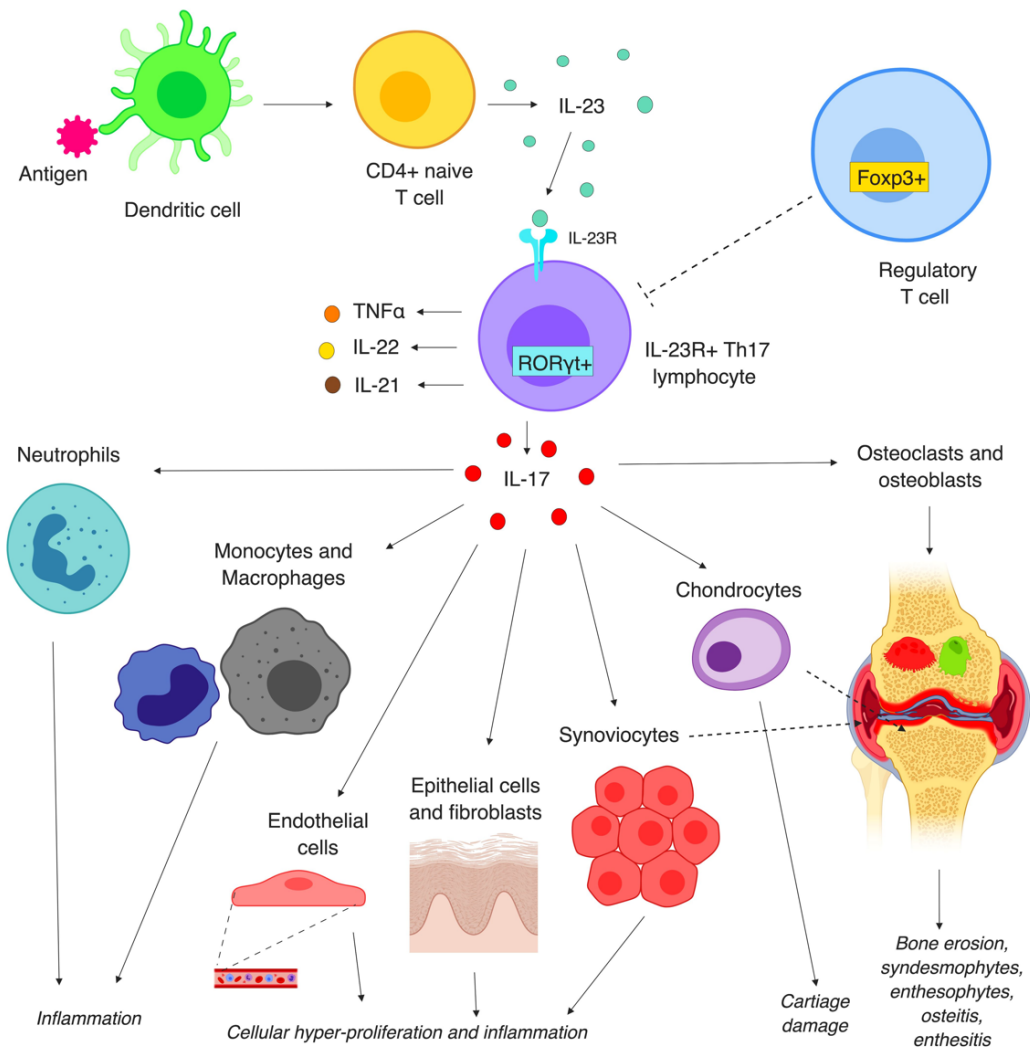


Figure 2:5 The pathogenic basis of IL-17 in SpA

Dendritic cells present antigenic peptides to IL-23 producing CD4+ T cells. Release of IL-23 by these cells leads to the recruitment of IL-23R+ Th17 cells from regulatory T cells via loss of Foxp3+ expression (Sherlock et al., 2015). This dysregulation and loss of T cell plasticity results in highly inflammatory Th17 lymphocytes. IL-23 signalling occurs via IL-23R-activated STAT3/STAT4 (signal transducer and activator of transcription-3/4) is also essential for the orchestration of Th17 mediated autoimmunity (Lee P. W. et al., 2017). The transcription factor ROR- γ T, present in resident IL-23R+ T cells, drives the differentiation of pro-inflammatory IL-17 producing Th17 cells (Sherlock et al., 2012). Increased cellular release of IL-17 by enthesal resident T cells leads to enthesitis. Several resultant pleiotropic pro-inflammatory effects follow including recruitment of neutrophils and resultant inflammation in synovial tissue, bone, skin, and endothelium, leading to enthesal, bone, joint and cartilage damage, and cutaneous psoriasis in SpA/PsA. Figure created with Biorender.com.

Further genetic associations in PsA/PsO

In both PsA and PsO, there is strong genetic association in families of affected first degree relatives (Chandran et al., 2009). Some reports suggest the risk may be as high as a 40-fold increase (Kammer et al., 1979). Identical and non-identical twin studies suggest 62-70% and 21-23% respective concordance rates (Elder et al., 1994). Unlike RA which is associated with MHC-II alleles (HLA-DR4), SpA diseases including PsA and PsO are associated with the MHC-I alleles. The commonality of clinical manifestations that occur in SpA diseases may be explained by the mutual association with MHC-I alleles indicative of similar genotypes within the SpA spectrum (McGonagle, Aydin, et al., 2015). However, there is a strong association with HLA-C*06:02 in PsO but not PsA. Studies have confirmed that the distribution of alleles (HLA-C*06:02 and HLA-B*57:01) were not the same in PsA as found in PsO, suggesting there may be more genetic heterogeneity within PsA (FitzGerald et al., 2015). More importantly, it was found that HLA-C*06:02 was associated with less joint involvement (Ho et al., 2007). In a study of 282 patients with PsA, the association between PsA pathologies reportedly indicated that specific HLA B and C haplotypes may be responsible for the genetic susceptibility of specific phenotypical subsets of PsA, including those that feature predominant enthesitis (B*27:05-C*01:02), synovitis (B*08:01:01-C*07:01:01), dactylitis (HLA-B*27:05 and B*08:01), or axial disease (symmetric sacroiliitis: B*27:05:02; asymmetric sacroiliitis: B*08:01) (FitzGerald et al., 2015).

2.9 Imaging SpA and heterogeneity

Imaging in SpA can involve multiple modalities given the heterogeneous features involved. Plain film radiographs of joints are feasible, quick to perform and low in cost, with the ability to assess progressive damage reasonably well. However, compared to US or magnetic resonance imaging (MRI), they lack sensitivity for the detection of early inflammatory arthritis and associated erosive damage (Wiell et al., 2007; Takase-Minegishi et al., 2018).

There are various advantages of US over MRI, including greater accessibility, lack of contraindications, overall reduced cost, and its availability as needed in the clinic. However, MRI has the advantage of allowing access to sites where US has a limited acoustic window e.g. axial skeleton and all osseous based pathology. Due to the heterogeneity of this disease, several multiple imaging modalities may be needed to investigate axial and peripheral disease e.g. plain film radiographs (X-ray) and/or MRI to confirm sacroiliitis/axial enthesal disease and/or US for peripheral joint synovitis.

Bone scintigraphy may have its advantages either to be used as a screening tool, to detect subclinical disease, or for imaging the anterior chest wall particularly useful in SAPHO (Gheita et al., 2015; Fu et al., 2016). In some cases where differentiating between active PsA *versus* crystal arthropathy is the problem, the use of dual energy CT (DECT) may help to exclude or confirm the latter (Bongartz et al., 2015). The same technique combined with an iodine contrast overlay promises superior resolution over MRI to depict enthesitis at finger extensor tendon and collateral ligaments, tenosynovitis of flexor tendons, and peritendinitis at extensor tendons, and for the imaging of small joints (Fukuda et al., 2017).

Currently plain film radiographs are conducted routinely to assess new bone formation in axSpA/AS, but research studies using radiolabelled sodium fluoride tracer and positron emission tomography CT (^{18}F -PET-CT), suggest it is a sensitive tool for monitoring of new bone formation may have a role particularly useful following the introduction of therapies. The mounting evidence on early treatment to ameliorate active inflammation for optimal outcomes, therefore implementation of sensitive imaging tools into routine practice is important.

2.10 Ultrasound imaging in SpA

Ultrasound is a well-recognised and sensitive imaging modality for the detection of active inflammatory disease in early or established peripheral joint disease. Given that US is a practical tool, able to be used in the clinic, its widespread use has been adopted in rheumatology practice. This imaging modality equips clinicians with additional information that may be useful to inform management decisions. The majority of studies in this arena are in PsA and PsO with less data specifically for pSpA where assessment strategies are adopted from PsA studies.

2.10.1 Diagnostic ultrasonography

Synovitis

The synovial US appearances in SpA are akin to that observed in RA including synovial hypertrophy and effusion on grey scale (GS) imaging, increased power Doppler (PD) signal, and erosion (Figure 2:6, A). However, the severity of synovitis described in RA literature suggest it is greater compared to PsA (Vreju et al., 2016; Zabotti et al., 2017). The heterogeneity of phenotypes in SpA (including PsA) suggest equal comparisons between diseases may not be justified given that severity of phenotypes can differ greatly. Specifically in PsA, studies have described frequent tendinitis and enthesitis in conjunction with synovial joints (Fournié et al., 2006; Zabotti et al., 2016). Absent PD signal at swollen joints, did not rule out active synovitis indicating the importance of interpreting GS changes (Zabotti et al., 2017). The preliminary SpA data suggests that intra-articular synovial pathology occurs following, not prior to, soft tissue and tendon involvement in the hands which is consistent with the hypothesis of SpA being a disease of primary enthesitis and secondary synovitis (McGonagle, Gibbon and Emery, 1998; Gutierrez et al., 2011; Zabotti et al., 2016).

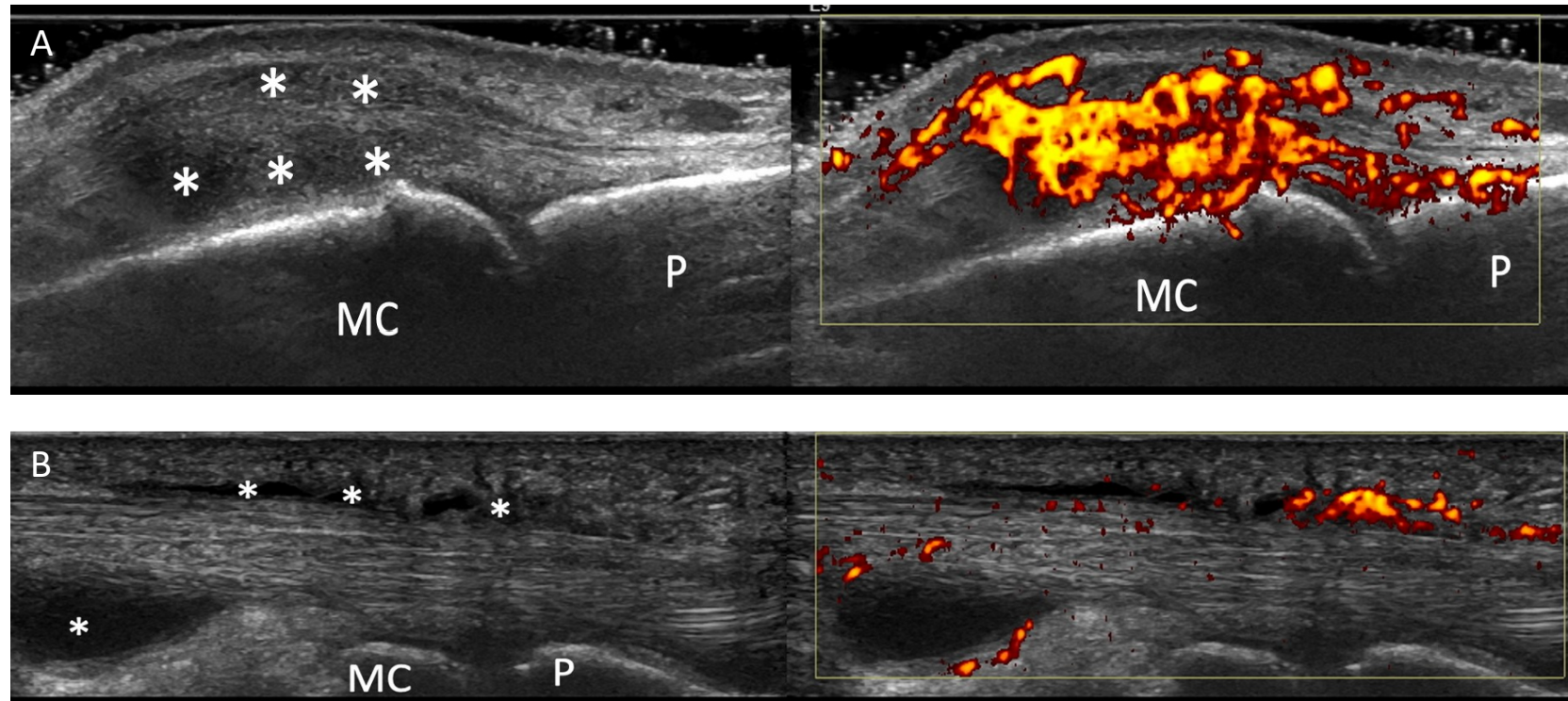


Figure 2:6 Ultrasound images in active PsA demonstrating synovitis, peritendinous oedema, and flexor tenosynovitis.

A: Longitudinal view through a metacarpophalangeal joint with synovitis. There is grey scale thickening (*between joint and tendon) and marked increased power Doppler signal (grade 3, right image) consistent with 'active' synovitis and peri-tendonitis (*above tendon). **B:** Longitudinal view through the flexor tendon of the middle finger also affected by dactylitis. The images demonstrate fluid and synovial thickening within the tendon sheath (*). There is also marked power Doppler signal within the tendon sheath (right image). MC= metacarpal; P=phalanx (Dubash SR, De Marco G et al., 2020).

Subclinical synovitis

Subclinical synovitis is a frequent finding in individuals with psoriasis detected by US in 12.4% of joints in PsA, 96% of patients (in at least one joint), and 34.7% with subclinical PD signal (Freeston et al., 2014). Healthy individuals may also show evidence of subclinical synovitis and synovial PD signal, but subclinical enthesal PD was not found in any healthy control in one study, and only found in PsA patients (Tang et al., 2018). Prevalent subclinical synovitis was also demonstrated in PsO patients without PsA (85%) and healthy controls (55%), corroborating with other studies indicating an association between PsO and subclinical joint disease (Zuliani et al., 2019). In this report, synovitis was determined by both GS synovial hypertrophy and PD signal and was exclusively found in individuals with PsO (27.5%) (Zuliani et al., 2019).

Evolution of subclinical pathology and its implications

Follow-up studies have subsequently reported on that subclinical synovitis, with or without subclinical enthesitis, is more frequent in people with PsO who were found to develop PsA over a 2 year period (Elnady et al., 2019). In PsO, US studies have demonstrated that enthesitis may be a predictor of developing PsA (Tinazzi et al., 2011). Subclinical synovitis is also prevalent in PsA and can lead to structural progression, equally, persistent synovitis or enthesitis in PsA are known risk factors for poor prognosis (El Miedany et al., 2015). In PsA patients in clinical remission or MDA, the presence of PD signal was shown to predict flare (Ruta et al., 2017).

Tendon and peri-tendon inflammation

Tendinopathic pathologies can exist in both PsA and RA but can be difficult to attribute specifically to either disease. Benjamin et al described the concept of a “functional enthesis”, an anatomical, biomechanical, and pathological feature that share fibrocartilaginous entheses proximal to regions of attachment to allow tendons or ligament to wrap around bony pulleys (Benjamin and McGonagle, 2009). It is at these sites that there is a propensity

for disease in PsA which has been confirmed through US (Zabotti, Errichetti, et al., 2018).

Flexor tenosynovitis can be detected by high-resolution US of the hand flexor tendons as illustrated in Figure 2:6, B. The presence of this lesion was significant in PsO with arthralgia compared to PsO alone, and may represent a “transition phase” towards PsA development, confirmed upon longitudinal follow up (Zabotti et al., 2019). This is consistent with the theory of primary enthesopathy leading to evolution of disease pathologies over time.

Peri-tendinous soft tissue oedema and PD signal have been reported in the 2nd -4th flexor tendon compartments of the dominant hand in one third of PsA versus no RA patients (Fournié et al., 2006; Tinazzi, McGonagle, Zabotti, et al., 2018). Additionally, flexor tendon insertional enthesopathy occurs at accessory pulleys including new bone formation, significantly more common in PsA, supportive of the “Deep Koebner” phenomenon associated with enthesal damage and repair (Tinazzi, McGonagle, Aydin, et al., 2018). A much higher percentage of peritendinous extensor digitorum tendon inflammation was observed in PsA compared to RA (Zabotti et al., 2016). Soft tissue oedema was detected almost exclusively in PsA when the most clinically involved finger was assessed. Further, central slip enthesitis at the PIP joints was exclusively found in early PsA. Ultrasound detection of extra-synovial features and at the synovio-enthesal complex may be helpful in the differential diagnosis between early RA and early PsA (Zabotti et al., 2016).

Expert based consensus research has that the most useful anatomical sites for identifying disease at tendons (with sheaths) are at the hand flexor tendons, extensor tendon compartment of the wrist, and for peri-tendonitis (inflamed tendons without sheath) hand extensor tendons are favoured over the feet extensor tendons (Zabotti, Piga, et al., 2018).

Further recent studies have also added to the literature on significantly greater tendon sheath synovial thickening and tendon sheath PD signal observed in PsA compared to PsO without PsA (Tang et al., 2020). On a practical level, a previous study demonstrated greater peritendon extensor tendon inflammation at the MCP level in PsA than RA, indicating that it is a key characteristic of PsA, valuable in differential diagnosis (Gutierrez et al., 2011). Importantly in PsA, the most recent evidence indicates that MCP swelling is

actually attributable to not only synovitis, but also peri-tendonitis (Figure 2:6 A), and are detectable at similar frequencies (Macía-Villa et al., 2018).

Enthesitis

Enteseal inflammation this is considered to be an inaugural feature of SpA (McGonagle et al., 1998). However, clinical assessment of enthesopathy is hindered by the lack of sensitivity and false positive assessments in fibromyalgia and pain augmentation syndromes (Macchioni et al., 2019). It is known that US examination of entheses is a more sensitive tool than clinical examination and this is reflected by the disconnect between clinical and US studies of entheses in PsA (Michelsen et al., 2017; Yamada et al., 2020).

The OMERACT definition for grading of enthesopathy involves assessment of a number of elementary lesions (Balint et al., 2018). Enthesitis is characterised by the following present at the enthesis: 1) inflammatory components: a) hypoechoogenicity, b) thickening, c) Doppler signal (<2mm from cortical bone); 2) structural components: a) calcifications (within 2 mm from cortical bone) or enthesophytes, b) erosions (Figure 2:7). However, these OMERACT definitions are not universally accepted and Doppler signal within 2mm from cortical bone may be too stringent given that the enthesis is avascular and is at least 3mm thick at the Achilles (Shaw et al., 2008). The presence of vascularised entheses detected by PD signal in at least one enthesis provided good predictive value for a diagnosis of SpA, with good sensitivity (76.5%) and specificity (81.3%) (D'Agostino et al., 2011). Interestingly, greater degree of enteseal microdamage and repair was found in PsA compared with AS, with more severe enteseal structural lesions suggesting peripheral enthesitis may be worse due to “deep Koebner” phenomenon contributed by the higher BMI of PsA patients and biomechanical injury/repair (Arslan Alhussain et al., 2019).

Nonetheless, the presence of enthesopathy scores alone could not differentiate between PsA related enthesitis and nodal osteoarthritis given the mutual presence of enthesophytes in both diseases (Yumusakhuylu et al., 2016). Moreover, implementation of the Madrid Sonographic Enthesitis Index

(MASEI), a scoring tool designed for enthesitis in SpA/PsA, could not differentiate US enthesitis in established or new PsA from healthy subjects (Wervers et al., 2018).

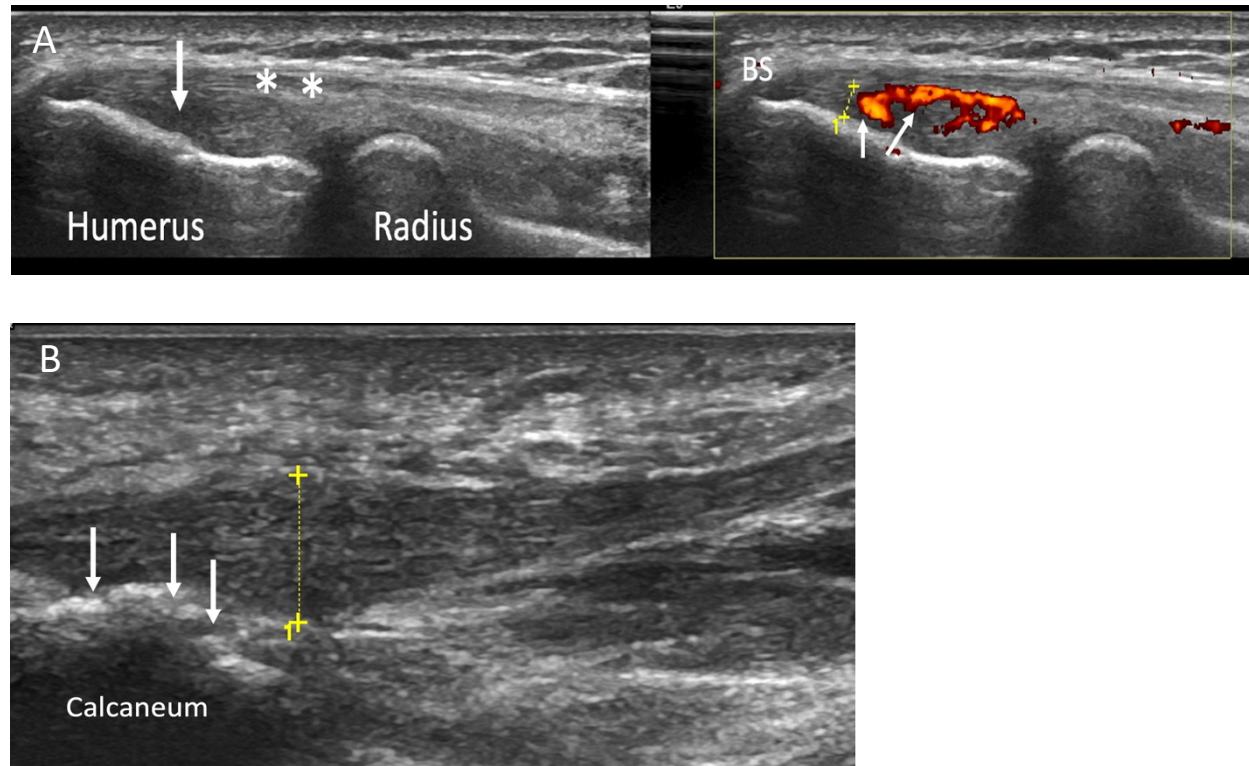


Figure 2:7. Enthesitis demonstrated on US.

A: Enthesitis of common extensor origin (CEO): Longitudinal view through the common extensor origin. Hypoechoogenicity (arrow to left), loss of fibrillary pattern (*), Bone spur (BS), increased Doppler signal (small arrows to right) within 2mm (dotted line) of bone surface. **B:** Longitudinal view through the plantar fascia of a patient with PsA. There is thickening of the fascia (dotted yellow line measuring 8.3 mm; normal <5mm). Power Doppler signal is rarely seen at the plantar fascia insertion. Bone irregularity is suggestive of erosive change (arrows) (Dubash SR, De Marco G et al., 2020).

Dactylitis

The use of US has added to the understanding of pathologies involved in dactylitis that extend beyond the presence of synovitis and flexor tenosynovitis. In a recent study of dactylitis in PsA patients, joint synovitis was detected by US in 40% of dactylitic digits and was associated with longer duration of dactylitis and the asymptomatic “cold” type characterised by swelling but not pain or tenderness (Girolimetto et al., 2019). Another study of psoriatic dactylitis identified PD at the accessory pulleys of affected digits, suggesting that these sites of mechanical stress may be more important in the disease process than previously thought (Tinazzi et al., 2019). Moreover, flexor tenosynovitis is most prevalent in the majority of PsA imaged dactylitis and over half of patients also display subcutaneous oedema and synovitis (McGonagle et al., 2019). Unlike the OMERACT US definitions aforementioned for synovitis and enthesitis, no widely accepted ultrasound definition was present for dactylitis. Recently a group of researchers have developed an US score for dactylitis, namely the dactylitis global sonographic score in PsA (DACTOS) (Zabotti et al., 2020). The dactylitis elementary lesions were evaluated via a Delphi exercise of 12 experts to reach a consensus on scoring which resulted in moderate-excellent reliability for US scored lesions (Zabotti et al., 2020). Imaging scores of such may assist in the diagnosis and evaluation of the response of tissue compartments to therapies (Kaeley et al., 2018).

Utility of US in SpA differential diagnosis

Given that US synovitis alone is indistinguishable between RA and SpA/PsA, this feature does not differentiate these two diseases for the purpose of diagnosis. Contrast enhanced US or MRI may hold additional benefit for the detection of synovitis due to its high sensitivity for synovial angiogenesis, and vascular patterns of lesions (Zhao et al., 2017). There is evidence suggesting potential for software driven quantitative analysis of parameters of synovial vascular perfusion patterns. Interestingly one study suggested that this

method may possess the ability to discriminate RA from PsA and other types of arthritis (Rizzo et al., 2015).

Much of the literature on US indicates that PsA may be distinguishable from RA by the non-synovial and peri-articular pathologies (Tinazzi, McGonagle, Zabotti, et al., 2018; Sapundzhieva et al., 2020). Specifically, enthesitis, peritendon inflammation of hand extensor tendons, thickening of pulleys of the flexor tendons in the hands, soft tissue oedema and bone proliferation associated with erosions. Extra-synovial features on US of the hands showed a sensitivity of 68% and specificity of 88.1% for the detection of early PsA (Zabotti, Errichetti, et al., 2018). Further additional use of dermoscopy at the proximal nail fold improved the specificity only slightly to 90.5%, but not the sensitivity. Given the fact that the diagnosis is often made clinically, this arena needs greater clarity into the clinical phenotypes being assessed. As crystal arthropathies are often a differential diagnosis to consider in early PsA, the presence of specific US features including the “double contour sign” is useful in their differentiation (Thiele and Schlesinger, 2007).

2.10.2 The limitations of US in clinical practice

On a practical level, clinical examination, which is subjective and not anatomically nor pathology specific, is complemented by the high sensitivity of US to detect inflammatory and structural lesions, clearly advantageous to identify characteristic PsA-related pathologies. Despite these significant benefits, a recent systematic review reported variable diagnostic accuracy for US in PsA, in fact confirmation of a PsA diagnosis remained heavily based on clinical diagnosis and classification criteria (CASPAR) (Sakellariou et al., 2020). It is important to be cognizant of the fact that US is dependent upon having a skilled operator for scanning and experienced reader for image interpretation, and a sensitive US machine and transducer, particularly relevant for PD signal detection. Moreover, it is not feasible to scan 68 joints and numerous entheses for every patient in routine clinical practice due to time constraints, therefore a focussed approach is needed to answer the clinical question. Comprehensive US assessment of a large number of joints and entheses therefore occur generally in the research setting. Practising

clinicians should factor in resource, staffing and costs including the purchase, operating, and servicing of the equipment.

2.10.3 Comparison of US with clinical examination and composite clinical scores

A recent study has confirmed that in fact there is a significant association between clinical and US assessment of the large entheses when assessing Achilles and Patellar tendon origins (Aydin et al., 2020). Furthermore, digital pain and tenderness in dactylitis was linked to US tenosynovitis $GS \geq 2$ (Girolimetto et al., 2019). However, large disparities have been reported between clinical examination and US findings including for synovitis and enthesitis (Husic et al., 2014). Conversely, a smaller longitudinal study of PsA patients reported that the presence of PD on US was associated with SJC66, CRP, ESR, DAS28 and the physician global assessment (Pukšić et al., 2018). These mixed findings between clinical and US examination need further research for greater clarity. However, a recent report on clinical low disease activity (LDA) states, (determined by DAPSA, PASDAS, CPDAI, or MDA) suggests such measures are able to differentiate between high and low US determined disease activity (Bosch et al., 2019). The unmet needs and suggested areas to focus US research in oligo/polyarticular PsA (1) and psoriatic dactylitis (2) are summarised in Table 2:3.

Table 2:3. Unmet needs and areas to focus US research in PsA

Unmet needs: (1) Psoriatic oligo/polyarthritis	
Diagnosis: Sensitivity and specificity:	<p>There is limited data on the specificity of US determined inflammatory arthritis pathologies to PsA. More research is needed on the added diagnostic value of US and differentiation of pathologies between diseases (e.g. PsA, crystal arthropathies, RA).</p> <p>Large PsA prospective cohorts that incorporate US are an ideal resource for unravelling specificities for PsA related US features.</p> <p>The high sensitivity of US to detect pathologies, even subclinical disease may be valuable, but more data is needed on implications of subclinical findings.</p>
Synovitis:	<p>Clinical and US observations in PsA do not correlate well despite paucity of data. Cohort studies are needed to understand this mismatch further. This is important because persistent synovitis leads to erosive damage, and structural and functional impairment. Less is known about whether clinically tender or swollen joints translate to underlying US synovitis.</p> <p>Greater depth of understanding is required on which PsA patients will benefit from an US assessment in the clinic and in which settings, there is little or no added value</p> <p>Further research is needed in longitudinal PsA/PsO cohorts such as whether subclinical synovitis translates into clinical signs at follow-up and its prognostic value.</p> <p>Whether disease should be measured clinically or via US needs addressing.</p> <p>The significance of subclinical synovitis in early PsA is still not fully clear, but links with the emerging research focus into early and Pre-PsA phase.</p> <p>The large number of joints in PsA joint counts are a time limiting factor, impractical in the clinical setting. An</p>

Unmet needs: (1) Psoriatic oligo/polyarthritis	
	implementable, condensed, time-sensitive, but valid and reliable US tool is needed.
Enthesitis:	<p>Some discordance exists between clinical/US enthesitis in PsA studies which needs further clarity.</p> <p>The need to distinguish between PsA and non-PsA disorders such as fibromyalgia is important for accurate diagnosis.</p> <p>How should enthesitis be defined? The US assessment of enthesitis is still not straightforward and there is debate amongst researchers between definitions (OMERACT). Whether or not a further US enthesitis composite score is needed, and how many and which entheses should be included remain unanswered.</p>
Tendon and peri-tendon inflammation:	<p>The differentiation between tendon pathologies observed in rheumatic diseases such as RA or Palindromic rheumatism in comparison to PsA is another area of focus where US may inform clinical practice.</p> <p>The imaging of tendon pulleys and sheaths could be of value to early diagnosis .</p> <p>Flexor and extensor tendinous and peritendinous regions are often involved and may inform early diagnosis but questions still remain such as the anatomical region, and when (symptomatic/asymptomatic) this should be performed, and what is the prognostic significance?</p>
Management: Disease activity and monitoring:	<p>How should disease activity be measured via US for individual patients?</p> <p>Several composite measures are available, but there is lack of research on which should be used.</p>
Disease remission:	<p>Clinical <i>versus</i> US remission: which should be used? How should US remission or low disease activity be defined?</p> <p>Further research will be required.</p>

Unmet needs: (1) Psoriatic oligo/polyarthritis	
Practicality:	Advanced technologies have emerged that apparently permit automation and quick and easy joint assessment. Whether such an approach is cost-effective or can be implemented and achieved reliably and validly is yet to be determined.

Unmet needs: (2) Psoriatic dactylitis	
Diagnosis: Sensitivity and specificity:	<p>Dactylitis is a unique lesion in PsA and SpA. Its significance is still unclear in PsA, and whether the lesion has any significance to the disease phenotype? Further research on the burden of disease afflicted by this lesion directly and indirectly will drive further understanding in PsA.</p> <p>The nature of dactylitis from early disease onset into chronic PsA is not fully understood. More research from large PsA cohorts may explain this further.</p> <p>High sensitivity US may be useful in detection of small microanatomical enthesal tissue in dactylitis research (e.g. tendons/pulleys).</p>
Synovitis:	<p>What is the relationship between dactylitis and synovitis? Does this differ depending upon disease course or treatment type?</p> <p>Are there any US predictors that determine why some people with dactylitis may be affected by worse outcomes?</p> <p>PsA cohorts with dactylitis may provide more insight into future dactylitis research.</p> <p>Is there a risk from dactylitis to overall disease related affliction and treatment in early disease?</p> <p>Does synovitis represent risk of dactylitis relapse/recurrence?</p>

Unmet needs: (2) Psoriatic dactylitis	
Enthesitis:	<p>The enthesis organ concept is highly implicated in PsA, yet little is known on whether dactylitis results in more clinical/US enthesitis?</p> <p>Does dactylitis represent an intermediary lesion in the disease spectrum, developing from enthesitis and progressing into synovitis, or could it be a more significant clinical marker of disease severity in early PsA? Assessment with US at time-points in PsA progression is needed. These questions may help to shape future US research.</p>
Tendon and peri-tendon inflammation:	<p>Tendon pathologies are key pathological features in dactylitis and correspond to the anatomical concept of swelling across the whole digit. Further understanding of tendinopathy in this lesion may improve targeted PsA therapy.</p> <p>Flexor tenosynovitis and flexor tendon sheath and pulley pathologies are key components of dactylitis to research.</p> <p>Peritendon inflammation: US vs MRI, disease course and response to therapy.</p>
Management: Disease activity and monitoring:	<p>Isolated US vs combined clinical and US features of dactylitis should be considered to assess dactylitis disease activity and monitor treatment response.</p> <p>Scoring dactylitis: validation of scoring methods can permit use in research and clinical settings.</p> <p>“Hot” and “cold” differentiation and active pathologies: clinical examination findings could be included to encompass the best representation of dactylitis status.</p> <p>Clinical trials and longitudinal cohort studies may provide further clues into this arena where the data is sparse.</p>

Table adapted from (Dubash S, De Marco G et al., 2020)

2.10.4 Management

Ultrasound for management decisions

The ability to detect active inflammatory disease or erosion makes US a valuable tool for the monitoring of disease. Indeed this is also supported by the EULAR recommendations indicating its place above clinical and laboratory assessment (Mandl et al., 2015). However, most strikingly in RA, recent data showed a dichotomy exists between clinical examination of tender and swollen joints and US synovitis, suggesting tenderness may not be associated with US synovitis (Hammer et al., 2019). Data from similarly large cohorts for PsA is still needed. It is important to understand the complex relationship between clinical and US examination given that US is not universally conducted in clinical practice. Despite these findings, the inclusion of US can assist the assessment of disease activity where clinical findings may have overlooked underlying occult PsA disease activity.

The monitoring and follow up of PsA

The presence of PD signal in PsA patients at baseline was associated with greater disease activity, but at 4 months no impact on treatment response was observed (Højgaard et al., 2019). In the imaging substudy of the TICOPA trial, GS and PD US scores were each semi-quantitatively graded (0-3) and MRI images were assessed via the OMERACT PsAMRIS score (synovitis, flexor tenosynovitis, periarticular inflammation, bone oedema, bone erosion, bone proliferation, and an additional global inflammation score) at baseline and 48 weeks. The US and MRI assessment methods demonstrated good responsiveness despite no significant differences between the standard care and tight control groups and an underpowered study (Helliwell et al., 2019). The potential of such imaging methods encourages research in this field. However, given several difficulties in PsA such as the high level of subclinical inflammation in PsA the importance of which has not yet been fully defined and may detract the clinical assessment, exactly how these modalities should be implemented for monitoring disease is an area of unmet need. In clinical

practice US is certainly useful to confirm or refute suspected pathologies from clinical examination.

Remission assessment

The minimal US disease activity (MUDA) score is defined by PD \leq 1 and US remission as PD=0, at joints, tendon/peritendons, and entheses. Drawbacks of these criteria include that many patients may have GS synovitis without PD activity. An estimated 20% of PsA patients achieved MUDA in one study reportedly predicted by DAPSA which correlated with GS and PD synovitis but not the CPDAI (Husic et al., 2014). However, there is poor correlation between clinical PsA activity measured by composite outcome measures and US inflammatory findings particularly PD signal (Michelsen et al., 2016). In a large cross-sectional study, there was disparity between US remission, found in 49.6% of patients, and clinical remission, achieved in only 5.7%-9.9%. This highlights the discordance and complexity of comparison in the assessment of disease states. Patient reported outcomes are often a component of the many composite measures used but these did not correlate well with US synovitis in comparison with the swollen joint count. Such measures remain research tools for now and there remains further questions to be answered such as how many joints should be scanned if these measures are implemented in practice.

2.10.5 Prognosis

In PsA patients clinically classified as oligoarthritis, US scanning has uncovered further subclinical disease in a polyarticular distribution suggesting that patients should be reclassified as polyarthritis (Østergaard et al., 2016). Whether subclinical inflammation should be treated or not is an unmet need in SpA US research and could improve early outcomes. It is still unconfirmed whether greater subclinical disease evolves into greater symptomatic PsA later on as suggested by other studies which has huge bearing on PsA prognosis.

The persistent presence of US synovitis were identified as risk factors for disease progression, and the presence of GS and/or PD \geq 2 predictors of poor prognosis (El Miedany et al., 2015). In the same study the presence of GS \geq 1 was found to be of limited prognostic relevance, however, presence of US enthesitis (GS and/or PD) also predicted structural progression of joint disease which was demonstrated with higher baseline GUESS scores in patients that later developed PsA (El Miedany et al., 2015).

Another study reported low levels of PD signal in PsA patients in clinical remission. Subsequent disease recurrence was high upon discontinuation of cs/bDMARDs (90%), however synovial hypertrophy at the time of therapy cessation was a predictor of relapse (Araujo et al., 2015). Further data on the assessment of remission and prognosis are expected from the UPSTREAM study (Zabotti, Piga, et al., 2018).

2.10.6 Composite US scores

In clinical research practice US disease activity may be scored using a number of validated methods for the joints and entheses.

Joints

Two composite scores have been specifically developed to monitor disease activity in PsA: the 5TPD and PsA-Son composite scores with good sensitivity to detect inflammation and feasibility, but not yet validated in any other series (Zabotti, Piga, et al., 2018).

Following the suit of many rheumatology clinical composite scores, Ficjan et al proposed two US scoring methods to assess inflammatory and structural PsA lesions, the PsA-Son13, (unilateral joints) and PsA-Son22 score (bilateral joints) (Ficjan et al., 2014). They reported sufficient construct validity, reliability and sensitivity to change for both scores. The reduced number of joints included may be considerably time saving, however there is potential to miss involved joints leading to a false reflection of overall disease activity, especially relevant for oligo/monoarticular phenotypes.

The “5 targets Power Doppler for Psoriatic disease” (5TDP) was based on joints, tendons, entheses, skin and nails scoring the highest expression of PD signal (Gutierrez et al., 2012). The limitations were that the score does not consider multiple joint involvement from single joint involvement and may lead to under estimation of disease activity in polyarticular disease (Gutierrez et al., 2012). A further drawback is that nail and skin US assessment is not commonplace in routine practice and therefore not practical outside of a research setting. Finally, it is notable that large joint involvement is frequent in PsA, therefore a tool initially developed for validation in RA, Sonography in large joints in rheumatology (SOLAR), has been reported for its suitability for PsA (Schäfer et al., 2013).

Entheses

Although study of the MASEI scoring tool failed to distinguish between enthesitis in PsA from healthy controls, it was found that by excluding the knee entheses thickness and refining PD severity, marked differences could be shown (Wervers et al., 2018). Given considerable overlap of features between groups, setting the best discriminative thresholds for detecting pathology is imperative. On the contrary, a recent systematic literature review concluded that the MASEI was feasible, reliable and a valid ultrasound score for assessing enthesitis, but did not find any studies assessing MASEI as an outcome for treatment response (Macía-Villa and De Miguel, 2019). Whether clinical tenderness is derived from enthesitis or fibromyalgia may be difficult to evaluate, but has recently been studied using US and scored via the Glasgow enthesitis scoring system (GUESS) (Fiorenza et al., 2020). It was found that US enthesitis was more prevalent in PsA alone and PsA with fibromyalgia compared to fibromyalgia alone, and clinical enthesal scores (LEI, MASES) were shown to overestimate active enthesitis in fibromyalgia (Fiorenza et al., 2020). A further preliminary enthesitis score developed in a recent GRAPPA study has reported the ability to differentiate between PsA and healthy controls (Tom et al., 2019). However this has led to further discussion/debate on whether a further enthesitis score is actually needed, and if so, how many entheses should be included, which suggests that a

research study to prioritise differentiation of PsA from PsO and osteoarthritis/mechanical causes should be implemented (D'Agostino and Coates, 2019).

Guided interventions (injections)

Ultrasound provides the ability to visualise the needle for injection procedures and therefore optimise placement accuracy. There are no specific recent studies on PsA and the effectiveness of US guided routine intra-articular injections. However, previous randomised controlled trials (RCT) in inflammatory arthritis reported significantly better accuracy of joint injection by US over the blind/palpation approach (Cunnington et al., 2010). In the same study, the benefit of short-term outcomes could not be demonstrated. Another larger RCT of 244 patients reported superior outcomes and cost-effectiveness with US guided injection *versus* the conventional blind/palpation technique, with an 81% reduction in injection pain, 35% reduction in pain scores and 38% increase in responder rate (Sibbitt et al., 2011). In contrast, a large randomised trial examining the benefit of US in a clinical tight control regimen in RA (ARCTIC) did not find any significant difference in treatment efficacy between US guided and blind/palpation guided joint injections (Nordberg et al., 2018). There is a clear advantage of targeting pathologically active disease through US assessment prior to US guided injection given that treatment efficacy was observed when moderate PD synovitis was present, independent of whether the joint was clinically swollen (Nordberg et al., 2018). Given the multiple pathologies in PsA, it would seem reasonable to study targeted US injections based on region and type of pathology. Further research may clarify whether US guided joint injection for routine intra-articular joint injections can produce superior outcomes over routine blind approach, but the most recent data is limited (Zabotti et al., 2017).

2.10.7 Conclusions

Ultrasound is complementary to clinical examination by adding sensitivity and specificity to sites of disease in PsA enhancing the qualitative assessment.

Several recent studies have shown added value of US in research by improving the understanding of disease. The clinical role of US for diagnosis is ever more assuring, yet there is discordance between clinical and US assessment that needs further research. Composite scoring measures remain research driven tools and are unlikely to be implemented in busy routine clinics in the near future. As US becomes more widely used, its function as a disease monitoring tool is promising, but further research is required to clarify its specific role in the clinic.

2.11 Management of SpA

2.11.1 Treatment of AS and nr-axSpA

Up to recently, the lack of understanding about the aetiopathogenic mechanisms in SpA translated into an absence of efficacious therapies. Exercise, however, has always been understood to alleviate symptoms and perhaps ameliorate disease progression. Robust evidence behind the role of self-exercise or structured physiotherapy in axSpA is however lacking (Millner et al., 2016; Sharan and Rajkumar, 2017). The same applies to the use of non-steroidal anti-inflammatory drugs (NSAIDs) which remain the mainstay of initial therapy in AS and nr-axSpA (Haroon et al., 2012). NSAIDs can alleviate symptoms very effectively but also have associated risks with long-term administration and may lead to gastrointestinal, cardiovascular and renal complications.

However, there is the recognition that up to 40% of affected individuals may never require treatment above NSAIDs and physiotherapy. An estimated two-thirds, may have active disease suitable for biologic disease modifying anti-rheumatic drugs (bDMARDs) as defined by a Bath Ankylosing Spondylitis Disease activity Index (BASDAI) questionnaire score of greater than 4 and spinal visual analogue scale (VAS) greater than 4, or an AS disease activity score (ASDAS) of 2.1 or above (Garrett et al., 1994; Barkham et al., 2005). The current ASAS -European League Against Rheumatism (ASAS-EULAR) guidelines recommend treating patients with bDMARDs when elevated CRP or radiological or MRI evidence of sacroiliitis is present, and there is a failure of at least 2 different NSAIDs each for 4 weeks in conjunction with the treating

rheumatologist's opinion (van der Heijde et al., 2017). The American college of rheumatology (ACR) and the Spondyloarthritis Research and Treatment Network (SPARTAN) have published complementary treatment recommendations (Ward et al., 2016).

The evidence for treatment with conventional disease modifying anti-rheumatic drugs (cDMARDs) is lacking but physicians may use these, especially for associated peripheral synovitis. The bDMARDs are the only proven efficacious therapies for the treatment of axSpA. Studies looking into the efficacy of TNF inhibitors identified that the best predictors of achieving a good response are: raised CRP, short symptom duration or young age, and active inflammation on MRI (Sieper and Poddubnyy, 2017).

On the other hand, the main indicator of poor response is smoking as shown by data from the German Spondyloarthritis Inception Cohort (GESPIC) demonstrating that smokers suffer a dose dependent deterioration on their structural damage over 2 years shown by changes to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), a composite index score characterising AS radiologic features in the spine used to determine radiographic structural progression in AS over time (Poddubnyy et al., 2013).

2.11.2 Treatment of pSpA

In some ways, the treatment of pSpA has mirrored RA treatment strategies for several years especially for PsA. Whilst some treatment strategies overlap amongst the SpA disorders, the majority have been trialled in PsA, where several studies are emerging including new therapies. More recently, treatment has been specific to pathogenic targets in SpA which have paved a route for the contemporary line of therapies some of which are not approved for RA such as the IL-17A blockers and phosphodiesterase 4 inhibition. Beyond the several drug trials in PsA, trials have now been conducted for pSpA as a disease entity, demonstrating efficacy of TNFi in patients who do not fulfill the mNY or CASPAR criteria. TNFi efficacy in non-psoriatic patients meeting the ASAS pSpA criteria and TNFi remission in very early disease has been demonstrated (Paramarta et al., 2013; Mease et al., 2015; Carron et al., 2017).

2.11.3 Measurement of treatment response

AxSpA/AS

Evaluation of treatment responses in SpA can be conducted by several methods. Clinical trials in axSpA have adopted to use the ASAS response criteria as shown (Table 2:4). Other methods include assessing for a 50% improvement in BASDAI (BASDAI50) usually after 12-16 weeks of treatment (Rudwaleit et al., 2004), or for a change in ASDAS of ≥ 1.1 as compared with baseline (clinically important improvement), or a response in ASDAS ≥ 2.0 (major improvement), and inactive disease defined by ASDAS < 1.3 (Poddubnyy et al., 2014).

PsA/Peripheral SpA

In those PsA with predominant axial disease, measuring clinical response to PsA treatment may be conducted through the above methods. For peripheral SpA, the American criteria of rheumatology (ACR) criteria can be used to measure responses at specified proportions (ACR20/50/70%) as shown in Table 2:5 (Felson et al., 1995). Alternatives such as the Psoriatic arthritis response criteria (PsARC) include no worsening of any measure, at least 30% improvement in tender and swollen joint count, and at least 1 point improvement on a 5 point Likert scale for patient's global assessment of disease activity and physician's global assessment of disease activity (Clegg et al., 1996). There are several other composite measures that can be used such as the disease activity in PsA (DAPSA), the composite psoriatic disease activity index (CPDAI) or the psoriatic arthritis disease activity score (PASDAS) each with their own advantages (Mease, 2011). For extra-articular domains other indexes may be used such as the PsO area and severity index (PASI), Nail Psoriasis Severity Index (NAPSI). Enthesitis can be measured clinically via several methods including the Mander enthesitis index (MEI) which includes the most (66) enthesal sites, the Spondyloarthritis research consortium of Canada (SPARCC), 16 sites, the Maastricht Ankylosing

Spondylitis Enthesitis Score (MASES), 13 sites, or the Leeds Enthesitis index (LEI), 6 sites.

Table 2:4. Assessment of Spondyloarthritis international Society (ASAS) response criteria

ASAS response criteria definition
<ul style="list-style-type: none"> • The ASAS Response Criteria (ASAS 20) is defined as an improvement of at least 20% from baseline and an absolute improvement of at least 10 units on a 0-100 scale in at least three out of four of the following domains, and no worsening of >10 in the remaining one of four domains: <ol style="list-style-type: none"> 1. Patient global assessment, 2. Spinal pain score, 3. Physical function (BASFI), 4. Inflammation/ morning stiffness (last 2 questions of BASDAI).
<ul style="list-style-type: none"> • The ASAS Response Criteria (ASAS 40) is defined as an improvement of at least 40% from baseline and an absolute improvement of at least 20 units on a 0-100 scale in at least three out of four of the following domains, and no worsening of >20 in the remaining one of four domains (above).
<ul style="list-style-type: none"> • ASAS partial remission is defined by a score of <20 in each of the four ASAS domains (above).

Table 2:5. The ACR50* response criteria

At least 50%* improvement in:
A: Tender joint count
B: Swollen joint count
C: At least 3/5 of:
<i>1. Patients' global assessment of disease activity</i>
<i>2. Physician's global assessment of disease activity</i>
<i>3. Patients' assessment of pain</i>
<i>4. Acute phase reactant (CRP / ESR)</i>
<i>5. Patients' assessment of disability (HAQ)</i>

HAQ: Health assessment questionnaire.

*ACR20/50/70/90% may be assessed.

2.11.4 Biologic pre-treatment considerations in SpA

It is recommended that prior to immunosuppression with bDMARDs, patients should undergo relevant screening to identify potential contraindications, comorbidities and risks. This process is the same for SpA as it is for other rheumatic diseases such as RA, and specifically includes checking for prior history of contraindications to TNFi such as history of demyelinating disease, malignancy, moderate to severe congestive heart failure using the New York Heart Association (NYHA) grade III or IV, and case history risk assessment for tuberculosis (TB) (Ding et al., 2010; Singh et al., 2016). It is routine practice for all patients to undergo pre-treatment chest radiograph, TB testing for latent and active disease with either interferon gamma release assay (IGRA) or tuberculin skin test or both, serology for hepatitis B and C, human immunodeficiency virus (HIV), varicella zoster virus (VZV), and anti-nuclear antibody (ANA).

There is paucity of data in SpA for infection risks with bDMARDs, but the risk appears to be lower in AS compared to RA and PsA. In a meta-analysis of 71 clinical trials with adalimumab, 4 in AS, the serious infection risk was 1.4/100 patient-years (pys) compared with 4.6/100pys for RA and 2.8/100pys for PsA (Burmester et al., 2013). An increased serious infection risk was also observed with etanercept at 3.01/100 pys in patients with AS compared with 3.75/100 pys for rheumatoid arthritis (Hamilton et al., 2017). There was an overall increased risk of any infection observed in 440 axSpA patients treated with TNFis at 15 per 100 pys, and for serious infections 1.3 per 100 pys (Wallis et al., 2015). It is therefore strongly recommended that patients are administered vaccinations against inactivated influenza and pneumococcus to protect from infection whilst on bDMARDs (van Assen et al., 2011). On the contrary, live attenuated vaccines such as measles mumps and rubella, live attenuated influenza, VZV, yellow fever, Ty21a oral typhoid, Bacillus Calmette-Guerin (BCG), and rotavirus should be avoided due to the increased risks of uninhibited bacterial or viral replication in patients on bDMARDs and in light of reports of severe complications (Ferreira and Isenberg, 2014).

The risks and benefits of initiating a bDMARD should always be fully considered and patient education for shared decision making between the

clinician and patient is key in the treatment discussion (Smolen et al., 2018). Finally, in wake of the covid19 pandemic, it is advised that SpA patients receive the vaccination to SARS-CoV-2, ideally before embarking on additional immunosuppression, however a risk/benefit assessment should be undertaken for each individual (Bijlsma, 2021).

2.11.5 Anti-TNF therapy and IL-17A inhibition

Axial SpA (AS and nr-axSpA)

There are currently five TNFi bDMARDs available for the treatment of AS: adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Most of the evidence for these drugs comes from phase 3 randomized double-blind placebo controlled clinical trials which included subjects with confirmed AS that were treated with anti-TNF versus placebo. All the bDMARD therapies display efficacy against placebo, but no direct comparison on efficacy can be made between biologics given the absence of head-to-head studies. Improved understanding of the IL23/IL17 axis in the pathogenesis of SpA has led to the recent advent of drugs targeting IL-17A such as secukinumab, which has opened up a new treatment avenue for people affected with axSpA, PsA and skin psoriasis. Evidence from RCTs have confirmed efficacious responses for secukinumab in AS (Baeten et al., 2015; Braun et al., 2016). The blockade of IL-17A via subcutaneous secukinumab in AS, revealed an efficacious ASAS40 response, albeit slightly less at 36% compared to the combined mean ASAS40 of 44.5% overall from the TNFi trials for AS (Baeten et al., 2015). Treatment responses in AS and nr-axSpA in phase 3 clinical trials are summarised in Table 2:6 (Dubash et al., 2017). A successful treatment response was sustained at 52 weeks in both studies for AS, but interestingly the 300mg monthly dose of secukinumab, which has not yet been examined in clinical trials for AS, has been shown to be more effective than the 150mg monthly dose in treating skin psoriasis alone (Langley et al., 2014).

It is recommended safe prescribing by usual pre-bDMARD screen occurs prior to bDMARDs (TNFi or anti-IL17 or other therapies) given the potential adverse

effects. The safety profile of secukinumab in AS appears to be comparable to that seen in the trials for skin psoriasis (Baeten et al., 2013; Blauvelt, 2016). Despite the concerns over suicide rates that halted the brodalumab trials (an IL-17A receptor antagonist which also inhibits IL-17F, IL-17A/F heterodimer and IL-17E), none occurred in the treatment group for secukinumab, although one suicide was recorded in the placebo group (Papp et al., 2012). Exacerbations of Crohn's disease and uveitis were reported as adverse events in the clinical trials which suggests TNFi, excluding etanercept, may have been more suitable treatment for those subjects (Baeten et al., 2013). The adverse gut effect in rare cases has been attributed to protective role of IL-17 on enterocyte tight junction formation (Lee J. S et al., 2015). Another IL-17A antagonist, ixekizumab, has more recently also demonstrated efficacy in phase 3 clinical trials which also appears to be efficacious in axSpA (van der Heijde et al., 2018; Deodhar et al., 2020).

PsA and peripheral SpA

The other SpA diseases are largely characterised by peripheral joint involvement and include psoriatic arthritis (PsA), inflammatory bowel disease (IBD) related arthritis and reactive arthritis (ReA), where the use of therapy in those with axial symptoms is extrapolated from AS. In the same way peripheral joint treatment response is often extrapolated from PsA trial data. In recent years efficacy has been shown for the IL-17A inhibitors to complement the efficacious TNFi data for PsA. Table 2:7 summarises the clinical trial data for bDMARDs and tsDMARDs in PsA.

Table 2:6. ASAS40/20 responses in AS/nr-axSpA

AS	Drug dosing regimen	Time of assessment (weeks)	ASAS 40 response (Vs placebo)	ASAS 20 response (Vs placebo)
Adalimumab (Van Der Heijde et al., 2006)	40mg S/C, Q2W	12	40% (13%)	58% (21%)
Etanercept (Davis et al., 2005)	25mg S/C twice weekly	12	45% (16%)	59% (28)
Golimumab (Inman et al., 2008)	50 mg S/C Q4W	14	45% (15%)	59% (22%)
Infliximab (Van Der Heijde et al., 2008)	5mg/kg, IV at weeks 0, 2, 6 and then Q6W thereafter.	24	47% (12%)	61% (19%)
Certolizumab pegol (Landewé et al., 2014)	200mg S/C, Q2W	12	40% (19%)	58% (38%)
Certolizumab pegol (Landewé et al., 2014)	400mg S/C Q4W	12	50% (19%)	64% (38%)
Secukinumab (Baeten et al., 2015)	IV loading doses at weeks 0, 4 and 8 at 10mg/kg then 150mg S/C, Q4W thereafter.	16	42% (13%)	61% (29%)
Secukinumab (Baeten et al., 2015)	S/C loading dose of 150mg weekly for 4 weeks and then Q4W thereafter.	16	36% (11%)	61% (28%)
Ixekizumab (van der Heijde et al., 2018)	80mg* S/C, Q2W	16	52% (18%)	69% (40%)
Ixekizumab (van der Heijde et al., 2018)	80mg* S/C, Q4W	16	48% (18%)	64% (40%)
Tofacitinib (Deodhar A et al., 2020)	5mg PO, twice daily	16	41% (13%)	57% (29%)

nr-axSpA	Drug dosing regimen	Time of assessment (weeks)	ASAS 40 response (vs placebo)	ASAS 20 response (vs placebo)
Adalimumab (Sieper et al., 2012)	40mg S/C, Q2W	12	36% (15%)	52% (31%)
Etanercept (Dougados et al., 2014)	25mg twice weekly, S/C	12	33% (15%)	52% (36%)
Certolizumab pegol (Landewé et al., 2014)	200mg S/C, Q2W	12	48% (16%)	59% (40%)
Certolizumab pegol (Landewé et al., 2014)	400mg S/C, Q4W	12	47% (16%)	63% (40%)
Golimumab (J. Sieper et al., 2015)	50 mg S/C, Q4W	16	57% (23%)	71% (40%)
Secukinumab (Deodhar et al., 2021)	S/C loading dose of 150mg weekly for 4 weeks and then 150mg S/C, Q4W thereafter.	16	42% (29%)	57% (46%)
Secukinumab (Deodhar et al., 2021)	No loading dose. 150mg S/C, Q4W	16	42% (29%)	58% (46%)
Ixekizumab (Deodhar et al., 2020)	i) 80mg* Q2W ii) 80mg* Q4W	16	i) 40% (19%) ii) 35%	NA

Data presented are for illustrative purposes and not for direct comparison. Partly adapted from Sieper et al (Sieper and Poddubnyy, 2017). Percentages in brackets refer to placebo responses. Q2W: every 2 weeks, Q4W: every 4 weeks, Q6W: every 6 weeks, *denotes patients randomly assigned, ratio (1:1), to have either 80mg or 160mg for their first dose, NA: not applicable. S/C: subcutaneous route, IV: intravenous route, PO: oral route.

Table 2:7. Summary of the PsA clinical trial data for bDMARDs/tsDMARDs.

PsA	Drug dosing regimen	Time of assessment (weeks)	ACR20 response (vs placebo)	ACR50 response (vs placebo)
Infliximab (Antoni et al., 2005)	5 mg/kg IV at weeks 0, 2, 6, 14, 22	24	54% (16%)	41% (4%)
Adalimumab (Mease et al., 2005)	40 mg S/C Q2W	24	57% (15%)	39% (6%)
Etanercept (Mease et al., 2004)	25 mg S/C twice weekly	24	59% (15%)	-
Golimumab (Kavanaugh et al., 2009)	50 mg S/C Q4W	24	52% (12%)	-
Certolizumab pegol (Mease et al., 2014)	400 mg S/C at weeks 0 and 2 and then 200 mg Q4W	24	64% (24%)	44% (13%)
Ustekinumab (McInnes et al., 2013)	45 mg S/C at weeks 0 and 4 and Q12W	24	42% (23%)	25% (9%)
Secukinumab (McInnes et al., 2015)	150 mg S/C at weeks 0, 1, 2, 3, 4, then Q4W	24	51% (15%)	35% (7%)
Ixekizumab (P.J. Mease et al., 2017)	80mg S/C. Two 80mg loading followed by maintenance [either i) Q2W or ii) Q4W]	24	i) 62% (30%) ii) 58%	i) 47% (15%) ii) 40%
Apremilast	i) 20mg BD or ii) 30mg BD	16	i) 40% (19%) ii) 31%	-
Tofacitinib (P. Mease et al., 2017)	i) 5mg (PO) ii) 10mg (PO)	12	i) 50% (33%) ii) 61%	i) 28% (10%) ii) 40%

Data presented are for illustrative purposes and not for direct comparison. Partly adapted from D'Angelo et al., 2017. Percentages in brackets refer to placebo responses. Q2W: every 2 weeks, Q4W: every 4 weeks, Q6W: every 6 weeks, Q12W: every 12 weeks. S/C: subcutaneous route, IV: intravenous route, PO: oral route.

2.11.6 Other therapeutic targets in SpA

IL-12 and IL-23 blockade

Ustekinumab is a monoclonal antibody that inhibits the p40 subunit of IL-12, and IL-23. It is licensed for the treatment of skin psoriasis, psoriatic arthritis, and more recently for Crohn's disease (Feagan et al., 2016). Over expression of IL-23 has been linked to the development of enthesitis in animal models which resembles human SpA which suggests ustekinumab may be effective in AS. A proof of concept, prospective, open-label trial in ankylosing spondylitis reported a clinically efficacious response against placebo at 24 weeks with 65% of participants achieving an ASAS40 response (Poddubnyy et al., 2014). Exploratory studies with IL-23 anti-p19 monoclonal antibodies have been performed but were ineffective in AS indicating that targeting inhibition of implicated pathogenic pathways in SpA may not necessarily translate into efficacy for clinical outcomes (Siebert et al., 2019). Conversely, guselkumab has demonstrated efficacy for PsO and PsA, and extension studies in PsO indicate that this therapy is safe over 3 years of treatment, which would similarly be anticipated in PsA (Deodhar et al., 2018; Reich et al., 2020).

IL-1 blockade

Interleukin-1 (IL-1) is a highly active pro-inflammatory cytokine that may play a role in certain patients particularly those with a high inflammatory burden of disease defined biochemically by a high CRP level. We already know from the treatment of patients with auto-inflammatory syndromes, where there are typically high levels of inflammation, that the blockade of IL-1 alone results in rapid and sustained disease remission (Dinarello et al., 2012). There are limited data from open label studies for the use of anakinra in AS, an antagonist to the IL-1 receptor. An early study from Leeds demonstrated efficacy to anakinra by clinical and MRI features in 20 patients with AS, however another study reported no significant effect as compared with placebo (Tan et al., 2004; Haibel et al., 2005). The latter study had low CRP levels compared to the former and since CRP is a predictor of response, it would be premature to suggest that blockade of the IL-1 pathway has no role.

IL-6 Blockade

The clinical trials using tocilizumab for the treatment of AS failed to achieve their desired endpoint for demonstrating efficacy (Sieper et al., 2014). Sarilumab is similar in action differing only by being the first fully human monoclonal IL-6 α antagonist. In phase II randomised controlled trials no statistical differences were demonstrated between ASAS20 responses over placebo despite the use of multiple dosing regimens (Joachim Sieper, Braun, Kay, et al., 2015). A recent report described refractory SpA with peripheral synovitis treated successfully with tocilizumab, in patients with high CRP demonstrating marked improvement in clinical symptoms and CRP normalisation (Merashli et al., 2016). These subjects were all TNFi non-responders with the additional burden of aggressive peripheral arthritis and consisted of an AS refractory disease phenotype. Interestingly, a TNF independent and IL-6 dependent model where disease starts at the synovio-entheseal complex has been recently described suggesting that a subgroup of SpA cases may be IL-6 dependent (De Wilde et al., 2016). However, an anti-IL-6 strategy is an unlicensed use of these agents and further research is needed to define rare and treatment recalcitrant phenotypes.

Anti-T-cell co-stimulation and anti-B cell targeted therapy

Abatacept is an inhibitor of T cell co-stimulation and has also been used to treat AS in a prospective open label study but without any significant difference as compared to placebo (Song et al., 2011). B-Cell inhibition has also been tested using rituximab, anti-CD-20 monoclonal antibody. The trial was small with only 10 patients in each of the anti-TNF naïve and anti-TNF experienced subjects. Interestingly, a higher response was achieved in the rituximab treated group in the anti-TNF naïve subjects as compared to placebo with the achievement of an ASAS40 response of 40% at week 24, despite no clinical efficacy seen in the anti-TNF experienced subjects (Song et al., 2010).

Targeted synthetic DMARDs

Targeted synthetic DMARDs are non-biologic smaller molecules and an emerging group of drugs within rheumatology. Apremilast is an inhibitor of

phosphodiesterase 4 (PDE4) and suppresses the activation of pro-inflammatory cytokines with activation of anti-inflammatory mediators. Studies in PsA and PsO have confirmed its efficacy for the treatment of psoriasis and psoriatic arthritis (Kavanaugh et al., 2014; Papp et al., 2015). In particular enthesitis responses were significantly improved at 24 weeks [MASES mean change from baseline -1.3 (vs -0.9) and 23.6% improvement] and the mean dactylitis count also significantly improved [-1.8 (vs-1.3)] (Gladman et al., 2018). However, despite overlap of pathologies in AS, trials were not successful. In a proof of concept trial, 36 AS patients treated for 12 weeks with either apremilast or placebo showed moderate reduction in the BASDAI but did not achieve statistical significance (Pathan et al., 2013). Results from a larger phase III placebo-controlled trial of 490 patients did not show any benefit for AS compared with placebo (Taylor et al., 2021). These disparities of efficacy between different AS/PsA studies highlight the complexity within SpA. Tofacitinib is an oral Janus kinase (JAK) inhibitor and also a small molecule. It inhibits cell signaling through JAK3 and JAK1 receptors and to a lesser extent JAK2. This drug appears to work in PsA including for enthesitis and has recent phase 3 trials have also demonstrated efficacy in axSpA (Table 2:6 and Table 2:7). Interestingly, this drug may be beneficial for IBD related SpA and was successful in trials of UC but not CD (Sandborn et al., 2017; Panés et al., 2017). Further, selective JAK inhibitors have emerged and are also already showing encouraging results for the management of PsA such as the JAK1 inhibitor filgotinib (Gladman et al., 2020). As others JAK inhibitors emerge, their off license use may reportedly have a role in refractory disease (Mease et al., 2021).

2.11.7 Radiographic progression in SpA

In pSpA structural radiographic progression is an important outcome and has been demonstrated with the TNFis (Goulabchand et al., 2014). This has been addressed in PsA including for the IL-17A blockers. Inhibition of structural progression has been demonstrated with secukinumab at 300mg or 150mg dosing at 6 months compared to placebo (Mease et al., 2021). Recent data is

encouraging suggesting that the inhibitor of IL-23 p19 subunit, guselkumab, inhibits structural progression at 6 months versus placebo (Mease et al., 2020). In axSpA true disease modification in terms of inhibition of radiographic disease remains an important consideration with regards to long term treatment with immunomodulatory therapies. Studies that involve established AS patients followed up over 2 to 4 years showed no evidence to support the inhibitory effect of TNFi drugs on radiographic progression (Van Der Heijde et al., 2008). However, there is some evidence that early treatment for more than 4 years may retard the radiographic progression if treatment with TNFi is given early (Haroon et al., 2013). By comparison, NSAIDs have an inhibitory effect on osteoclast activity, and this translates to clinical trial evidence of inhibition of radiographic progression in AS over 2 years of continuous use, as compared to on demand use which was shown to have a lesser effect (Wanders et al., 2005). Continuous NSAID use also slowed radiographic progression in patients with raised acute phase reactants (Kroon et al., 2012). In contrast to NSAIDs, TNFi has been shown to normalise the ESR confirming its efficacy and potency in clearing the symptoms in AS (Haroon et al., 2012). We are yet to fully understand axSpA including which individuals will or will not progress to radiographic disease. We do know that individuals who are HLA-B27 positive, have elevated CRP levels, inflammation of the sacroiliac joints on MRI, and are smokers have been identified as the most likely to develop radiographic progression (Sieper and Van Der Heijde, 2013; Navarro-Compán and Machado, 2016).

It has been estimated that 5-12% of nr-axSpA will progress to develop radiographic disease over a 2 year period and this increases to 20% in nr-axSpA patients with active spinal inflammation on MRI (Sieper and Van Der Heijde, 2013; Navarro-Compán and Machado, 2016). Equally, study estimates suggest 15-20% of axSpA will never develop radiographic sacroiliitis (Sieper and Van Der Heijde, 2013). Further data has emerged indicating that MRI positive patients with axSpA predict radiographic sacroiliac changes in 5-8 years through data accrued from both the DESIR and Leeds and cohorts respectively (Bennett et al., 2008; Dougados et al., 2017).

2.11.8 Summary: SpA treatment

Although for many patients TNFi treatment has been highly successful, there remains an unmet need for those who do not respond or cannot tolerate them. Further understanding of SpA disease phenotypes may unlock potential opportunities to identify new treatment targets for early tailored approach without the 'one size fits all' sequence to follow before a response is obtained. The IL-17A inhibitors have brought further of choice in targeted mode of action beyond TNFi and along with oral tsDMARDs (JAK inhibitors and PDE4 inhibitors) provide further alternatives for administration route and mode of action.

2.11.9 Treatment related paradoxical manifestations

Etanercept induced IBD

An increasing array of immunotherapies are being used in the treatment of immune mediated inflammatory diseases (IMIDs) which explain why there have been increasing reports of paradoxical reactions, particularly in the treatment of SpA. These appear to be somewhat rare events but have been reported in SpA and IBD. Etanercept has been a good example as it is effective for several IMIDs, but has been known to cause the development of de novo IBD, and was reported to the food and drug administration (FDA) in 443 patients (O'Toole et al., 2016).

IL-17A induced IBD or uveitis

The IL-17A inhibitor, secukinumab which is also efficacious in treating skin PsO, PsA, and axSpA/AS, is not suitable for individuals with Crohn's disease due the triggering of exacerbations when given to patients with RA, PsO and uveitis (Hueber et al., 2012; Colombel et al., 2013). In fact IL-17A blockade also failed to improve responses in trials of non-infectious Behcet's uveitis, and reports of IL-17A inhibition inducing uveitis still being reported in SpA (Dick et al., 2013; Nadwi et al., 2020). This highlights that clinicians should be

mindful of the paradoxical responses to treatment in diseases of the SpA family.

Sarcoid induced by TNFi

Several reports of pulmonary sarcoidosis induced by TNFi (monoclonal antibodies or soluble receptors) have been reported including in SpA, which appears to occur in an estimated 1/2800 TNFi treated patients (Daïen et al., 2009). Such reactions are surprising because TNFi may also be effective agents for the treatment of sarcoidosis (Hostettler et al., 2012). However, this paradox appears to be self-limiting improving upon cessation of TNFi and steroid therapy.

Paradoxical psoriasis

Although TNFi can be used for the treatment of psoriasis, reports of paradoxical psoriasis have been recognised with literature pointing towards differences between the classical and paradoxical psoriasis phenotypes. With blockade of TNF, there is an innate driven inflammatory response with increased type 1 interferon expression which has been reported in certain cases (Mylonas and Conrad, 2018). This is a side effect of TNF and does not represent de novo psoriasis.

Vedolizumab induced SpA

In comparison to etanercept causing IBD, the reverse has been reported following treatment for IBD with a recently approved humanized IgG1 monoclonal antibody to $\alpha 4\beta 7$ integrin (vedolizumab (VDZ)) that resulted in the induction of mild cases of sacroiliitis or arthritic flare (Varkas et al., 2017). Further SpA therapy was added for disease control in these patients. Although VDZ was continued in these reported cases, such reactions could pose difficult management decisions in clinical practice, especially if associated with other phenotypes that warrant cessation of the offending drug. Given the close association between IBD and SpA, this is an important area that need further investigating. These paradoxical reactions are poorly understood including

mechanisms of disease pathogenesis and why the immune system reacts in such a way in the presence of the immunotherapy.

2.11.10 Immunogenicity to biologic drugs

Development of anti-drug antibodies (ADAs)

Repeated administration of bDMARDs can result in the development of anti-drug antibodies (ADAbs). These were formerly known as human anti-murine antibodies (HAMA) having been first detected in patients given murine monoclonal antibodies administered for leukaemia, lymphoma, and melanoma (Schroff et al., 1985). Subsequently therapies have become more humanised in an attempt to improve safety and reduce immunogenicity to maximise treatment longevity given that the formation of anti-drug antibodies (ADAs) to bDMARDs are associated with loss of response to treatment (LOR). Increased drug related adverse events and hypersensitivity reactions may also occur related to high ADA levels.

For the chimeric monoclonal antibody infliximab, LOR was first identified in patients with CD (Baert et al., 2003). Subsequently several biological monoclonal antibodies have been developed all with associated with ADA formation. The two exceptions being etanercept and abatacept, both receptor fusion proteins, which are not linked to neutralising antibody formation, due to the absence of the antigen-binding fragment (Fab) (Strand et al., 2017). Given that SpA patients develop LOR to monoclonal TNFi estimated at 30-40%, it is thought that ADAs are responsible for a substantial proportion of LOR (Saad et al., 2010; Glintborg et al., 2013). In one study of AS patients, 27% (31/115) developed ADAs to adalimumab within the first 24 weeks of therapy (Kneepkens et al., 2015). A similar percentage (24.8%; 31/125) was found in another study at 12 months, which reported that presence of ADAs at 3 months with simultaneous low DLs were predictors of LOR (Jani et al., 2015). Large registry studies in SpA/PsA have indicated that LOR occurs in 56% of those switching therapy with a mean drug survival of 0.7 years for the first TNFi, and is more likely to occur in women and in those with a shorter disease duration (Glintborg et al., 2013). Collectively, several studies suggest at least

one third of patients switch to a second bDMARD within the first year of TNFi therapy (Costa et al., 2017).

Drug trough levels (DL) and therapeutic drug monitoring (TDM)

Indeed registry data have confirmed stepwise reductions in treatment response and drug survival following subsequent lines of therapy. Studies in AS have shown that in first line bDMARD treatment at 6 months, a mean BASDAI reduction of 3 units occurred, but for third line bDMARDs there was only a BASDAI reduction of 1.5 units (Glintborg et al., 2013). Drug retention across all diseases was less than 50% over 5 years (Simard et al., 2011). It is therefore imperative that the best chances for optimal responses are from the first line bDMARD therapy. Monitoring of the TNFi drug trough levels (DLs) known as therapeutic drug monitoring (TDM), may be a method to optimise plasma drug concentration which has been shown in several studies (Fobelo Lozano et al., 2019). Studies in have shown that DLs correlate with clinical responses and are significantly lower in the presence of ADAs (Kneepkens et al., 2015). Further, presence of low DLs at 3 months has been shown to predict LOR at 6 months (Daïen et al., 2012). In combination use of DL/ADAs for monoclonal TNFi may be effective to identifying patients that have developed LOR to therapy. The potential for bDMARD monitoring and therapy optimisation may facilitate earlier intervention where necessary offering a personalised approach for each individual (Figure 2:8).

Neutralising and non-neutralising ADAs

The ADAs against TNFi monoclonal antibodies target idiotypes, antibodies against the variable portion of other antibodies, at the epitope binding regions of the Fab fragments of monoclonal antibodies thereby preventing binding to TNF. These anti-idiotypic antibodies are therefore important as they directly interfere with the drugs ability to achieve its therapeutic mode of action (i.e. for TNFi, that is to bind TNF). The ADA response typically results in high affinity IgG antibodies and following their binding to the TNFi monoclonal antibody, resultant formation of immune complexes leads to enhanced

clearance of the drug (Atiqi et al., 2020). The TNFi ADAs may be neutralising or non-neutralising. The non-neutralising or “binding” antibodies, bind to the drug but do not affect the drug-target interaction. Neutralising antibodies interfere with the ability of the drug to bind to its target rendering the drug functionally inactive (Atiqi et al., 2020).

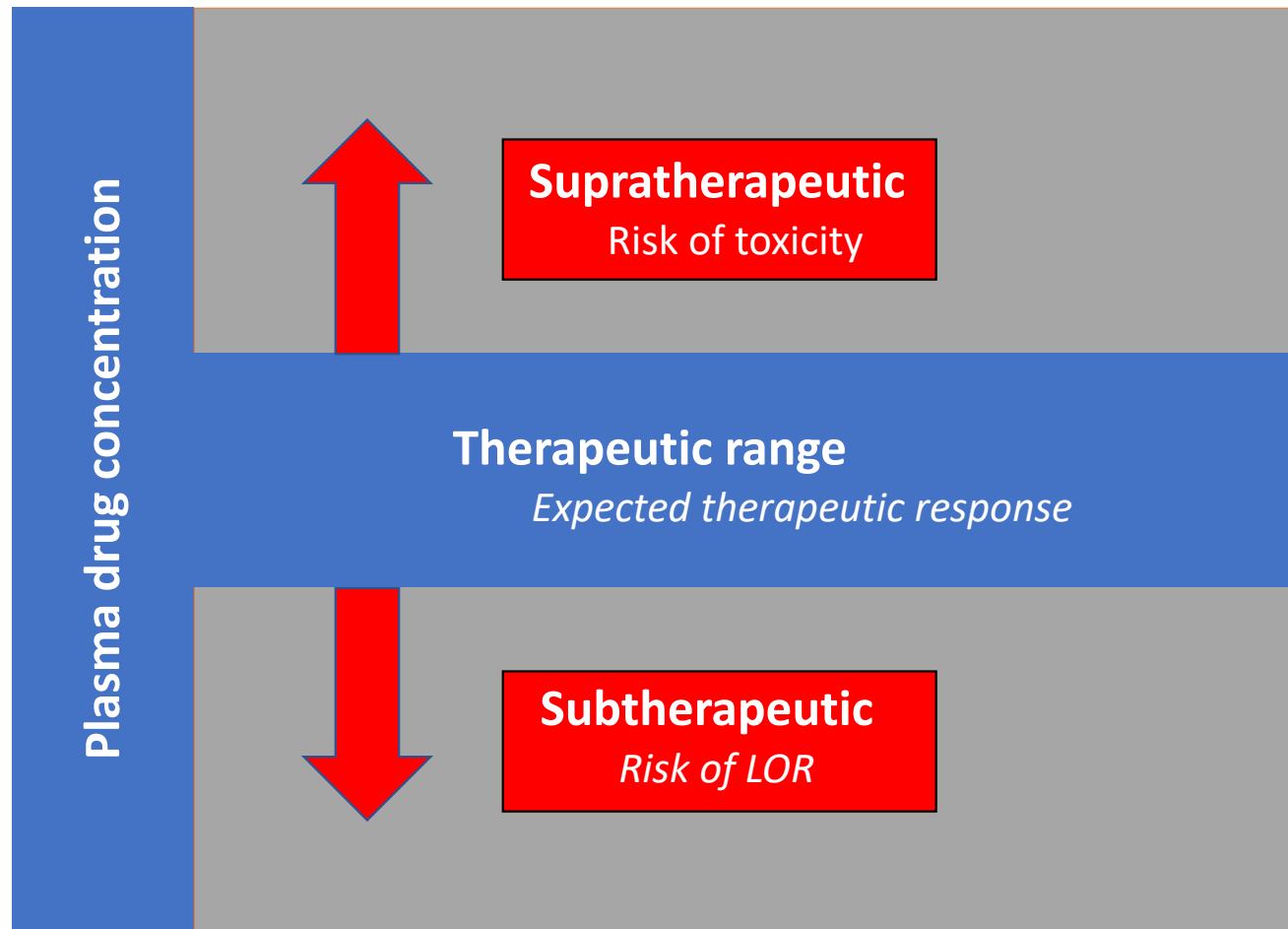


Figure 2:8. Plasma drug concentrations and the concept of therapeutic drug monitoring (adapted from Aronson and Hardman, 1992; Kang and Lee, 2009)

Immunogenicity test methods (immunoassay)

Various assays may be used to detect the ADAs, the most commonly used method being bridging ELISA. This method is more widely used but lacks the ability to detect ADAs in the presence of drug and therefore underestimate the actual ADA level (Bendtzen, 2015). The most sensitive assay is the electrochemiluminescent assay (ECL), able to detect low-affinity antibodies which was used in the biosimilar equivalence studies for CT-P13 and its reference medicinal product (infliximab (IFX)) in RA and AS (Kim et al., 2015). The radio-immunoassay (RIA) is not as sensitive as ECL in detection of ADAs, but its advantage is the low false positive rate of ADAs (Kim et al., 2015). However, this is a more complex method, requiring longer incubation period and needs storage of radioactive substances. The homogeneous mobility shift assay (HMSA), also has a better sensitivity than ELISA, and has the advantage of being able to measure ADAs when IFX is present in serum (Wang et al., 2012).

Guidance for DL/ADA measurement and assays

Guidance is emerging for DL/ADA measurement in other specialties where there is sufficient data generated to demonstrate effectiveness. Recently, scientific data reported in IBD patients led to the implementation of guidance from the American Gastroenterology Association (AGA) recommending measurement of TNFi drug trough levels (DTLs) and ADA in the presence of active IBD treated with TNFis (Feuerstein et al., 2017; American Gastroenterology Association, 2017). However, more evidence is required in SpA to determine whether the measurement of DL/ADAs or TDM of bDMARDs in SpA should be implemented in routine practice.

2.12 Summary of the chapter

These data from this review of the literature in SpA, provide an overview of the breadth and depth of knowledge accrued in this field over many years, and the unmet needs in research that are necessary for improving the prospects of patients with these diseases. The possibility of diagnosing SpA early, together with the advent of new therapeutic options for the treatment of SpA, have significantly improved the care of affected individuals. The utilisation of US has improved the potential for early accurate diagnosis. The heterogeneous nature of disease within the umbrella of SpA indicates that characterisation of SpA phenotypes is important to understand similarities and differences further and will be useful in light of the various different management approaches. The introduction of IL-17A blockade, and the tsDMARDs (JAK and PDE4 inhibition) in addition to TNFi, marks a step forward in the management of SpA, and may be suitable therapy for a large proportion of the SpA disease spectrum. However, up to now only limited data exist on their effect on clinical outcomes longer term, and radiographic progression as possible disease modifiers. Defining what should be the most effective method of detecting treatment non-response (LOR) and choosing the next sequence of bDMARD therapy is an area of unmet need and together with the search for biomarkers of treatment response, careful study of SpA cohorts, remain key areas of research for the next decade.

Chapter 3. Hypotheses, aims and objectives

3.1 Hypothesis (1)

- Enthesitis is a significant pathological event in early, new onset SpA and may be a biomarker for disease evolution.

3.2 Hypothesis (2)

- Measuring drug and antibody levels in infliximab (IFX) treated SpA patients can rationalise treatment non-response.

3.3 Aims and objectives (a-f)

- a. To identify and understand the current literature including areas of unknown knowledge and unmet needs.
- b. To explore the pathogenesis of severe SpA related enthesal pathology at the axial and peripheral skeleton in different SpA phenotypes following acute inflammatory and infective events.
- c. To explore baseline clinical and ultrasound characteristics in early PsA.
- d. To explore the significance of dactylitis, as a marker of disease severity in early PsA.
- e. To explore mechanisms of treatment non-response in SpA patients receiving the monoclonal antibody infliximab.
- f. To rationalise treatment based upon the IFX drug level.

Table 3:1 summarises the components of the thesis.

Table 3:1 Review table of thesis components

Exploring Pathogenesis and Treatment Response in Different Disease Phenotypes in Spondyloarthritis			
Hypothesis	Aims	Methods	Chapters
			1. Introduction.
	a. To identify and understand the current literature including areas of unknown knowledge and unmet needs.	PubMed search for the available scientific literature on pathogenesis and treatment of SpA.	2. Background literature review.
			3. Hypotheses and aims.
1) Enthesitis is a significant pathological event in early, new onset SpA and may be a biomarker for disease evolution.	b. To explore the pathogenesis of severe SpA related enthesal pathology at the axial and peripheral skeleton in different SpA phenotypes following acute inflammatory and infective events.	Two clinical case series.	4. Acute severe enthesal pathology as a significant event in reactive and inflammatory bowel disease related SpA.
	c. To explore baseline clinical and ultrasound (US) characteristics of early PsA.	Clinical prospective, cross-sectional observational study (SpARRO cohort)	5. Exploring the relationship between clinical examination of joints and ultrasound synovitis: a cross-sectional study of DMARD-naïve early PsA.
	d. To explore the significance of dactylitis, as a marker of disease severity in early PsA.	Clinical prospective, cross-sectional observational study (SpARRO cohort)	6. Exploring the significance of dactylitis in DMARD-naïve early PsA: a study of clinical characteristics, ultrasound synovitis and erosion.
2) Measuring drug and antibody levels in IFX treated SpA patients can rationalise treatment non-response.	e. To explore mechanisms of treatment non-response in SpA patients receiving the monoclonal antibody infliximab.	Real-world observational clinical evaluation	7. Infliximab drug trough and anti-infliximab antibody levels as biomarkers of treatment response in SpA.
	f. To rationalise treatment based upon the infliximab drug level.		
			8. Discussion
			9. Future directions
			10. Conclusions

Chapter 4. Acute severe enthesal pathology as a significant event in reactive and inflammatory bowel disease related spondyloarthritis

4.1 Overview of chapter

This chapter addresses the second aim of this thesis, to explore the pathogenic relationship between severe SpA and enthesal related pathology at the axial and peripheral skeleton in different SpA phenotypes following acute inflammatory and infective events.

Enthesitis is a hallmark pathological feature of SpA and frequently occurs as part of this disease spectrum. More specifically, it is also a feature of axSpA, the axial clinical entity, with characteristic clinical and imaging features. Often axSpA including AS, the prototypical disease, presents with insidious onset of symptoms. However, less is known about acute severe presentations of *de novo* SpA, in particular such presentations have several differential diagnoses for rheumatic and non-rheumatic disorders, namely infection, arguably the most important of which should not be missed. Reactive arthritis, often occurring following exposure to an infection, can also present acutely and can involve joint and enthesal tissue. The acute nature of the diseases can result in clinical and MRI infective mimicry leading to acute emergency care and comprehensive workup. Although MRI is sensitive and specific for diagnosing SpA, it is not without its limitations and is always open to interpretation based on the clinical context. Lack of clinical biomarkers in axSpA might add to the diagnostic difficulty associated with such presentations.

The wide spectrum of extra-articular manifestations permits the possible development of SpA following isolated non-articular/enthesal features, such as uveitis, PsO, or IBD in the future. Little is known about why such development of SpA occurs. The second case series in this chapter describes patients with IBD treated with biologic drugs subsequently developing severe SpA-related enthesal pathology and is the first reported case series of severe SpA disease of this kind, compared with an earlier report of milder cases. In conjunction with successfully treated IBD, the development of severe SpA related enthesitis was

a paradoxical manifestation poorly understood. This part of the chapter investigates relationship between diseases including their shared pathogenesis, and proposition of a model of such is discussed.

4.2 Acute severe unilateral sacroiliitis presenting with MRI appearances mimicking infection

4.2.1 Introduction

Sacroiliitis is associated with SpA including AS, PsA and ReA. It is the predominant manifestation of axSpA, yet it may also be present in other rheumatic and non-rheumatic disorders. Inflammatory disease of the sacroiliac joint (SIJ) commonly presents with sacroiliac pain and usually accompanies inflammatory back pain typically in axSpA. Symptoms of sacroiliitis often occur with gradual onset in AS, however acute unilateral presentations are described more often as representing joint infection. In the early stages of disease in axSpA, the sensitivity of MRI is greater than plain film radiographs to visualise sacroiliitis. Equally it is also the imaging modality of choice in acute presentations of sacroiliitis to identify features compatible with SIJ related infection or significant inflammation.

4.2.2 Hypotheses, aims and objectives

Hypothesis

Enthesitis is a significant pathological event in early, new onset SpA and may be a biomarker for disease evolution.

Aims and objectives

To explore the pathogenic relationship between severe spondyloarthropathy related enthesal pathology at the axial and peripheral skeleton in different SpA phenotypes following acute inflammatory and infective events.

4.2.3 Methods

Study design:

A retrospective case series evaluation was conducted.

Research methods:

Patients presenting with acute severe enthesal pathology were recruited via identification from case records. Communication with colleagues at this institution (LTHT) and one other centre permitted the recruitment of cases that presented similarly over a one-year period (2017-2018). All patients gave written consent for a retrospective clinical evaluation of their case notes, laboratory results, and MR images. Institutional review board approval for ethics was not required as the management of patients was conducted according to generally accepted standards of care. Herein, four patients are reported with acute unilateral sacroiliitis and florid MRI appearances that mimicked infection but demonstrated a prompt and complete response to non-steroidal anti-inflammatory drugs (NSAIDs).

4.2.4 Results

All four patients were HLA-B27 negative males and presented with a rapid symptom onset of acute unilateral sacroiliac pain suggestive of unilateral sacroiliitis ranging from 2 days to 4 weeks duration (Table 4:1). One patient had a previous history of ulcerative colitis (case 2) in remission, and one had scalp psoriasis (case 3). There were prodromal symptoms in two patients (cases 1, 4) with short-lived fever at presentation. Case 4 had a sore throat preceding the presentation with neutrophilia ($12.4 \times 10^9/L$) which therefore prompted an extended infection screen. All four patients demonstrated significant elevation in acute phase markers with a mean serum C-reactive protein (CRP) of 115 mg/L. There were no prolonged overt clinical features of systemic inflammatory response.

At presentation, MRI confirmed florid bone marrow oedema (BMO) in 3 cases (1, 2 and 4) affecting >75% of the SIJs and moderate (affecting 25-75%) in case 3 (Figure 4:1). High signal was reported in surrounding muscle and soft tissue on MRI in all four patients by the reporting radiologists who advised the need to exclude infection. Sacroiliac joint aspiration and/or biopsy was considered in all

cases but not conducted due to the prompt symptom response after NSAID treatment with improvement in clinical parameters and a negative septic screen. Case 2 was advised to continue empirical dual combined oral antibiotics for four weeks. In addition he continued NSAID therapy for 8 weeks until complete symptom resolution. Group A Streptococcus was cultured from a throat swab from case 4 including a borderline anti-streptolysin titre test result of 466 iU/mL and 406 iU/mL respectively, suggesting plausible post-streptococcal reactive arthritis. Repeat MRI was performed in 3 patients at a mean follow up of 5 weeks and demonstrated improved but persistent inflammatory changes. Additional imaging thereafter revealed significant improvement in BMO changes in cases 1 and 3, at 2 and 5 months respectively.

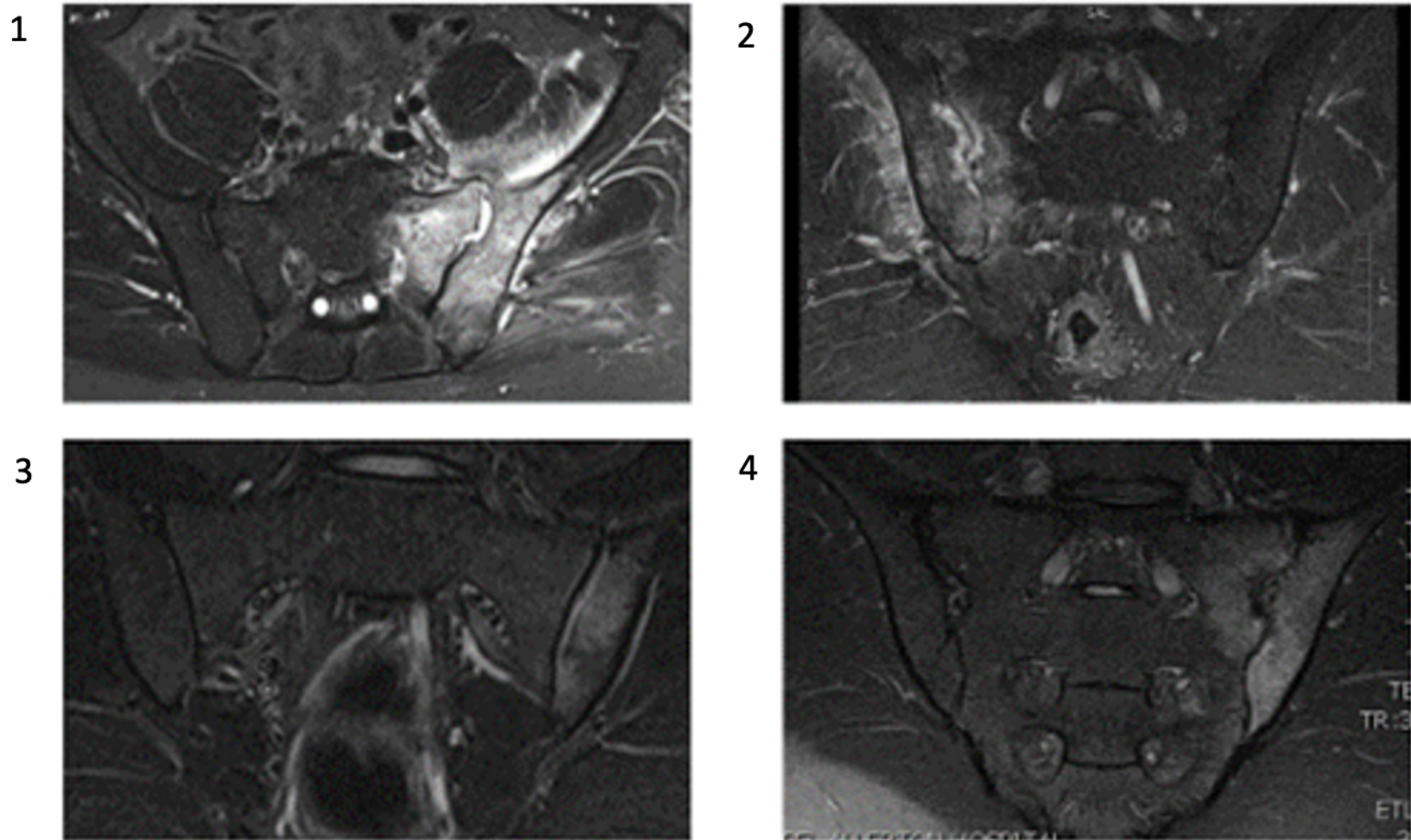


Figure 4:1 Coronal oblique MRI (STIR) examination of the sacroiliac joints in all four patients. Images labelled by corresponding case number. STIR: short-tau inversion recovery (Dubash et al., 2018)

Table 4:1 Clinical characteristics of four HLA-B27 negative subjects presenting with acute unilateral sacroiliitis

	Case 1	Case 2	Case 3	Case 4
Age (years)	19	41	19	19
Sex (M/F)	M	M	M	M
Symptom onset to presentation (days)	7	30	11	2
Symptom onset to MRI (days)	35	14	12	7
Extra-articular features (IBD, PsO)	N	IBD (UC)	Scalp PsO	N
Fever	Y	N	N	Y (38 ⁰ C inpatient)
CRP mg/L	83	15	100	262
ESR (mm/hr)	90	65	-	-
Infection screen and other workup	WBC N Chlamydia antigen -ve	WBC N (7.1) Empirical antibiotic given for one month.	WBC N BC negative Urine M,C&S -ve Procalcitonin -ve ASOT-ve HBV-ve No GU/GI symptoms	WBC 15.6 (Neut 12.4) BC -ve x3 Urine M,C&S -ve TTE: no vegetation's Chlamydia/ gonorrhoea swabs negative ASOT borderline Throat swab: Group. A <i>Strep.</i> Infectious mononucleosis (Paul-Bunell) test -ve, serology for EBV, CMV, measles, HIV were all -ve

	Case 1	Case 2	Case 3	Case 4
NSAIDs	Naproxen 500mg bd, (Diclofenac 75mg bd for initial 2 weeks)	Etoricoxib 90mg od	Ibuprofen 400mg tds	Etoricoxib 120mg od
Initial pain response from NSAID (days)	14	5	1	7
Initiation of NSAID to complete resolution of symptoms* (weeks)	4	4	4	8
Symptom onset to complete resolution (weeks)	8	8	4	8

*Complete resolution of symptoms (i.e. disappearance of symptoms); GU: genitourinary; GI: gastrointestinal; WBC: white blood cells; BC: blood cultures; MC&S: microscopy culture and sensitivity; TTE: transthoracic echocardiogram; ASOT: anti-streptolysin O titre; EBV: Epstein-Barr virus; CMV: cytomegalovirus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; od: once daily; bd: twice daily; tds: 3 times daily.

4.2.5 Discussion

Sacroiliitis typifies SpA, representing enthesitis (inflammation of the fibrocartilage insertion into bone) and osteitis (bone inflammation/ BMO on MRI), yet can also occur in sepsis where diffuse soft tissue and periarticular muscle oedema is characteristic (Slobodin et al., 2016). The symptom onset in SpA may be acute and can include fever and raised CRP, therefore mimicking infection. Bilateral sacroiliitis is invariably inflammatory, however, an acute unilateral presentation is described in the medical literature as pyogenic or suspicious for atypical organisms (Slobodin et al., 2016). This case series demonstrates that acute unilateral sacroiliitis with “extreme” MRI appearances, particularly extensive sacroiliac BMO and adjacent periarticular muscle and/or soft tissue oedema, despite resembling infection, can represent a reactive process suggestive of an inflammatory SpA. This case series illustrates the diagnostic challenge of differentiating infection versus inflammation. This is particularly important given that such patients typically present acutely via urgent appointments or the emergency department as per cases 3 and 4 where hospitalisation was required. All four patients demonstrated a good response to NSAIDs. Although the dose and duration of NSAIDs needed to alter BMO is unclear, these data support previous reports in the literature (Varkas et al., 2016). It is acknowledged that the effect of NSAIDs cannot be quantitatively measured from these series particularly as post-inflammatory changes were still visible in two patients after five weeks. Remarkably, however, all patients became symptom free within eight weeks. Acute unilateral sacroiliitis can represent a manifestation of a reactive arthritis (ReA) (Oates and Young, 1959; Timo Hannu et al., 2004). It was noted that during a *Campylobacter jejuni* outbreak, out of fifteen cases of ReA, one presented with sacroiliitis (Timo Hannu et al., 2004). Sacroiliitis may also occur rarely as a manifestation of post-streptococcal reactive arthritis (PSRA) (Mackie and Keat, 2004). This condition presents with self-reported sore throat symptoms and there is frequently presentation with asymmetrical migratory polyarthritis that may be associated with extra-articular manifestations such as uveitis, similarly also associated with SpA/ReA, or erythema nodosum or glomerulonephritis which may differentiate PRSA from SpA/ReA (Mackie and Keat, 2004; Bawazir et al., 2020). Interestingly, pseudo-sepsis has been observed in psoriasis, palmo-plantar pustulosis, acne, and the synovitis acne pustulosis hyperostosis osteitis

(SAPHO) syndrome, however it is an unusual cause for de novo acute unilateral sacroiliitis (Inman, 2006). The severity of sacroiliitis at presentation regardless of HLA-B27 status, has been shown to be a predictor of poor prognosis for radiographic progression, but little is known for acute reactive arthritis specifically (Hannu et al., 2006). When managing such patients, it is essential not to overlook infectious sacroiliitis typified on MRI by periarticular muscle oedema, despite the cases described which demonstrate that inflammatory disease can mimic such appearances (Kang et al., 2015). While these cases fit within the spectrum of SpA, they could not be classified according to the ASAS classification criteria given the acute onset of symptoms of less than 3 months duration (van der Heijde et al., 2017). Limitations of this research include its case series design, few subjects included, and possible case selection bias. Nevertheless the observations made from these detailed case series may help to focus future research into this poorly understood area.

In line with the aims of this study, the presence of severe unilateral sacroiliitis confirmed that enthesitis and osteitis were significant features of disease initiation and progression to soft tissue and periarticular muscle oedema reflected the severity of the lesions.

4.2.6 Conclusion

In conclusion, this case series indicates that significant reactive inflammatory sacroiliitis can yield MRI appearances mimicking infection. A thorough investigation should always be prioritised, but following exclusion of infective aetiologies, NSAIDs alone can be effective in resolving symptoms over several weeks with subsequent patient recovery.

4.3 Emergence of severe spondyloarthropathy related enthesal pathology following successful vedolizumab therapy for inflammatory bowel disease

4.3.1 Introduction

The Spondyloarthritides (SpA) represent the most common extra-intestinal manifestation of inflammatory bowel disease (IBD) being present in approximately 30% of patients (Salvarani et al., 2001). Equally, subclinical IBD is present in the region of 50-60% of patients with axial SpA (Ciccia et al., 2016). Indeed, both IBD and SpA share common overlaps in terms of immunopathogenesis, clinical and therapeutic features (Wright, 1978). IBD and SpA both show good responses to anti-tumour necrosis factor inhibitor (TNF) therapy. However, etanercept, a soluble receptor fusion protein anti-TNF, and anti-IL-17 blockers, are efficacious in SpA but ineffective in IBD and are even associated with de novo IBD development (O'Toole et al., 2016). Vedolizumab (VDZ), a humanized IgG1 monoclonal antibody that inhibits $\alpha 4\beta 7$ integrin, has been approved for the treatment of IBD and works through the selective blocking of lymphocytes homing to the gut. A paradoxical reaction has been observed with VDZ for IBD, notably in cases of ameliorated IBD disease activity, where individuals experienced predominantly mild flares of inflammatory spinal disease, and continued VDZ thereafter (Varkas et al., 2017; Wendling et al., 2017). This chapter of the thesis characterises a series of VDZ treated patients that developed a new diagnosis of de novo severe SpA including severe enthesitis/osteitis, that resulted in VDZ treatment discontinuation, substitute biologic or additional therapy.

4.3.2 Hypothesis, aims and objectives

Hypothesis:

Enthesitis is a significant pathological event in early, new onset SpA and may be a biomarker for disease evolution.

Aims and objectives:

To explore the pathogenic relationship between severe spondyloarthropathy related enthesal pathology at the axial and peripheral skeleton in different SpA phenotypes following acute inflammatory and infective events.

4.3.3 Methods**Study design:**

A multi-centre case series evaluation was conducted.

Research methods:

The initial presentation of an index case with severe SpA-related enthesal pathology at LTHT prompted communication with other centres globally to identify other cases of such in order to determine whether new or existing severe SpA diagnoses had presented following VDZ treated IBD. Clinical, biochemical and imaging characteristics within case records were identified as part of a clinical evaluation. Information was collected at baseline and up to 6 months where available via a specifically designed proforma to obtain key characteristics about the development of disease including onset and phenotype. Written consent was obtained from all patients. Research ethics approval was not required given that patients had already been managed as part of routine standard practice and were identified for evaluation retrospectively. Depending on the site of maximal disease severity patients underwent either vendor specific fat suppression or short tau inversion recovery (STIR) sequence performed with MRI and/or musculoskeletal ultrasound of affected entheses at their host institutions as part of their medical investigation. This research encompassed patients assessed in a total of seven different institutions.

4.3.4 Results

Data was collected from a total of 11 patients (5 male, 6 female) with IBD, all treated with VDZ and with development of severe SpA or Enthesitis features. There were 9 patients who developed de novo SpA and only 2 patients who developed a flare of known SpA which was quiescent at the time of therapy

initiation. The mean age of onset was 42.5 years (SD 13.7 years). The median time from VDZ initiation to flare was 12 weeks (IQR 7-20 weeks), with IBD disease activity well controlled in 7 of 10 patients (no data for 1 patient). Available data showed that only 1/7 patients (no data in 4 patients) were HLA-B27 positive. Psoriasis was present in 4/11 patients and 2/9 patients were smokers (no data in 2 patients). The majority of patients (n=9) had previously failed treatment with tumour necrosis factor inhibitors (TNFi) for IBD. Severe SpA enthesitis/ osteitis was evident on MRI or US, including acute sacroiliitis (n= 5), extensive vertebral osteitis (n= 1), peri-facetial oedema (n=1) and isolated peripheral enthesitis (n= 3). Due to arthritis severity, VDZ was discontinued in 9 patients and changes to therapy were instigated, including alternative TNFi.

Due to the severity of SpA or enthesal disease 4 patients were hospitalised and were investigated for suspected sepsis initially prior to confirmation of SpA/ enthesopathy. For example, patient 1 presented with intense back pain and an initial low grade fever mimicking sepsis that was subsequently excluded after an extensive infection screen and blood cultures following a 3-week period of hospitalisation. The clinical SpA phenotypes identified were axial SpA (8/11), peripheral SpA (8/11), both axial and peripheral SpA involvement in (5/11), and ultrasound or MRI positive peripheral enthesitis in 3/11 (Table 4:2 and Table 4:3). All patients fulfilled either the axial (6/11) or peripheral (7/11) assessment of spondyloarthritis international society (ASAS) classification criteria. Of the 7 peripheral SpA patients, axial involvement was also present in 5. ASAS axial criteria was not met in 4 cases due to disease of too short duration, disease onset above 45 years of age, axial disease not involving the sacroiliac joints, and HLA-B27 negative status. Serum C-reactive protein (CRP) was raised in 9/11 patients with a median value of 33 mg/L. The baseline characteristics are summarised in Table 4:4.

Acute bilateral sacroiliitis determined by MRI was demonstrated in 5 patients, one of whom also showed evidence of radiographic bilateral grade 2 sacroiliitis suggesting previous indolent undiagnosed SpA. Patient 4 developed new-onset SpA with extensive spinal vertebral body and end-plate oedema at T6-11 on MRI (STIR) and inflammatory Romanus lesions (IRLs) at T12, L3, and L4 vertebral bodies (Figure 4:2, images A and B). Extreme spinal peri-facetial oedema was identified on MRI (STIR) in patient 1 (image C), and marked Achilles tendinitis with power Doppler signal and retrocalcaneal bursitis in patient 8 (image D).

Disease activity in IBD was well controlled or low in 7 of 10 VDZ treated patients during SpA onset or flare, and active in only 3 of 10 patients (no data 1 patient). Vedolizumab was discontinued in 9 patients: 8 patients switched to alternative therapies including golimumab, adalimumab, certolizumab pegol, sulphasalazine, ustekinumab, bilateral sacroiliac joint injections, and one patient was given compassionate treatment with tofacitinib and zoledronate for enthesitis having failed prior anti-TNF. Only 2 patients continued VDZ, one combined with oral corticosteroid and methotrexate (having trialled apremilast and stopped due to symptoms of depression) and the other in combination with etanercept. The corresponding outcomes per patient are summarised in Table 4:5.

Table 4:2. Detailed baseline characteristics of severe SpA or enthesitis including patient outcomes (patient number 1-5)

Patient number	1	2	3	4	5
Age, M/F	28, M	48, M	33, F	50, M	35, F
Hospitalised	Y	N	N	N	Y
Vedolizumab exposure (weeks)	14	20	20	6	8
Pre-existing SpA	Y	N	N	N	N
axSpA	Y	Y	Y	Y	Y
perSpA	Y	Y	N	N	N
Osteitis or Enthesitis	+++	++	++	+++	NA
MRI/USS (imaging feature)	<u>MRI</u> : Extreme Peri-facetal spinal vertebral oedema	<u>MRI</u> : Bilateral sacroiliitis	<u>MRI</u> : Bilateral sacroiliitis	<u>MRI</u> : Extensive severe thoracolumbar vertebral oedema/ osteitis and IRLs	<u>MRI</u> -ve, nr-axSpA
HLA-B27	N	NA	NA	N	Y
Smoker (cpd)	15	NA	NA	25	N
EAMs (Uveitis, PsO)	N	N	PsO	N	PsO
IBD type/ activity	CD/ Low/ controlled	IC/ Low/ controlled	CD/NA	CD/ Active (high)	UC/ Low/ controlled
CRP at flare (mg/l)	216	<5	<5	24	24
Concomitant DMARD	MTX 15mg o.w	AZA 150mg o.d	Pred 0.5mg o.d	None	None

Patient number	1	2	3	4	5
TNFi failure	Y	Y	Y	Y	Y
Previous TNFi /DMARDs	IFX ADM CZP	ADM IFX	AZA IFX ADM	IFX ADM	MSZ CYSP IFX ADM
Vedolizumab discontinued	Y	Y	Y	Y	Y
Treatment change	GLM	Patient declined treatment for SpA.	Bilateral sacroiliac joint injection and switched to UST	CZP	CZP: intolerance. SZP: intolerance. Switched to GLM.
Outcome	Moderate IBD and SpA activity at 6 months, CRP 58 BASDAI 6.9 (previous 8.8)	IBD in remission at 6 months (colonoscopy normal) SpA outcomes: NA	NA	IBD: controlled SpA: mild to moderate activity at 6 months, CRP 19	IBD in remission. SpA activity is moderate at 6 months.

Table 4:3. Detailed baseline characteristics of severe SpA or enthesitis including patient outcomes (patient number 6-11)

Patient number	6	7	8	9	10	11
Age, M/F	40, F	21, F	52, M	45, F	44, F	72, M
Hospitalised	Y	N	N	Y	N	N
Vedolizumab exposure (weeks)	10	5	12	4	52	20
Pre-existing SpA	N	N	N	Y	N	N
axSpA	N	Y	N	Y	Y	N
perSpA	Y	Y	Y	Y	Y	Y
Osteitis or Enthesitis	++	++	+++	+++	+++	+++
MRI/USS (imaging feature)	<u>MRI:</u> Enthesitis/peri ostitis distal tibio-fibular	<u>MRI:</u> Right sided sacroiliitis (also XR +ve, fulfilling mNY criteria)	<u>USS:</u> Marked Achilles enthesitis PD +ve	<u>MRI:</u> Bilateral sacroiliitis	<u>MRI:</u> Bilateral sacroiliitis <u>USS:</u> Knee synovitis, hand flexor tenosynovitis, PD +ve	<u>USS:</u> elbow, knee and wrist synovitis, common extensor enthesitis.
HLA-B27	NA	N	N	N	N	NA
Smoker (cpd)	N	N	N	N	N	N
EAMs (Uveitis, PsO)	N	N	N	PsO	N	PsO
IBD type/ activity	UC/ Low/ controlled	IC/ Low/ controlled	CD/ Active (moderate)	UC/ Low/ controlled	CD/Active (high)	UC/ Low/ controlled
CRP at flare (mg/l)	28	55	68	33	80	88
Concomitant DMARD	Pred 4mg o.d	None	None	MTX 7.5mg o.w	No	Pred 15mg o.d
TNFi failure	Y	Y	N	Y	Y	N

Patient number	6	7	8	9	10	11
Previous TNFi /DMARDs	6-MP AZA ADM	IFX	6-MP, AZA	IFX Secukinumab ADM	IFX CZP GLM	None
Vedolizumab discontinued	Y	Y	Y	N	N	Y
Treatment change	TOFA+ ZOL	ADM	ADM+Pred	VDZ +Pred 10mg o.d (+ Apremilast; developed significant depression, switched back to MTX 7.5mg o.w)	ETN+ VDZ	ADM
Outcome	Periostitis and enthesitis resolved at 6 months.	Mild axSpA. Skin and perSpA in remission at 1 month.	Achilles enthesitis much improved. Moderate CD activity at 1 month	IBD/ SpA /Skin PsO all well controlled at 6 months.	IBD and SpA in drug-controlled remission at 6 months.	NA

Y: yes; N: no; NA: not available; cpd: cigarettes per day; EAMs :extra-articular manifestations; o.d: once daily; o.w: once weekly; osteitis or enthesitis: +mild, ++moderate, +++severe, IC: intermediate colitis; XR: X-ray; ADM: adalimumab; CZP: certolizumab pegol; CYSP: cyclosporine; GLM: golimumab; IFX: infliximab; MSZ: mesalazine; MTX: methotrexate; Pred :prednisolone; TOFA: tofacitinib; UST: ustekinumab; VDZ: vedolizumab; ZOL: zolendronate.

Table 4:4. Aggregate baseline characteristics in severe SpA or enthesitis

	Total: n=11 patients
M:F	5:6
Age; mean \pm SD (years)	42.5 \pm 13.7
VDZ exposure; median (IQR)	12 weeks (7-20)
Hospitalised	4/11 patients (36.4%)
De novo SpA: known SpA	9:2
Psoriasis	4/11 patients (36.4%)
HLA B27 +ve	1/7 (no data in 4)
Smoker	2/9 (no data in 2)
IBD type	CD 5/11, UC 4/11, IC 2/11
IBD disease activity	Controlled 7/10, active 3/10, no data 1
ASAS peripheral criteria	8/11 (72.7%)
ASAS axial criteria	8/11 (72.7%)
Both criteria fulfilled	5/11 (45.4%)
CRP; median (IQR) mg/L	33 (24-77) [CRP elevated in 9/11 patients; mean 56.7 (SD 60.1)]
Previous TNFi failure	9/11 (81.8%)

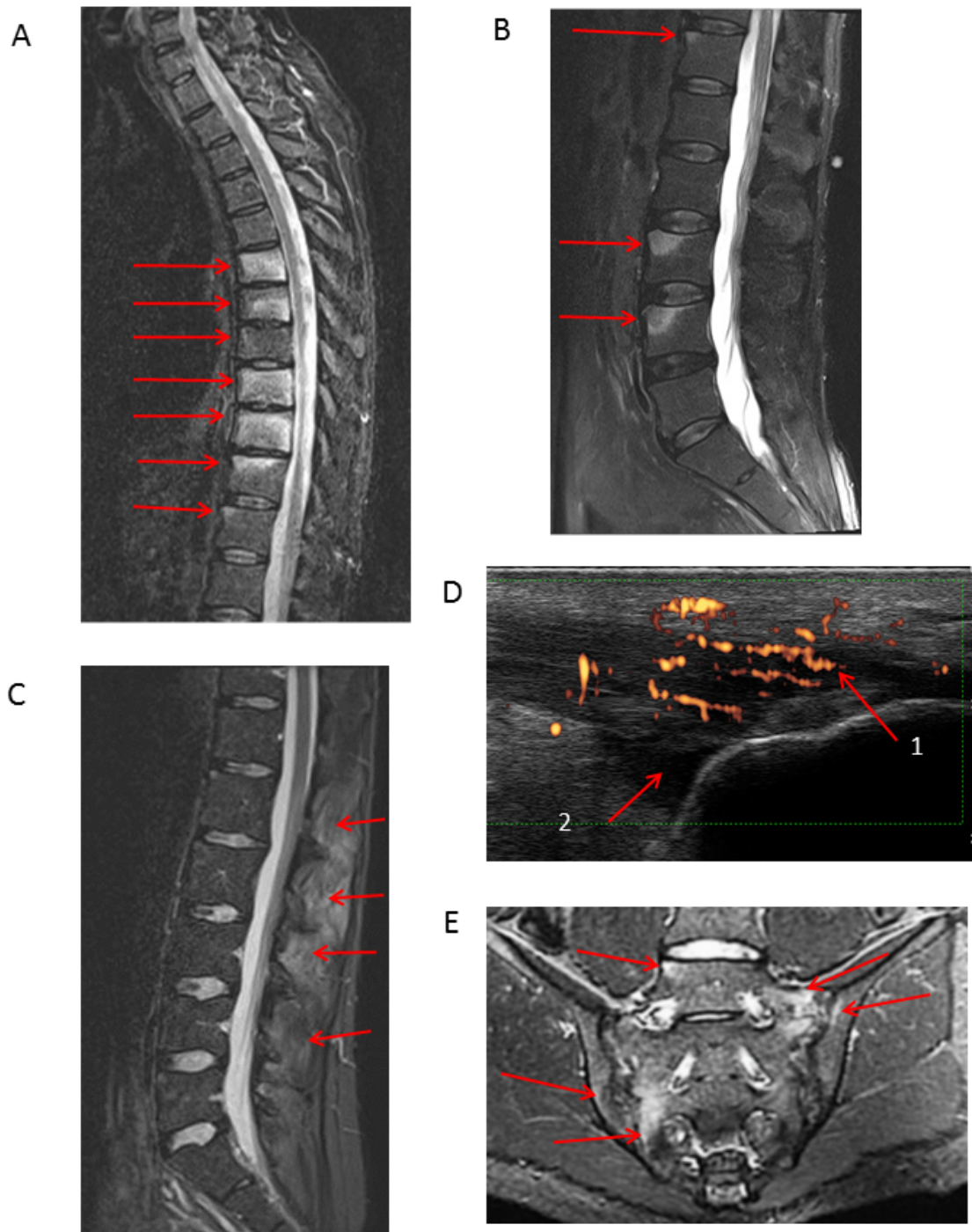


Figure 4:2 Observed MRI and ultrasound imaging appearances of severe SpA related enthesal pathology

Images adapted (Dubash et al., 2019)

Figure 4:2 (legend)

Images A and B (patient 4): MRI sagittal STIR images showing extreme multilevel thoracolumbar osteitis with severe high signal vertebral body and endplate changes from T6-11 including large inflammatory Romanus lesions at T12, L3, L4 vertebrae.

Image C (patient 1): MRI sagittal STIR images of severe peri-facetial oedema extending into adjacent para-lumbar tissue as indicated by the relevant arrows.

Image D (patient 8): Achilles tendon enthesitis, demonstrated on ultrasound (longitudinal plane) with increased tendon thickness, hypoechogenicity, loss of the tendon fibrillar pattern and increased power Doppler signal indicating hypervascularity from inflammation at the tendon enthesis insertion into the calcaneum (1) and retrocalcaneal bursitis (2).

Image E (patient 10): Severe bilateral sacroiliitis with BMO (high signal) predominantly at the sacral side of the joint (Leeds grade 3) and also IRL at the region of anterior L5 corner demonstrating osteitis.

Table 4:5. Summary of aggregate outcomes in severe SpA or enthesitis

VDZ/TNFi treatment changes:	No. of Patients (n=11)
VDZ discontinued	9
Alternative TNFi treatment	7
VDZ +TNFi combined	1
Tofacitinib + Zolendronate	1
No treatment (declined)	1
Bilateral sacroiliac joint injections	1
IBD/SpA outcomes (1-6 month follow up):	
IBD – controlled	5/7 (no data 4)
IBD – active	2/7 (no data 4)
SpA activity - controlled/ low	5/8 (no data 3)
SpA activity – moderate /high	3/8 (no data 3)

4.3.5 Discussion

Herein, this report describes severe, mostly de novo SpA development which occurred in 9/11 (82%) cases post-VDZ treatment. Such was the severity of SpA that 80% of patients required VDZ treatment discontinuation despite predominantly successful gut responses for IBD. This current series demonstrates more aggressive disease including severe enthesitis/osteitis compared with the two previous studies that reported milder disease and therapy continuation (Varkas et al., 2017; Wendling et al., 2017). The severity of this current case series is established by a high CRP at presentation in 9 out of 11 patients, grade 2-3 MRI-determined bone marrow oedema lesions on axial imaging demonstrated in 6 patients, severe enthesitis lesions displayed by MRI or ultrasound imaging (Figure 4:2, D) in 3 patients, and hospitalisation of 4 patients. These patients were also predominantly HLA-B27 negative, which is not unusual for IBD, but atypical for AS, and previous anti-TNF failures which might suggest a phenotype of treatment-resistant IBD. Although 5 of 7 patients responded well to TNFi retreatment at 6 months, some cautiousness about possible secondary non-response should be considered given the history of prior TNFi treatment failure. Conversely, prior treatment resistance may be drug specific rather than a complete class effect, given that these patients mostly failed infliximab and adalimumab but responded to other TNFi drugs. One intriguing aspect of this series is that these VDZ treated cases were at the highest severity for SpA flares and possibly more severe than flares linked to “conventional” IBD associated SpA -the latter of which are linked to gut activity in peripheral SpA (Brakenhoff et al., 2010).

In the previous two reports, the first case series included 5 subjects with new SpA, 3 axial and 2 peripheral SpA, in patients with IBD following VDZ, and 4/5 cases with controlled gut activity (Varkas et al., 2017). In the second study, there were 4 patients with CD, 3 with new axSpA and pSpA, 1 with enthesitis, and 1 pSpA reactivation despite controlled gut activity in 2/4 cases (Wendling et al., 2017). The former study reported only 1/5 patients as having severe sacroiliitis and 1/5 with severe tenosynovitis, and generally milder disease in the remaining patients. These cases, particularly the latter study, seem comparatively mild in severity given only one had positive axial disease features (sacroiliitis) defined by MRI imaging, another with only inflammatory polyarthralgia, and one case of

exacerbation of pre-existing polyarthralgia without reported imaging evidence of synovitis (Wendling et al., 2017). However, all these reported patients demonstrated either active imaging defined disease, elevated CRP, or both in line with marked disease severity.

Efficacious gut responses were observed in 7/10 (no data in 1/11) cases, a predominant axial phenotype (8/10), and in line with the trend in the severe aforementioned case series, HLA-B27 negativity (6/7, no data in 4/11). The distinguishing phenotypical features compared to this reported case series in comparison were the severity of disease encountered including extensive multilevel thoracolumbar osteitis, extreme peri-facetial oedema on MRI and elevated CRP levels. The previous reports were milder overall, and the calibre of axial disease demonstrated by MRI appeared to be mild to moderate for sacroiliitis in three cases in the first series with only one MRI positive axial case in the second case series (Varkas et al., 2017; Wendling et al., 2017). Severity grading for MRI did not feature in the reports of the two prior studies, although ultrasound evidence of a wrist effusion and severe tenosynovitis was described in one case supporting the pattern of severe enthesopathy and peripheral SpA. Hospitalisation was warranted in 4 of our cases in comparison to the prior reports, which significantly highlights the symptom severity and associated acute disease impact and disability.

Interestingly, in common with the second series, most of our cases had failed anti-TNF, but in the former series 4/5 subjects were anti-TNF naïve (Varkas et al., 2017). This variation suggests that the induced SpA is independent of previous anti-TNF use and therefore not linked to lag effect from cessation of anti-TNF. Crucially, unlike the other reports, VDZ therapy needed to be discontinued in most (n=9) of our cases due to SpA severity and alternative therapy was initiated. It remains to be determined whether TNFi failure in some way represents a predisposition to a more severe musculoskeletal pathology.

Given that 9/11 (81.8%) patients were TNFi failures, it could be argued that discontinuing anti-TNF therapy may have played a role in unmasking and facilitating SpA, albeit the absence of TNF inhibition no longer inactivating subclinical or undetected SpA, and therefore, increasing the susceptibility of SpA development or flare. The expectation would be to flare soon after anti-TNF discontinuation, but instead the temporal relationship observed between VDZ initiation and SpA development or flare, median duration of 12 weeks, may be

more suggestive of a mechanistic link between blockade of $\alpha 4\beta 7$ and the induction or facilitation of SpA or enthesitis. In comparison with other reported case series where the mean time to flare was less, approximately 9 weeks, slightly longer duration to flare might also contribute to the severity of these cases. Nonetheless, the effects of TNFi discontinuation may be linked with the SpA flares through possible previous suppression of underlying clinically unrecognised SpA pathology. Another limitation of this study is the lack of accurate data on the incidence of VDZ induced SpA which would require large observational cohort studies. Although the existing data is currently limited, some cohort studies suggest VDZ may be effective for extra-intestinal manifestations including arthritis (Tadbiri et al., 2017; Orlando et al., 2017). However, an analysis of data from 6 clinical trials of vedolizumab in IBD did not report on significant SpA disease onset or flares (Colombel et al., 2017). Arthralgia was recorded in adverse event reporting in phase 3 studies for UC and CD and there was no difference between VDZ treated subjects in comparison to placebo with arthralgia present in 13.5% of the vedolizumab treated group compared with 13.3% for placebo in CD, and 9% *versus* 9.1% respectively in UC (Feagan et al., 2013; Sandborn et al., 2013).

Inhibition of $\alpha 4\beta 7$ integrin mechanistically prevents lymphocyte homing and subsequent inflammatory cascade amplification at the intestinal level but may not restore underlying or primary abnormal gut permeability. It is noteworthy that over half of SpA cases have subclinical gut inflammation with an abnormal intestinal barrier function (Brakenhoff et al., 2010). Such a scenario would permit bacterial antigens, cytokine, adjuvant, and pathogen-associated molecular pattern molecules (PAMPs) access to the systemic circulation and deposition at regions of enthesal tissue within the human skeleton. T-lymphocytes that express $\alpha 4\beta 7$ integrin bind to specific adhesion molecules for their transportation into regions of intestinal tissue. Mucosal vascular addressin cell adhesion molecule-1 (MADCAM-1) is exclusive to gut mucosal tissue and is important for the adhesion and facilitation of migration of $\alpha 4\beta 7$ integrin expressing lymphocytes from the circulating blood vessels to the intestine. MADCAM-1 and vascular cell adhesion molecule-1 (VCAM-1) bind to $\alpha 4\beta 7$ integrin and behave as a ligand by permitting the interception of $\alpha 4\beta 7$ integrin expressing T-lymphocytes (CD4+ or CD8+) and their distribution into mucosal or vascular tissue respectively. The likely non-dependence of enthesal and joint tissue on $\alpha 4\beta 7$ -MADCAM-1/

VCAM-1 interaction would not hinder adaptive T cell responses at those locations and propose an explanation for these severe SpA/enthesitis paradoxical reactions (Figure 4:3 In essence, compartmentalisation of both innate and adaptive immune mechanisms between the gut-enthesis/bone axis may also account for these differential therapy responses.

Some limitations of this research include the case series design, selection bias of cases, and absence of total denominators for number of VDZ treated cases. Further data from another case series demonstrated agreement with the findings from these current data, indicating that vedolizumab (VDZ) can induce SpA or enthesitis associated pathology (Alivernini et al., 2019). In this case series the prevalence of this manifestation accounted to a total of nearly 5% of cases which is higher than the previous reported SpA prevalence in other VDZ treated IBD cohorts (Paccou et al., 2018). This is surprisingly high given that this complication was completely unreported in the large phase 3 studies of vedolizumab in IBD. These cases fulfilled ASAS criteria in all 8 patients, were HLA-B27 negative, and similarly all failed at least one previous TNFi, and had well controlled IBD (S Dubash et al., 2019). In comparison, the disease severity of patients in that series appeared lower with a median CRP of 15.9 compared to much higher CRP values observed in this current case series; median 33 mg/L (24-77).

In another study of VDZ associated SpA, synovial biopsy was conducted in two cases of knee synovitis showing synovial infiltration with CD68+, CD138+, and CD20+ macrophages indicating B cell lineage and CD3+ cells, a pan-T-cell marker. While it is known that macrophages are linked to the destruction of synovial tissue through the T-cell mediated release of pro-inflammatory cytokines (Tak and Bresnihan, 2000). This series did not report on VDZ relevant protein expression including anti- $\alpha 4\beta 7$ integrin or MADCAM-1, its corresponding receptor but suggest literature that reported such $\alpha 4\beta 7$ expression from synovial lymphocytes previously in SpA (Ciccia et al., 2015). However, prior studies failed to demonstrate MADCAM-1 expression in inflammatory synovitis (Salmi et al., 1997). Salmi et al previously reported on adhesion molecules on HEVs in inflamed synovium identifying that intercellular adhesion molecule-1 (ICAM-1/CD54) plus vascular adhesion protein-1 (VAP-1) were prominently expressed within synovial high endothelial venules (HEVs), with all the other adhesion molecules present at much lower levels and complete absence of mucosal addressin (MADCAM-1) (Salmi et al., 1997). Studies have suggested that $\alpha 4\beta 7$

on lymphocytes binds to VCAM-1 preferentially at the $\alpha 4$ subunit and is linked to chronic established synovitis whereas ICAM-1, which is overexpressed in tissue from early synovitis, is pivotal in activation and cell binding into inflamed synovial tissue (Salmi and Jalkanen, 2001; Riccieri et al., 2002).

Reports of adherence of immunoblasts (activated lymphocytes) to HEVs in rheumatoid arthritis (RA) synovium showed only partial inhibition by monoclonal antibody (mAb) to $\alpha 4\beta 1$ (25%) and very little inhibition (5%) by mAb to $\alpha 4\beta 7$ which suggests no functional significance of $\alpha 4\beta 7$ in RA synovitis (Mojcik and Shevach, 1997). And the rate of lymphocyte migration into synovium in RA was shown to be determined by expression of ICAM-1 on HEVs (Lowin and Straub, 2011). In contrast to the specificity of MADCAM-1, selectively present in gut mucosal lymphoid organ HEVs, the role of ICAM-1 and VAP-1 in synovial HEVs are more likely to contribute to the influx of circulating immune cells during blockade of $\alpha 4\beta 7$. However, possible differences in adhesion molecule pathways between SpA and RA synovitis could exist (Elewaut et al., 1998). Therefore synovial tissue staining for these relevant adhesion molecules and ligands in synovial biopsy samples of VDZ induced severe SpA may further add to research knowledge in this field.

Definitive data on the presence of adhesion molecules at the spinal and peripheral joint entheses is lacking, yet increased $\alpha 4\beta 7$ expressing type 3 innate lymphoid cells (ILC3s) were described in a small study in the gut and non-enthesal iliac crest bone marrow of patients with ankylosing spondylitis (AS) (Ciccia et al., 2015). The same study reported MADCAM-1 in iliac crest bone marrow aspirates from a small number of patients where the immunohistochemistry staining showed arguably non-specific or stromal staining in addition to marrow venule staining (Ciccia et al., 2015).

Interestingly, just as there were no reports of arthritis in clinical trials for VDZ in IBD, neither have there been any reports of arthritis with natalizumab (NTZ), a humanised monoclonal antibody that binds $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin, which was trialled successfully in Crohn's disease (CD) and multiple sclerosis (MS), but increased reports of progressive multifocal leukoencephalopathy, have posed a limitation (Targan et al., 2007). The synovial blockade of the lymphocyte $\alpha 4\beta 1$ -synovial VCAM-1 interaction may be expected to lessen this development of paradoxical arthropathy, since unlike MADCAM-1, VCAM-1 synovial expression

has been confirmed and NTZ would seemingly block $\alpha 4\beta 1/\alpha 4\beta 7$ driven – VCAM-1 interaction (Figure 4:4). Any cohort data on natalizumab may shed light to address this topic since $\alpha 4\beta 1$ and its receptor would be expressed in the synovium. Natalizumab therapy in one patient with both AS and multiple sclerosis was reported suggesting $\alpha 4\beta 1$ and $\alpha 4\beta 7$ blockade may be effective for co-treatment of both diseases (Ciccia, Rizzo, Guggino, et al., 2016). However, the evidence for synovitis is supportive toward an underlying MADCAM-1 independent process for lymphocyte infiltration into the synovium via other mechanisms including an inflammatory effect from adjacent entheses. Ultimately, the underlying complex pathogenic link between IBD and SpA in the context of VDZ associated SpA is not yet fully understood and this research will inform future studies to confirm such mechanisms (Dubash et al., 2019).

4.3.6 Conclusion

Following VDZ therapy, a predominant pattern was observed with clinically quiescent IBD associated with severe SpA and/or enthesitis in mostly HLA-B27 negative individuals. The severity of the event led to VDZ discontinuation. There have been some reports of continuation of VDZ combined with an anti-TNF or ustekinumab, but these reports were in patients with refractory IBD in the face of a milder SpA, and more comprehensive safety and efficacy data will be required with such combined biologic approaches (Bethge et al., 2017; Roblin et al., 2017; Liu and Loomes, 2017). As the increasing use of $\alpha 4\beta 7$ blockade is anticipated, awareness of this paradoxical reaction and specific phenotype amongst rheumatologists and gastroenterologists alike, can facilitate shared management decisions for effective treatment of IBD and VDZ associated SpA or enthesitis.

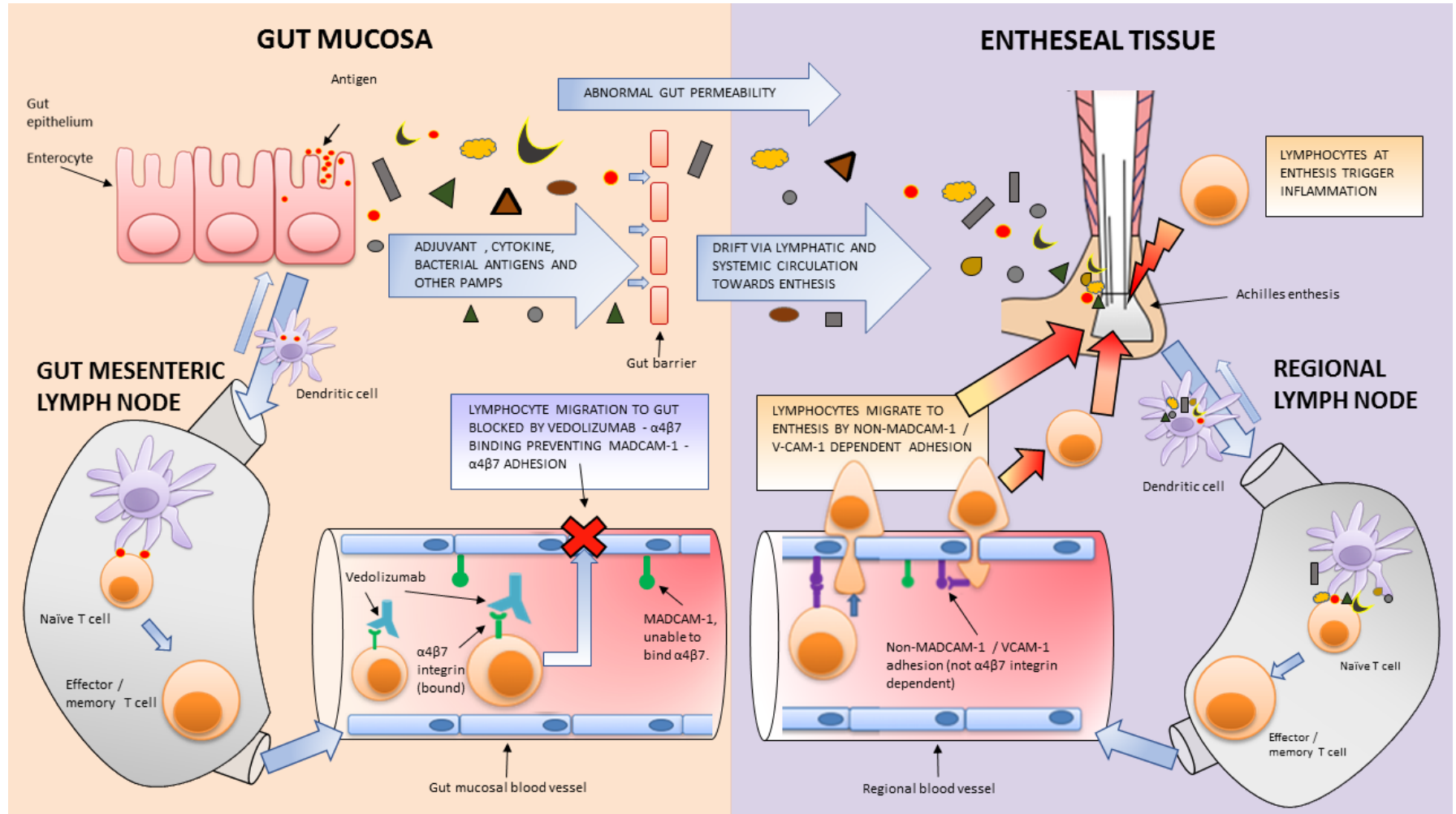


Figure 4:3 A proposed model to explain new onset severe SpA occurring with successful VDZ therapy for IBD (Dubash et al., 2019)

Figure 4:3 (legend)

Subclinical gut inflammation is a hallmark of SpA and is connected to the magnitude of MRI determined spinal osteitis. Successful therapy with vedolizumab can alleviate symptoms but would be unlikely to restore intrinsic barrier dysfunction which has been demonstrated genetically and experimentally in IBD. Such a scenario permits systemic translocation of adjuvant, cytokines, other bacterial PAMPs and antigens to the systemic circulation including to entheses and bone. These components contribute to innate immune activation via biomechanical stressing and interactions with tissue resident myeloid and innate immune cells. Dendritic cell migration from the entheses to the regional lymph nodes then prime and expand T cells which subsequently home to the entheses in a non-MADCAM-1 dependent fashion. It remains to be determined whether $\alpha 4\beta 7$ reactive lymphocytes locate to entheses by virtue of being trapped outside the gut compartment and then gain access to enthesal tissue via one of several adhesion molecules activated at sites of inflammation. The inadvertent deposition of gut-derived antigens at entheses and the inappropriate homing of these cells may explain these severe paradoxical inflammatory arthropathies in successfully treated IBD. Finally, prior TNFi therapy cessation might contribute to the timing of such VDZ induced disease or flare.

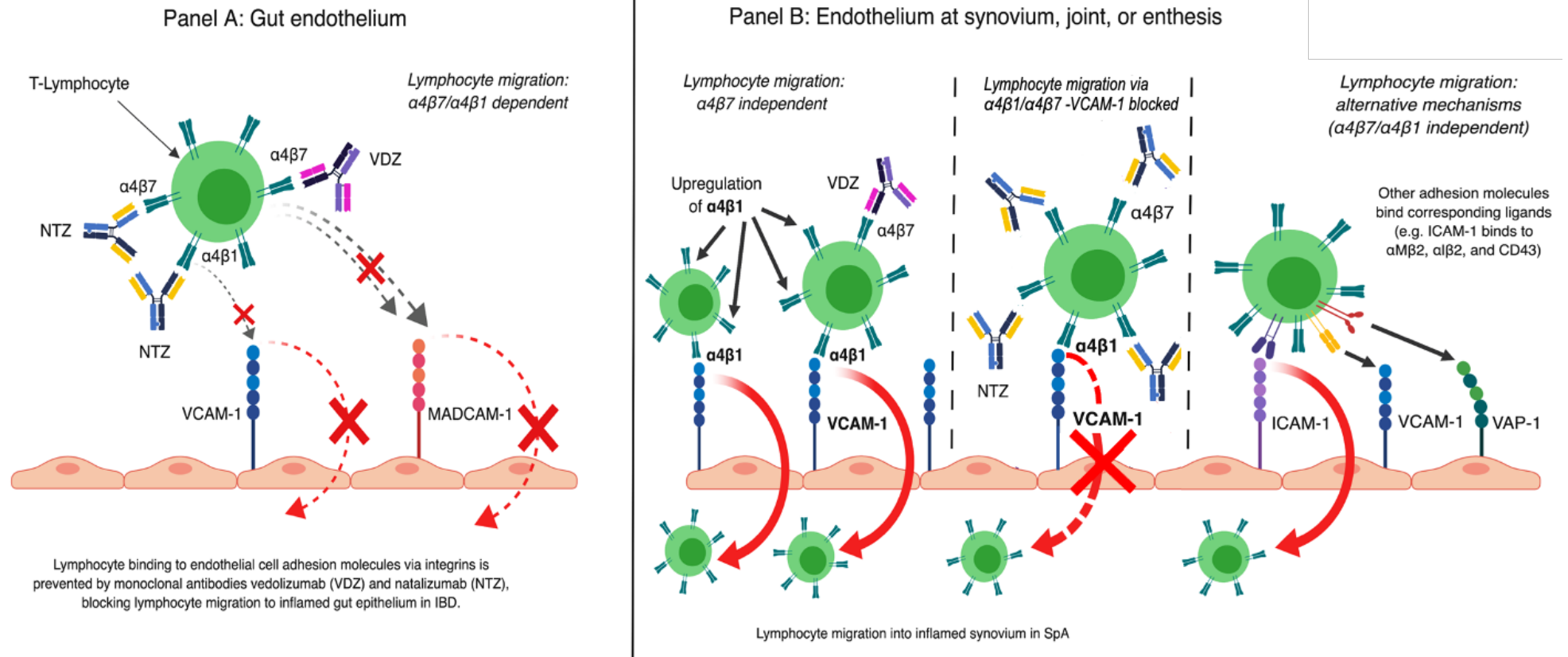


Figure 4:4. Proposed model to explain why VDZ induces SpA, but SpA is less likely with NTZ.

Expression of $\alpha 4\beta 1/\alpha 4\beta 7$ on lymphocytes permits binding to VCAM-1 at entheses/synovium. NTZ blocks $\alpha 4\beta 1/\alpha 4\beta 7$ -VCAM-1 interaction. Upregulation of $\alpha 4\beta 1$ blockade may occur at lymphocytes bound to VDZ which may increase lymphocyte migration to synovium promoting inflammation at cells under mechanical stress. Figure created with Biorender.com

4.4 Summary of chapter

In this chapter, the pathogenic relationship between severe SpA and enthesal pathology has been explored in different SpA phenotypes. The two case series' discussed have provided an insight into the clinicopathological, biochemical and imaging characteristics of specific entities of the SpA disease spectrum.

Patients presenting acutely with unilateral sacroiliac pain, that were HLA-B27 negative and demonstrated high acute phase markers (CRP) underwent urgent MRI examination which confirmed extensive bone marrow oedema, joint inflammation, extra-capsular and soft tissue oedema which was described by the radiologist as suspicious for septic arthritis. Yet, these patients improved after NSAIDs alone lacking any confirmation of infection, the sequence of events of symptoms following one of improvement and eventual patient recovery. The imaging features indicate that severe joint and enthesal inflammation, mimicking infection, can manifest as part of a likely ReA and may settle down with NSAIDs. These features show how SpA, specifically ReA, can demonstrate MRI features mimicking infection.

The latter series identified IBD patients that were mostly TNFi failures, HLA-B27 negative and showing successful gut responses to VDZ. These patients developed severe SpA and related enthesitis, so severe that the VDZ was in fact discontinued despite predominantly quiescent IBD. Most patients showed an elevated marker of acute phase (CRP), SpA related enthesal pathology, and nearly one-third were hospitalised due to symptom severity. Imaging by MRI (STIR or T2 fat suppressed sequence) and ultrasound with power Doppler confirmed severe SpA/enthesitis, acute sacroiliitis, extensive vertebral osteitis, marked severe peri-facetial oedema or isolated peripheral enthesitis. These results clearly demonstrate the spectrum of severe pathological features in a variety of phenotypes in SpA/enthesitis associated with VDZ treated IBD. Although, exact mechanisms of disease pathogenesis remain unconfirmed, further research into adhesion molecules and diseased entheses may improve scientific knowledge and understanding within this complex area to improve clinical care.

Chapter 5. Exploring the relationship between clinical examination of joints and ultrasound synovitis: a cross-sectional study of DMARD-naïve early psoriatic arthritis

5.1 Introduction

Psoriatic arthritis (PsA) is associated with considerable heterogeneity, including different phenotypes and lack of laboratory biomarkers which can lead to diagnostic difficulty (Wright, 1956). The initial diagnosis and assessment of PsA is dependent upon identifying joint swelling and tenderness by clinical examination, a fundamental skill and core outcome in the clinician's assessment of disease activity. Joint examination findings are not only central to management decisions, but they are crucial elements of inclusion criteria in randomised controlled clinical trials and of eligibility criteria for biological drugs prescription in clinical practice. The tender/swollen joint counts (TJC/SJC) are considered ubiquitous measures of disease activity and are also key components in composite outcome measures including the PsARC, DAS28, CPDAI, DAPSA, and PASDAS (Mease, 2011) and constitute separate domains needed to achieve the PsA treatment targets for minimal disease activity (MDA), or very low disease activity (VLDA) criteria (Coates and Helliwell, 2016). Ultimately, persistent joint swelling is associated with progressive joint erosion, pain and functional loss (Gladman et al., 1995; Siannis et al., 2006). However, PsA patients often report joint pain and may have tender joints without swelling, the significance of which is not clearly understood.

Ultrasonography (US) is increasingly used in PsA diagnosis and management, most importantly to identify joint synovitis, and peri-tendon/tendon/entheseal inflammation, due to its superior sensitivity over clinical examination which has been well demonstrated and validated (Wiell et al., 2007). Previous studies have shown disparity between clinical and US findings and a high prevalence of subclinical synovitis (Wakefield et al., 2004; Husic et al., 2014; Freeston et

al., 2014; Pukšić et al., 2018). However, recent analyses of disease modifying anti-rheumatic drugs (DMARD) treated established rheumatoid arthritis (RA) patients, demonstrated an association between clinically swollen joints and US synovitis, which was not found in the context of tender joints (Hammer et al., 2019). Pathophysiological evidence indicates that PsA differs from RA, with primary enthesopathy followed by secondary synovial inflammation in PsA, in contrast to primary synovitis in RA (McGonagle et al., 1998; Kaeley et al., 2018). Therefore, the relationship between clinical/US findings may not be the same in both diseases. However, similar to RA, the literature in PsA overwhelmingly indicates that persistent synovitis also leads to structural and functional damage over time, and is one of the main reasons for initiating systemic therapy due to responsiveness to bDMARDs (Van Der Heijde et al., 2020). Structural damage in PsA is also linked with reduced quality of life and increased risk of death (Gladman et al., 1998). Though some PsA patients may exhibit minimal disease, other can suffer greater articular inflammation which needs identifying and treating. The inhibition of synovitis with DMARDs therefore plays a key role in halting structural damage in PsA (Mease et al., 2004; Mease et al., 2009).

Early US imaging is an excellent confirmatory tool in the diagnosis and management of PsA, yet not all patients will undergo this investigation in “real-world” practice, due to several factors such as lack of resource, finances, and time constraints. In the clinical examination, visible and palpable articular swelling often negates the need for US, an assumption that it translates to synovitis, but tender joints are more difficult to interpret given their wider association to pathologies. Yet clinicians frequently face challenging clinical decisions centred on disease activity status based on tender/swollen counts. Tender joints, especially in the absence of swelling, have not been well characterised in early PsA. In DMARD treated cohorts tenderness may be influenced by non-inflammatory pathologies, particularly in advanced disease, such as osteoarthritis and fibromyalgia which can result in disproportionately high TJC (Scott and Scott, 2014). In clinical practice this problem is highly relevant and therefore understanding the relationship of clinical joint tenderness/swelling to ultrasound synovitis is crucial for disease classification, early identification of disease, decision making, and therapeutic intervention.

5.2 Hypothesis, aims and objectives

5.2.1 Hypothesis

Enthesitis is a significant pathological event in early, new onset spondyloarthritis and may be a biomarker for disease evolution.

5.2.2 Aims and objectives

The aim was to explore the association between baseline clinical examination and ultrasound (US) synovitis in early PsA.

The study objective was to determine the association between tender/swollen joints and US synovitis in early PsA, a stage when accurate diagnosis and therapy is paramount. To avoid possible confounders as discussed above, I chose to explore a cohort of DMARD-naïve early PsA patients.

5.3 Methods

5.3.1 Study design

Prospective cross-sectional observational cohort study.

5.3.2 Patients

In this single-centre study, 155 consecutive DMARD-naïve, early PsA patients attending the Leeds Early Arthritis clinic between December 2013 and October 2019, were prospectively recruited into the Leeds Spondyloarthropathy Register for Research and Observation (SpARRO).

5.3.3 Study eligibility criteria

Inclusion was determined by a new diagnosis of PsA, age (≥ 18 years) and $\geq 3/5$ points scored in the classification for PsA (CASPAR) criteria. Exclusion criteria included previous or current exposure to DMARDs (Taylor et al., 2006).

5.3.4 Ethical approval

Ethical approval was granted by the Leeds West Research Ethics Committee (LG03/028) and all patients provided written informed consent in accordance with the declaration of Helsinki.

5.3.5 Clinical details and examination

A full clinical history and examination was conducted by the study rheumatologist unaware of US findings. Examination of individual joints were recorded as tender or non-tender, and swollen or non-swollen, as per TJC/SJC (78/76) and matched for the corresponding 44 US scanned joints per patient. Clinical enthesitis was assessed via the MASES (13 physical sites of enthesial insertion: Achilles, 1st and 7th costochondral joints, anterior superior iliac spines, posterior superior iliac spines, iliac crest and 5th lumbar spinous process).

5.3.6 Ultrasound examination

Image acquisition

Examination of 44 joints per patient was conducted using the GE Logiq E9 US machine and linear ML 15-6 MHz or small-footprint linear array 18-8 MHz transducer by trained and experienced sonographers blinded to clinical details, laboratory results and previous imaging. The clinical/US examinations occurred on the same day and followed a protocol driven procedure standardised as per EULAR guidelines (Möller et al., 2017). The wrists (radio-carpal, intercarpal, and ulnar-carpal regions), metacarpophalangeal joints

(MCP)1-5, proximal interphalangeal joints (PIP) 1-5, distal interphalangeal joints (DIP) 2-5, knees (suprapatellar pouch, medial and lateral recesses), ankles (tibiotalar), and metatarsophalangeal (MTP) 1-5 joints were scanned in longitudinal/transverse planes at the dorsal aspect. Five enthesal sites were assessed via US as part of the modified Glasgow ultrasound enthesitis scoring system (mGUESS) which included the Achilles enthesis, plantar fascia, proximal and distal insertion of the patellar ligament, and the quadriceps tendon insertion into the patella. Hypoechoogenicity, thickening, power Doppler, calcifications, enthesophytes, and bursitis (except at the quadriceps tendon) were assessed as per Outcome MEasures in Rheumatology (OMERACT). One of four experienced sonographers each with over 5 years of experience conducted the US scans and sonographer calibration was regularly conducted at least twice per year at the same institution to ensure performance, quality, image interpretation, scoring and recording of results were maintained to a high and consistent standard and in line with the study protocol.

Image scoring

Semi-quantitative scoring for grades of grey scale (GS) and power Doppler (PD) were recorded individually for each scanned joint on a 0-3 scale with the highest GS and PD documented at sites in the wrists and knees. Semiquantitative GS and PD grades were dichotomised to enable analysis to explore US synovitis. Ultrasound GS=0–1 was defined as normal because it is frequently prevalent in healthy controls whereas GS 2-3 is more frequently associated with disease (Padovano et al., 2016). Ultrasound synovitis was defined as $GS \geq 2$ (i.e. $GS \geq 2 + PD \geq 0$) or $PD \geq 1$ (i.e. $GS \geq 1 + PD \geq 1$; $GS \geq 2 + PD \geq 1$ was also assessed).

5.3.7 Statistical analysis

Percentages were used to describe categorical variables, means/medians and standard deviations/interquartile range (IQR) for continuous variables. Baseline clinical and US assessments were analysed at the patient level

(TJC/SJC) and individual joint level. Statistical agreement was calculated between TJ/SJ (individual joint level) independently and US synovitis, dichotomised for GS/PD grades using the prevalence-adjusted and bias-adjusted kappa (PABAK). The kappa value (PABAK) for agreement was interpreted using a probabilistic benchmarking method: poor=0.00; slight=0.01–0.20; fair=0.21–0.40; moderate=0.41–0.60; substantial=0.61–0.80; almost perfect=0.81–1.00 (Landis and Koch, 1977).

Mixed effects logistic regression was used to model the odds of ultrasound synovitis in a joint, according to clinical tenderness, swelling and joint type. Each ultrasound outcome ($GS \geq 2$, $PD \geq 1$, $GS \geq 2 \& PD \geq 1$) was modelled separately; predictors were entered simultaneously for each model. Joints (level 1) were nested within patients (level 2) in these random intercepts and slopes models. Interactions between tenderness and swelling, which allowed the extent to which tenderness predicted the US outcome to vary according to whether swelling was also present, were investigated using likelihood ratio tests. All tests were two-tailed, the level of statistical significance pre-specified at 5% ($p < 0.05$) and estimates derived with 95% confidence intervals (CI).

To reflect the fact that underlying odds of US synovitis differ between sites of joints, a further variable was created for the site of joint affected (JSite) for conducting the logistic regression analysis and receiver operating characteristic (ROC). Negative binomial regression was also used to assess the relationship between clinical examination and US enthesitis [modified Glasgow ultrasound enthesitis scoring system (mGUESS) including all domains except bursitis at the quadriceps tendon]. Statistical analyses were performed using Stata version 16.1 (StataCorp) and WinPEPI 11.4.

5.4 Results

5.4.1 Patients and characteristics

The mean (\pm SD) age was 44.4 years (\pm 12.8) and 52.9% were female. The median duration from PsA diagnosis was 1.1 months (IQR 0–3.0) and median symptom duration was 12 months (IQR 7–30) indicating an early PsA cohort. An oligoarticular phenotype was most prevalent [99/155 (63.9%) patients;

polyarticular in 56/155 (36.1%]). The characteristics of the cohort are detailed in Table 5:1. Baseline characteristics of the early DMARD-naïve PsA cohort

Table 5:1. Baseline characteristics of the early DMARD-naïve PsA cohort

Baseline characteristics	n=155 (patients)
Age, mean (SD) years	44.4 (12.8)
Male, n (%)	73 (47.1%)
Symptom duration, median (IQR), months	12 (7-30)
Diagnosis to recruitment, median (IQR), months	1.1 (0-3.0)
Early morning stiffness, median (IQR) minutes	60 (15-120)
TJC (78), median (IQR)	7 (3.0-14.0)
SJC (76), median (IQR)	2 (1.0-7.0)
<i>TJC (44), median (IQR)</i>	5 (2-10)
<i>SJC (44), median (IQR)</i>	2 (1-6)
Dactylitis, n (%)	69 (44.5%)
Current Psoriasis, n (%)	153 (98.7%)
PASI, median (IQR)	2.7 (0.5- 4.6)
Nail Dystrophy, n (%)	93 (60%)
mNAPSI, median (IQR)	0 (0-6)
Clinical enthesitis, n (%)	71 (45.8%)
MASES, median (IQR)	0 (0-2)
BMI, median (IQR)	28.5 (24.6-32.0)
Disease phenotype	
Oligoarthritis	99 (63.9%)
Polyarthritis	56 (36.1%)
<i>DIP joint disease</i>	17 (11.4%)
<i>Axial disease</i>	22 (14.6%)
<i>Arthritis Mutilans</i>	0 (0%)
Inflammatory markers	
CRP (mg/L), median (IQR)	<5 (<5-14.9)
<i>Elevated (>10)</i>	54 (34.8%)
<i>Not elevated (≤10)</i>	101 (65.2%)
ESR, median (IQR)	13 (6-26)
Serological markers	
HLA-B27 Positive, n (%)	15 (12.6%)
ANA Positive, n (%)	3 (2.0%)
RF Positive, n (%)	3 (2.1%)
ACPA Positive, n (%)	8 (5.3%)
Patient reported outcomes	
PsAQoL, median (IQR)	6 (1-12)
DLQI, median (IQR)	3 (0-7)
HAQ-DI, median (IQR)	0.732 (0.25-1.375)

5.4.2 Prevalence of clinical examination and US synovitis

Of the 5,616 joints evaluated, a cumulative total of 1039/5616 (18.5%) were clinically tender, 550/5616 (9.7%) were clinically swollen, 462/5616 (8.2%) were both tender and swollen, and 577/5616 (10.3%) were tender in the absence of swelling (tender non-swollen). Grey scale ≥ 2 synovitis was detected in 152/155 (98.1%) and PD ≥ 1 in 130/155 (83.9%) of patients in at least one joint. In total, GS ≥ 1 was present in 2273/5616 (40.5%) joints, GS ≥ 2 in 1144/5616 (20.4%) joints, and PD ≥ 1 in 292/5616 (5.2%) joints, and combined GS ≥ 2 &PD ≥ 1 in 162/5616 (2.9%) joints. Total GS=1 was present in 1129/5616 (20.1%) whereas GS=1&PD ≥ 1 was only observed in 50/5616 (0.89%).

Clinical swelling with GS ≥ 2 synovitis was present in 385/5616 (6.9%), and subclinical GS ≥ 2 synovitis was present in a greater number of joints 759/5616 (13.5%). Clinical PD ≥ 1 synovitis occurred in greater number of joints than subclinical PD ≥ 1 synovitis [172/5616 (3.1%) vs 120/5616 (2.1%)]. Subclinical GS=1 synovitis was present in a greater number of joints than GS=1 synovitis with clinical swelling [891/5616 (15.9%) vs 238/5616 (4.2%) respectively]. The frequencies of GS/PD changes in combinations of tender/swollen joints are shown in Table 5:2, and prevalence of individual US GS/PD observed grades listed in Table 5:3.

The joint specific prevalence of TJ, SJ, GS and PD grades are outlined in Table 5:4. In the feet, GS ≥ 2 was frequently detected in 495/1034 (47.9%). The most prevalent site of GS ≥ 2 was at the MTP1 (46.5%; also a frequently observed site for osteoarthritis) followed by MTP2-4 (range 37.5% - 51.7%) and wrists (30.1%). Power Doppler (PD ≥ 1) was most prevalent at the wrists (17.5%) and MTP1 (12.6%)

Table 5:2. The number of clinically tender and swollen joints for grades of ultrasound synovitis. Results are as a percentage of the category specific clinical combination and the percentage of the total patient cohort (brackets).

Tender/swollen joints	GS≥2	PD≥1	GS≥2+PD=0	GS≥2+PD≥1
Total tender (n=1039/5616)	353; 34.0% (6.2%)	156; 15.1% (2.8%)	216; 20.8% (3.8%)	137; 13.2% (2.4%)
Total swollen (n=550/5616)	237; 43.1% (4.2%)	137; 24.9% (2.4%)	115; 20.9% (2.0%)	122; 22.2% (2.2%)
Both tender and swollen (n=462/5616)	205; 44.4% (3.7%)	121; 26.2% (2.2%)	98; 21.2% (1.7%)	107; 23.2% (1.9%)
Tender and not swollen (n=577/5616)	148; 25.7% (2.6%)	35; 6.1% (0.6%)	118; 20.5% (2.1%)	30; 5.2% (0.5%)
Swollen and not tender (n=88/5616)	32; 36.4% (0.6%)	16; 18.2% (0.3%)	17; 19.3% (0.3%)	15; 17.1% (0.3%)
Neither tender nor swollen (n=4489/5616)	759; 16.9% (13.5%)	120; 2.7% (2.1%)	666; 14.8% (11.9%)	93; 2.1% (1.7%)

Table 5:3 Ultrasound GS/PD synovitis per grade in combinations of tender and swollen joints.

All joints	GS=0	GS=1	GS=2	GS=3	PD=0	PD=1	PD=2	PD=3
All tender (n=1039/5616)	471 (45.3%)	215 (20.7%)	255 (24.5%)	98 (9.4%)	883 (85.0%)	63 (6.1%)	75 (7.2%)	18 (1.7%)
All swollen (n=550/5616)	206 (37.5%)	107 (19.5%)	154 (28.0%)	83 (15.1%)	413 (75.1%)	53 (9.6%)	69 (12.6%)	15 (2.7%)
Both tender and swollen (n=462/5616)	173 (37.5%)	84 (18.2%)	133 (28.8%)	72 (15.6%)	341 (73.8%)	46 (10.0%)	61 (13.2%)	14 (3.1%)
Tender and not swollen (n=577/5616)	298 (51.7%)	131 (22.7%)	122 (21.1%)	26 (4.5%)	542 (93.9%)	17 (3.0%)	14 (2.4%)	4 (0.7%)
Swollen and not Tender (n=88/5616)	33 (37.5%)	23 (26.1%)	21 (23.9%)	11 (12.5%)	72 (81.8%)	7 (8.0%)	8 (9.1%)	1 (1.1%)
Neither tender nor swollen (n=4489/5616)	2839 (63.2%)	891 (19.9%)	657 (14.6%)	102 (2.3%)	4369 (97.3%)	85 (1.9%)	31 (0.7%)	4 (0.1%)

Table 5:4 Prevalence of tender joints, swollen joints, ultrasound GS/PD synovitis per grade per joint.

Joint	Tender	Swollen	GS=0	GS=1	GS=2	GS=3	PD=0	PD=1	PD=2	PD=3
Wrist (n=309)	70 (22.7%)	35 (11.3%)	95 (30.7%)	121 (39.2%)	84 (27.2%)	9 (2.9%)	246 (82.0%)	31 (10.3%)	23 (7.7%)	0 (0%)
MCP1 (n=190)	42 (22.1%)	37 (11.0%)	105 (55.3%)	40 (21.1%)	33 (17.4%)	12 (6.3%)	174 (91.6%)	9 (4.7%)	6 (3.2)	1 (0.5)
MCP2 (n=310)	67 (21.6%)	49 (15.8%)	161 (51.9%)	112 (36.5%)	27 (8.7%)	10 (3.2%)	288 (92.9%)	9 (2.9%)	9 (2.9%)	4 (1.3%)
MCP3 (n=310)	72 (23.2%)	51 (16.5%)	177 (57.1%)	93 (30.0%)	28 (9.0%)	12 (3.9%)	287 (92.6%)	7 (2.3%)	11 (3.6%)	5 (1.6%)
MCP4 (n=190)	35 (18.4%)	17 (9.0%)	106 (55.8%)	61 (32.1%)	14 (7.4%)	9 (4.7%)	179 (94.2%)	8 (4.2%)	2 (1.1%)	1 (0.5%)
MCP5 (n=190)	24 (12.6%)	8 (4.2%)	124 (65.3%)	46 (24.2%)	14 (7.4%)	6 (3.2%)	183 (96.3%)	4 (2.1%)	2 (1.1%)	1 (0.5%)
PIP1 (n=190)	27 (14.2%)	15 (7.9%)	123 (64.7)	24 (12.6%)	39 (20.5%)	4 (2.1%)	179 (98.4%)	2 (1.1%)	1 (0.6%)	0 (0%)
PIP2 (n=309)	64 (20.7%)	35 (11.3%)	253 (81.9%)	25 (8.1%)	21 (6.8%)	10 (3.2%)	285 (96.0%)	4 (1.4%)	6 (2.0%)	2 (0.7%)

Joint	Tender	Swollen	GS=0	GS=1	GS=2	GS=3	PD=0	PD=1	PD=2	PD=3
PIP3 (n=310)	66 (21.3%)	39 (12.6%)	250 (80.7%)	26 (8.4%)	23 (7.4%)	11 (3.6%)	289 (97.0%)	5 (1.7%)	3 (1.0%)	1 (0.3)
PIP4 (n=190)	29 (15.3%)	13 (6.8%)	154 (81.1%)	13 (6.8%)	17 (9.0%)	6 (3.2%)	176 (97.8%)	2 (1.1%)	2 (1.1%)	0 (0%)
PIP5 (n=190)	19 (10.0%)	8 (4.2%)	159 (83.7%)	13 (6.8%)	16 (8.4%)	2 (1.1%)	177 (98.3%)	1 (0.65)	2 (1.1%)	0 (0%)
DIP2 (n=190)	21 (11.1%)	14 (7.4%)	160 (84.2%)	11 (5.8%)	17 (9.0%)	2 (1.1%)	187 (98.45)	1 (0.5%)	1 (0.5%)	1 (0.5)
DIP3 (n=190)	20 (10.5%)	12 (6.3%)	151 (79.8%)	19 (10.0%)	19 (10.0%)	1 (0.5%)	187 (98.4%)	1 (0.5%)	2 (1.1%)	0 (0%)
DIP4 (n=190)	15 (7.9%)	7 (3.7%)	157 (82.6%)	18 (9.5%)	13 (6.8%)	2 (1.1%)	187 (98.4%)	1 (0.5%)	2 (1.1%)	0 (0%)
DIP5 (n=190)	20 (10.5%)	10 (5.3%)	166 (87.4%)	12 (6.3%)	11 (5.8%)	1 (0.5%)	186 (97.95)	2 (1.1%)	2 (1.1%)	0 (0%)
Knee (n=308)	59 (19.2%)	34 (11.0%)	192 (62.3%)	64 (20.8%)	42 (13.6%)	10 (3.3%)	299 (97.1%)	4 (1.3%)	5 (1.6%)	0 (0%)
Ankle (n=310)	47 (15.2%)	21 (6.8%)	263 (84.8%)	33 (10.7%)	9 (2.9%)	5 (1.6%)	306 (98.7%)	4 (1.3%)	0 (0%)	0 (0%)

Joint	Tender	Swollen	GS=0	GS=1	GS=2	GS=3	PD=0	PD=1	PD=2	PD=3
MTP1 (n=310)	64 (20.7%)	19 (6.1%)	70 (22.6%)	96 (31.0%)	104 (33.6%)	40 (12.95)	271 (87.4%)	24 (7.7%)	13 (4.2%)	2 (0.7%)
MTP2 (n=310)	69 (22.3%)	31 (10.0%)	68 (21.9%)	82 (26.5%)	140 (45.2%)	20 (6.55)	296 (95.5%)	11 (3.6%)	3 (1.0%)	0 (0%)
MTP3 (n=310)	71 (22.9%)	33 (10.7%)	89 (28.7%)	82 (26.5%)	122 (39.4%)	17 (5.5%)	295 (95.2%)	7 (2.3%)	8 (2.6%)	0 (0%)
MTP4 (n=310)	74 (23.9%)	42 (13.6%)	119 (38.4%)	75 (24.2%)	100 (32.3%)	16 (5.2%)	293 (94.5%)	9 (2.9%)	7 (2.3%)	1 (0.3%)
MTP5 (n=310)	64 (20.7%)	20 (6.5%)	201 (64.8%)	63 (20.3%)	40 (12.9%)	6 (1.9%)	293 (94.5%)	9 (2.9%)	6 (1.9%)	2 (0.7%)

5.4.3 Analysis: clinical *versus* US examination

Agreement at individual joint level split by joint type

Statistical agreement at the individual joint level was highest between SJ/US synovitis. The highest agreement occurred with $PD \geq 1$ (82.6 – 96.3%, PABAK 0.65- 0.93), closely followed by $GS \geq 2$ (except feet), as illustrated in Figure 5:1. Agreement between TJ/US synovitis was also high, but lower than that observed for SJ (72.9 - 91.1%, PABAK 0.46 – 0.82) as shown in Figure 5:2. It is noteworthy that in tender joints [1039/5616 (18.5%)], $GS \geq 2$ was found in 353/1039 (34%), and in non-tender joints [4577/5616 (81.5%)] $GS < 2$ was present in 686/1039 (66%); whereas in swollen joints [550/5616 (9.8%)] there was $GS \geq 2$ in 237/550 (43.1%), and in non-swollen joints [5066/5616 (90.2%)] $GS < 2$ was observed in 313/550 (56.9%). There was much lower agreement for SJ and $GS \geq 2$ in the feet, particularly MTP1-4 (53.3- 64.5%, PABAK 0.07- 0.29) with the exception of MTP5 where it remained high (GS 83.9%, PABAK 0.68; PD: 90.7%, PABAK 0.81). Overall agreement with $GS \geq 2$ was further segregated into percentage positive and negative agreement which highlighted the higher overall negative agreement in comparison to mixed results specific to each joint for positive agreement. Figure 5:3 illustrates these differences for TJ/SJ and $GS \geq 2$ synovitis.

Joint level agreement: combining all joints

Combining all joints, the highest agreement was observed between SJ/US synovitis which was higher than TJ/US [SJ/ $PD \geq 1$: 89.9% (89.1-90.7), PABAK 0.80 (0.78-0.81), SJ/ $GS \geq 2$: 78.3% (77.2-79.4), PABAK 0.57 (0.54-0.59); TJ/ $PD \geq 1$: 81.9% (80.9-82.9), PABAK 0.64 (0.62-0.66), TJ/ $GS \geq 2$: 73.7% (72.6-74.9), PABAK 0.47 (0.45-0.50)] (Table 5:5). Assessment of category specific proportions of positive and negative agreement identified much higher proportions of category negative agreement along with much lower percentage positive agreement. Additionally, agreements were also conducted for tenderness depending upon SJ status; higher positive agreement was present for joint tenderness if swollen [$GS \geq 2$: 58.7% (PABAK

-0.05); PD \geq 1: 40.4% (PABAK -0.30)], compared with lower values for joint tenderness if not swollen [GS \geq 2: 19.9% (PABAK 0.53); PD \geq 1: 9.6% (PABAK 0.74)] as shown in Table 5:6. To further understand the interplay between tenderness, swelling and ultrasound findings, I proceeded to model synovitis as a function of tenderness and swelling simultaneously by logistic regression analysis.

Clinical examination of entheses and US enthesitis

Compared to 71/155 (45.8%) with clinical enthesitis (MASES), US enthesopathy (mGUESS) was present in 133/155 (85.8%) patients, median (IQR); 3 (1-6). However, no significant meaningful statistical association was found between mGUESS and SJC, TJC, or MASES (negative binomial regression; $p>0.05$).

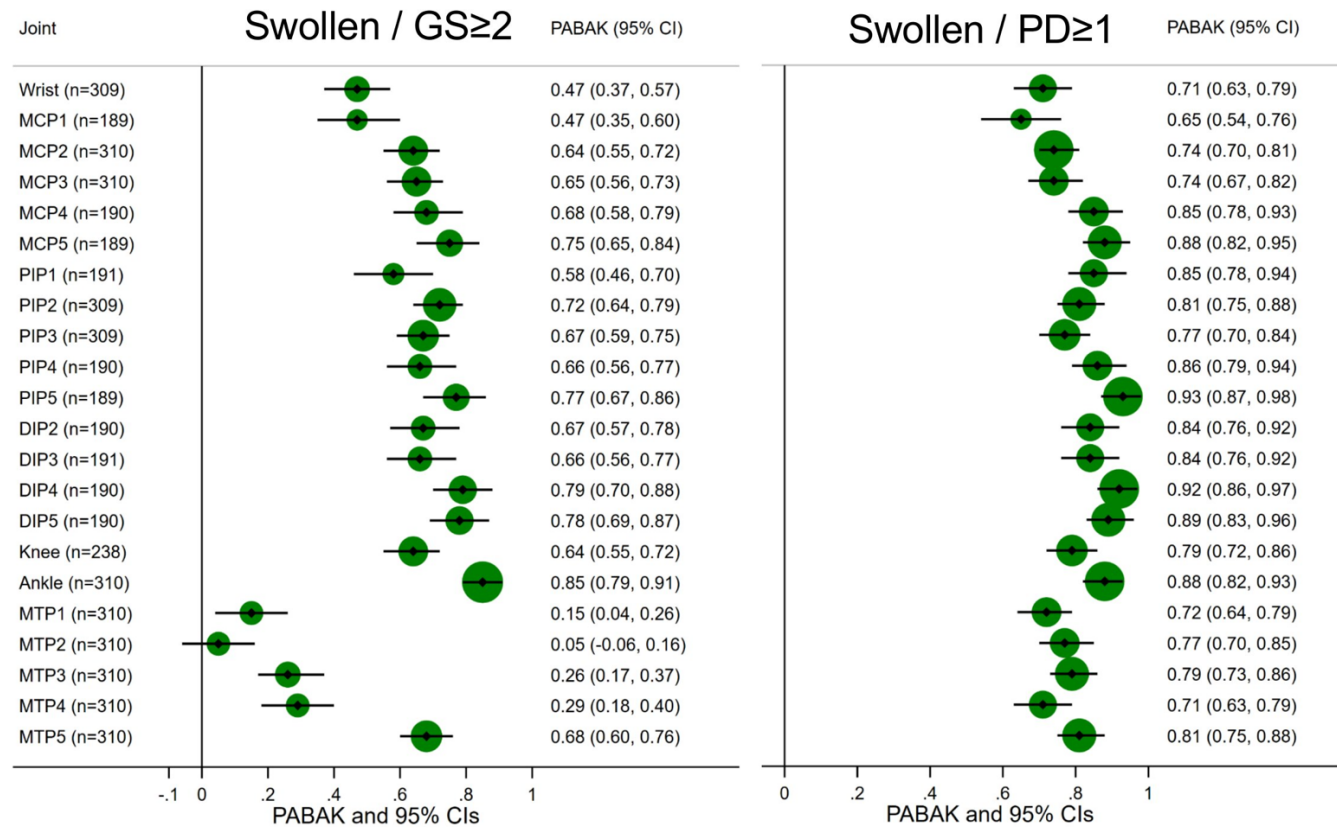


Figure 5:1. Forest plot illustrating overall statistical agreement between swollen joints and ultrasound synovitis (GS \geq 2 / PD \geq 1) for individual joints.

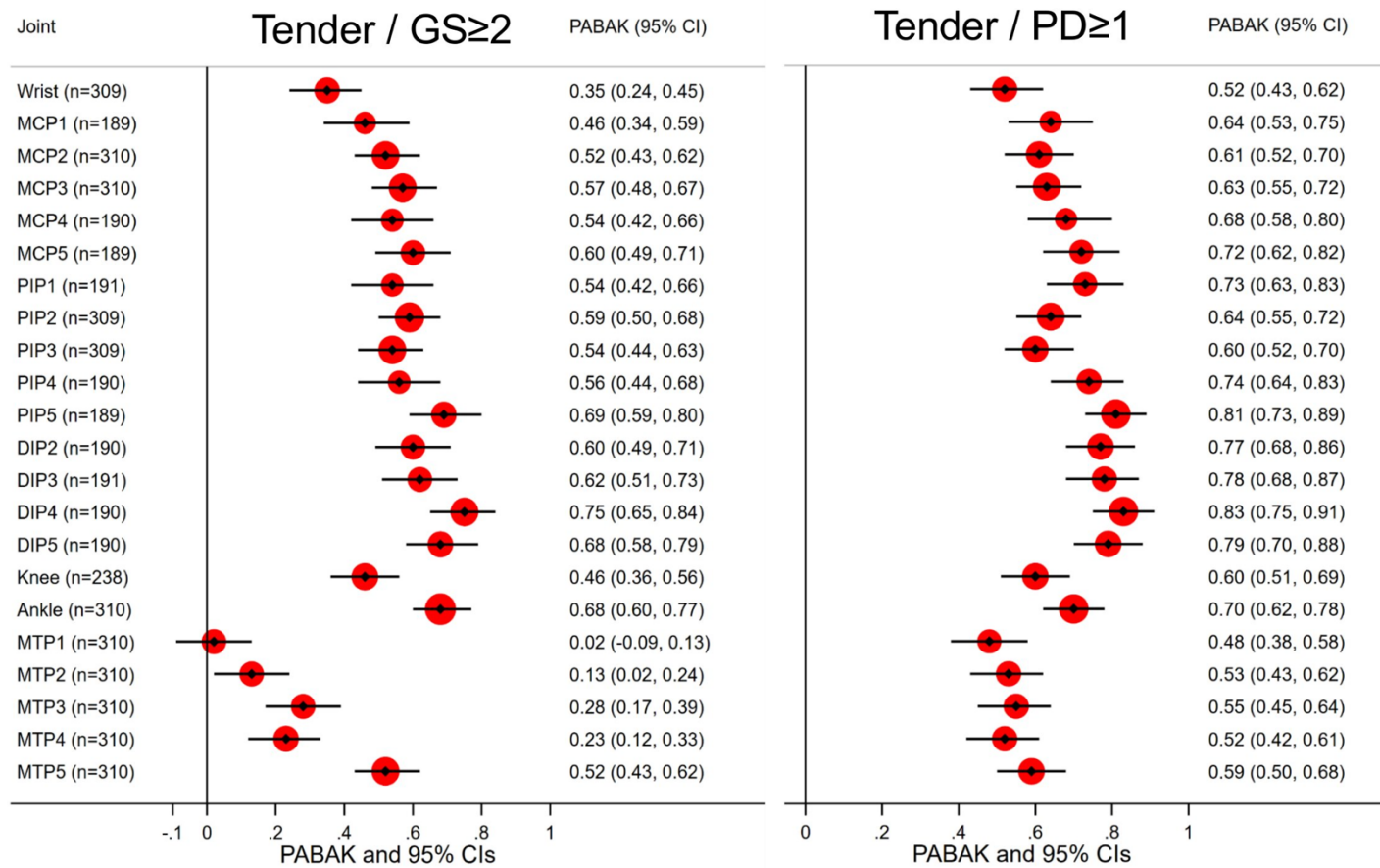


Figure 5:2. Forest plot illustrating overall statistical agreement between tender joints and ultrasound synovitis (GS ≥ 2 / PD ≥ 1) for individual joints.

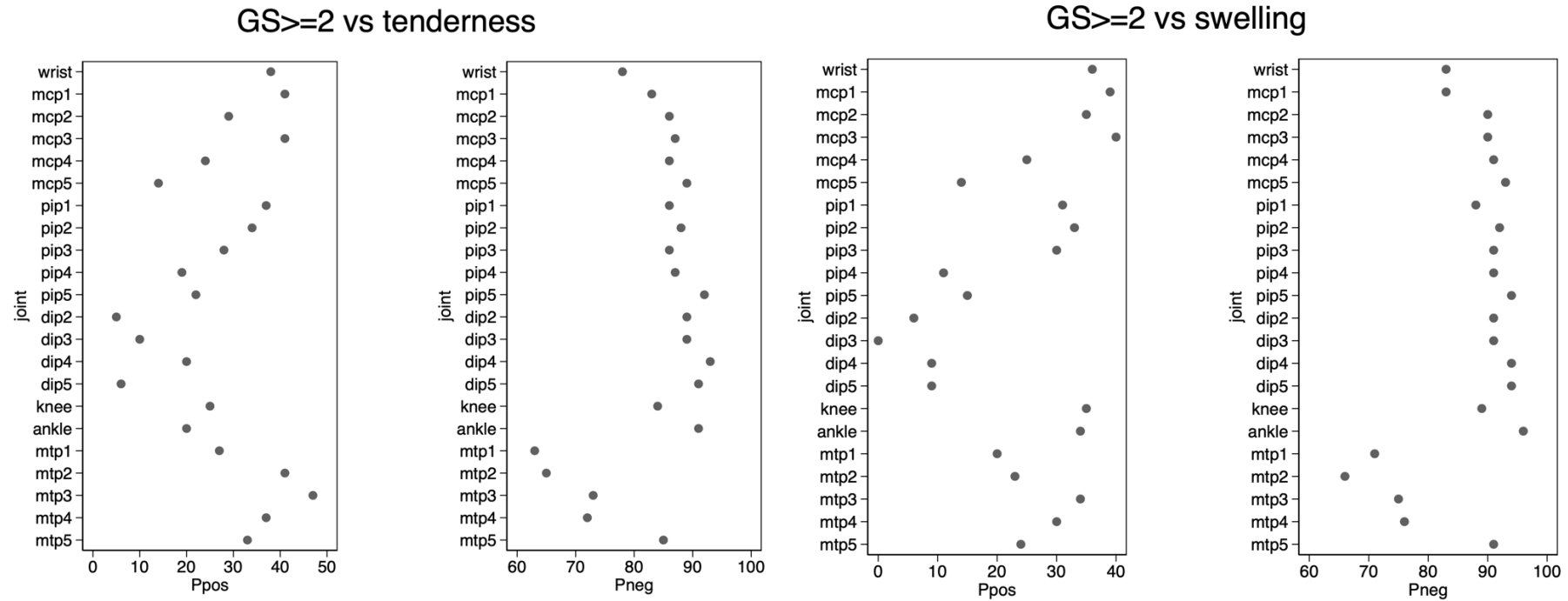


Figure 5:3. Forest plots illustrating percentage positive and negative agreement (Ppos/Pneg) for joint tenderness or swelling and GS \geq 2 ultrasound synovitis for individual joints.

Table 5:5 Percentage overall agreement for tender/swollen joints and US synovitis.

Percentage overall agreement (%) including category-specific proportions of positive (Ppos) and negative (Pneg) agreement and adjusted kappa (PABAK) with 95% confidence intervals for tender/swollen joints and ultrasound synovitis at the joint level (all joints combined).

All joints	GS (2-3 vs 0-1; 1144/5616)				PD (1-3 vs 0; 292/5616)				GS \geq 2+PD \geq 1 vs GS 0-1 and/or PD 0 (245/5616)			
	Agreement (95% CI)	Pneg (95% CI)	Ppos (95% CI)	PABAK (95% CI)	Agreement (95% CI)	Pneg (95% CI)	Ppos (95% CI)	PABAK (95% CI)	Agreement (95% CI)	Pneg (95% CI)	Ppos (95% CI)	PABAK (95% CI)
Tender (1039/5616)	73.7% (72.6, 74.9)	83.7% (82.8, 84.5)	32.3% (29.8, 34.9)	0.47 (0.45, 0.50)	81.9% (80.9, 82.9)	89.7% (89.1, 90.3)	23.4% (20.4, 26.6)	0.64 (0.62, 0.66)	82.0% (81.0, 83.0)	89.8% (89.2, 90.5)	21.3% (18.2, 24.3)	0.64 (0.62, 0.66)
Swollen (550/5616)	78.3% (77.2, 79.4)	87.2% (86.5, 87.9)	28.0% (25.2, 30.8)	0.57 (0.54, 0.59)	89.9% (89.1, 90.7)	94.5% (94.1, 95.0)	32.5% (28.5, 36.6)	0.80 (0.78, 0.81)	90.2% (89.4, 91.0)	94.7% (94.3, 95.1)	30.7% (26.5, 34.8)	0.80 (0.79, 0.82)
Tender and/or swollen (1127/5616)	73.3% (72.1, 74.4)	83.2% (82.4, 84.1)	33.9% (31.3, 36.4)	0.47 (0.44, 0.49)	80.9% (79.8, 81.9)	89.0% (88.4, 89.7)	24.2% (21.3, 27.3)	0.62 (0.60, 0.64)	81.0% (80.0, 82.0)	89.2% (88.5, 89.8)	22.2% (19.5, 25.2)	0.62 (0.60, 0.64)
Tender and swollen (462/5616)	78.7% (77.6, 79.8)	87.6% (86.3, 88.3)	25.5% (22.7, 28.3)	0.57 (0.55, 0.60)	90.1% (90.1, 91.6)	95.1% (94.7, 95.5)	32.1% (27.9, 36.4)	0.82 (0.80, 0.83)	91.2% (90.5, 92.0)	95.3% (94.9, 95.7)	30.3% (25.9, 34.8)	0.82 (0.81, 0.84)

Table 5:6 Percentage overall agreement with US synovitis for tender joints if swollen and tenderness if not swollen.

Percentage agreement (%), category-specific proportions of positive (Ppos) and negative (Pneg) agreement and adjusted kappa (PABAK) with 95% confidence intervals for tender joints and ultrasound synovitis at the joint level, separately for swollen and non-swollen joints.

All joints	GS (2-3 vs 0-1; 237/550)				PD (1-3 vs 0; 137/550)				GS \geq 2+PD \geq 1 vs GS 0-1 and/or PD 0 (122/550)			
	Agreement (95% CI)	Pneg (95% CI)	Ppos (95% CI)	PABAK (95% CI)	Agreement (95% CI)	Pneg (95% CI)	Ppos (95% CI)	PABAK (95% CI)	Agreement (95% CI)	Pneg (95% CI)	Ppos (95% CI)	PABAK (95% CI)
Tender if swollen (462/550)	47.5% (43.3, 51.6)	27.9% (22.3, 33.8)	58.7% (54.2, 62.9)	-0.05 (-0.13, 0.03)	35.0% (31.1, 39.1)	28.7% (23.7, 34.1)	40.4% (35.5, 45.2)	-0.30 (-0.38, -0.22)	32.7% (28.8, 36.7)	28.3% (23.2, 33.5)	36.6% (31.7, 41.6)	-0.35 (-0.42, -0.27)
	GS (2-3 vs 0-1; 907/5066)				PD (1-3 vs 0; 155/5066)				GS \geq 2+PD \geq 1 vs GS 0-1 and/or PD 0 (577/5066)			
	Agreement (95% CI)	Pneg (95% CI)	Ppos (95% CI)	PABAK (95% CI)	Agreement (95% CI)	Pneg (95% CI)	Ppos (95% CI)	PABAK (95% CI)	Agreement (95% CI)	Pneg (95% CI)	Ppos (95% CI)	PABAK (95% CI)
Tender if not swollen (577/5066)	76.6% (75.4, 77.8)	86.3% (85.5, 87.0)	19.9% (17.4, 22.7)	0.53 (0.51, 0.55)	86.9% (86.0, 88.0)	93.0% (92.4, 93.5)	9.6% (6.8, 12.7)	0.74 (0.72, 0.76)	87.4% (86.5, 88.3)	93.2% (92.6, 93.7)	8.6% (6.1, 11.7)	0.75 (0.73, 0.77)

5.4.4 Prediction modelling: logistic regression analysis

Preliminary modelling in 5616 joints from 155 patients offered no evidence that the difference in the odds of US synovitis associated with joint swelling varied according to whether a joint was also tender (GS \geq 2 p=0.404; PD \geq 1 p=0.463; GS \geq 2&PD \geq 1 p=0.744). Interaction terms were removed from the final models. In the average patient, swelling was associated with higher odds of there being GS \geq 2 in a joint (odds ratio (OR)=4.37 (95% CI 2.62, 7.29), p<0.001); however, in the presence or absence of swelling, tenderness was not associated with an additional increase in the odds of GS \geq 2 being present (OR=1.33 (0.87, 2.06), p=0.192; Figure 5:4 (a)). Independently, swelling (OR=8.78 (3.92, 19.66), p<0.001) and tenderness (OR=3.38 (1.53, 7.50), p=0.003) were associated with a higher odds of PD \geq 1 in a joint (Figure 5:4(b)). Similar results were obtained for GS \geq 2&PD \geq 1 (swelling OR=8.21 (3.24, 20.81), p<0.001; tenderness (OR=3.66 (1.41, 9.46), p=0.008; Figure 5:4 (c)).

However, the ROC model produced only very marginal differences between the area under the curve (AUC) for TJ, SJ, TJ&SJ. The additional predictive value of adding TJ to SJ and vice versa was an additional 0.01 for TJ, and 0.02-0.03 for SJ, for TJ&SJ&JSite, the highest AUC achieved for all US synovitis categories. Despite being associated with the US outcomes that included PD independently of SJ, tenderness did not add substantively to the prediction of each outcome over and above swelling alone, and comparably neither did SJ for US synovitis outcomes (Figure 5:5 (a-c)).

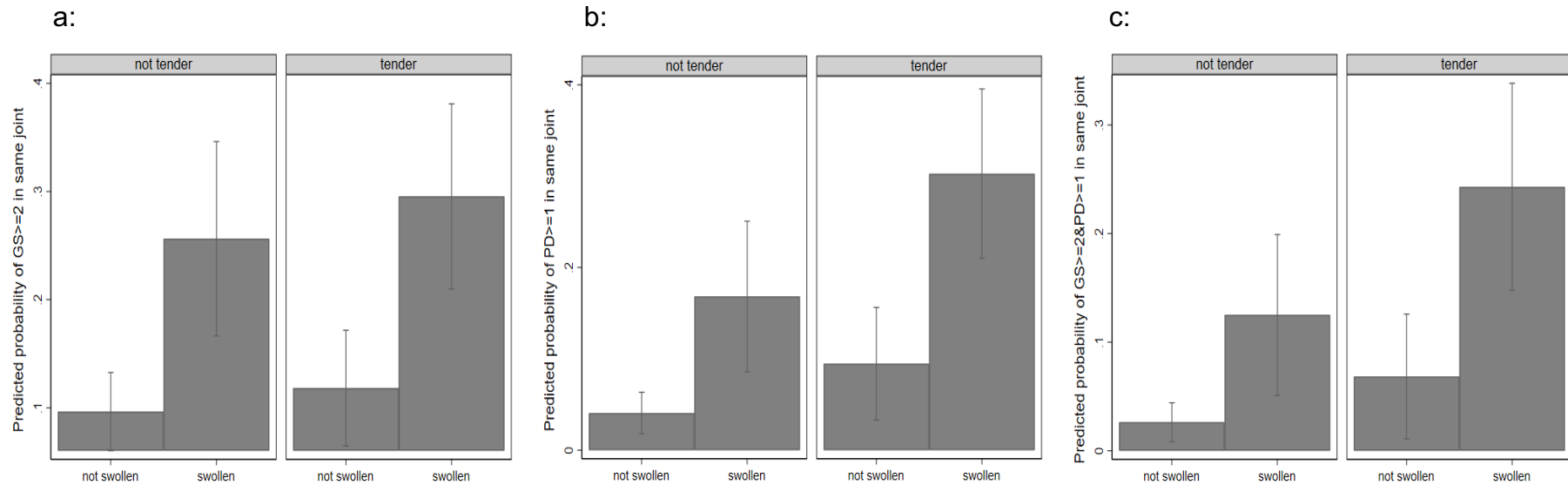
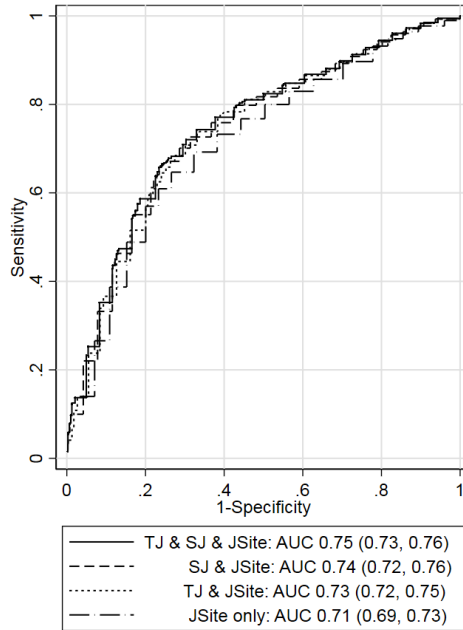


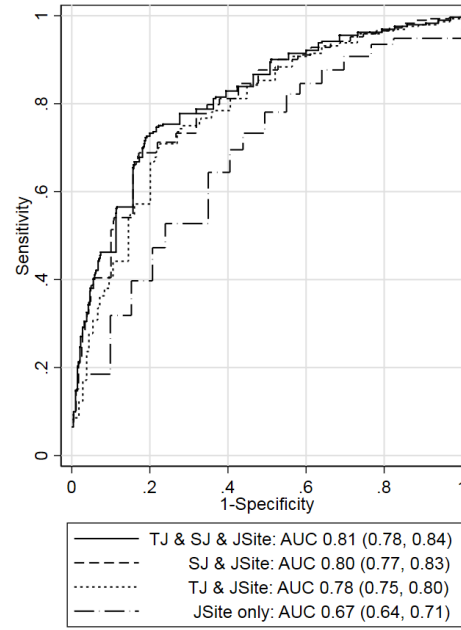
Figure 5:4. Predicted probabilities of a) GS \geq 2 b) PD \geq 1 c) GS \geq 2 & PD \geq 1 synovitis in tender/swollen joints.

Predicted probabilities of a) GS \geq 2 b) PD \geq 1 c) GS \geq 2 & PD \geq 1 according to tenderness and/or swelling (estimated for MCP2 for illustration). Swollen joints were associated with a greater probability of (a) GS \geq 2 synovitis, but tender joints were not. Joint swelling or tenderness were independently associated with higher odds of (b) PD \geq 1 and (c) GS \geq 2 & PD \geq 1 synovitis.

a:



b:



c:

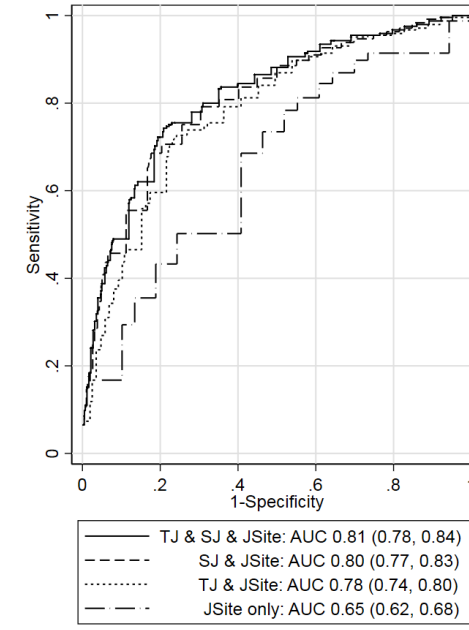


Figure 5:5. Receiver Operating Characteristic (ROC) curves for the fixed prediction models.

Prediction model for a) $GS \geq 2$ b) $PD \geq 1$ c) $GS \geq 2$ & $PD \geq 1$ at the joint level, including different combinations of predictors for tenderness (TJ), swelling (SJ) and joint site (JSite). The graph plots show the true positive rate (sensitivity) versus the false positive rate ($1 - \text{Specificity} = 1 - \text{true negative}$) illustrating the diagnostic ability of clinical examination (TJ or SJ or TJ&SJ) in detecting US synovitis. The site of joint affected (JSite) influenced the model for each US synovitis parameter and was therefore included in the analysis as variable.

5.5 Discussion

This is the largest cross-sectional study to explore clinical joint findings in relationship to US synovitis in a DMARD-naive early PsA cohort. The results from this study confirm that SJ were associated with a greater probability of having US synovitis ($GS \geq 2$ or $PD \geq 1$) than TJ. A stronger association between SJ/US synovitis over TJ has been previously shown in other settings (Husic et al., 2014; Hammer et al., 2019). Further, statistical agreement was generally high for clinical examination and US synovitis outcomes at individual joints, however, positive agreement was much lower which indicated that the presence of clinically tender or swollen joints was still insufficient as a proxy for the presence of US synovitis.

Joints that were both tender and swollen (TJ&SJ) attained low percentages of positive agreement with US synovitis comparable to SJ. Positive agreement was higher for TJ in the presence of swelling, whereas TJ without swelling rendered lower agreements ($GS \geq 2$: 58.7% vs 19.9%; $PD \geq 1$: 40.4% vs 9.6%). This indicated that the concomitant presence of tenderness and swelling had the greater association with US synovitis, and tender joints without swelling were least associated. Although it is noteworthy that tender non-swollen joints may not be representative of synovitis on the whole, and may be indicative of PsA related extra-synovial pathologies (including enthesitis), this was not assessed in the present study given the proven link between synovitis and joint erosions leading to progressive structural and functional damage (Gladman et al., 2010).

Results from this study are in agreement with previous reports in other settings showing stronger association between SJ and US synovitis over TJ in early and established RA (Rees et al., 2007; Tan et al., 2019; Hammer et al., 2019). Moderate correlation was shown between clinically SJ and US (GS/PD) synovitis compared to TJ (weak/not significant) in PsA at the patient level but no association found with extra-capsular disease (Husic et al., 2014). In a longitudinal study of 47 PsA patients, an association between PD and SJC, CRP, ESR, DAS28 score, was reported, but not for TJC nor the DAPSA (Pukšić et al., 2018).

Similar to previous studies in PsA, subclinical synovitis (no clinical swelling or tenderness and presence of $GS \geq 2$) was observed in 13.5% of patients, but its relevance for prognostication is unknown (Wakefield et al., 2004; Freeston et al., 2014). In $GS \geq 2$ synovitis the presence of PD rather than GS was more strongly associated with swollen than tender joints. In comparison to joint swelling, tenderness was not considered to increase the odds of $GS \geq 2$ [OR: 4.37 (SJ) vs 1.33 (TJ)]. However, the probability of detecting PD synovitis ($PD \geq 1$ or $GS \geq 2 \& PD \geq 1$) was increased for tender joints and for swollen joints independently [OR: 8.78, 8.21 (SJ) vs 3.38, 3.66 (TJ) respectively]. Thus, the association seemingly appeared to be driven by SJ more than TJ, and US synovitis by PD established stronger associations with SJ/TJ than GS. The ROC curve analysis confirmed that there was little difference to the odds of a swollen joint having $GS \geq 2$ synovitis when joint tenderness was added. Only marginal differences existed between TJ, SJ, TJ&SJ for each US synovitis category and the area under the ROC (AUC) did not alter substantially when TJ was added to SJ (AUC improved by 0.01) for each US synovitis outcome either.

Synovitis was determined by $GS \geq 2$, however in certain joints $GS = 1$ may indeed be relevant, and there remains uncertainty over what represents physiological vs pathological synovitis for $GS = 1$ grade, including whether it is PsA or non-PsA related change. Indeed, the EULAR-OMERACT consensus-based scoring system recognise $GS \geq 2$ / $PD \geq 1$ in the definition for grading synovitis (D'Agostino et al., 2017). These guidance also include low grade GS without PD ($GS 1-2$) detectable in healthy individuals, despite a known propensity for specific joint sites and which may also be affected by osteoarthritis (e.g. MTP1) (Padovano et al., 2016).

These study results confirmed a high prevalence of synovitis, particularly subclinical GS in the feet (47.9%) than hands, which may be explained by the greater degree of biomechanical stressing subjected to weight bearing joints (Jacques et al., 2014). This resulted in paradoxically lower statistical agreement at small joints of the feet (MTP5 excluded). Whether low grade GS resembles healthy physiology or early pathological findings can be indistinguishable, particularly in the absence of clinical findings, but regression

of GS following treatment suggests some may represent “active” disease (Terslev et al., 2018).

Yet examination of joints is not without subjectivity. Tender joints are common in PsA but may be misjudged as swollen. Obesity, for example, is highly prevalent in PsA (37%), PsO (29%), compared to RA (27%) or the general population (18%) thus making clinical assessments for synovitis more difficult (Bhole et al., 2012). Distinguishing tenderness from enthesitis, synovitis or fibromyalgia for example, is a frequent clinical challenge. To mitigate the effect of disproportionately high tender count, the swollen and tender joint count ratio (STR) and tender-swollen joint count difference (TSJD) have been developed but these outcomes may not reflect underlying pathology (Kristensen et al., 2014; Hammer et al., 2020).

In acute dactylitis, tenderness may be associated with flexor tenosynovitis more often than synovitis, where chronicity corresponds with the ‘cold’ non-tender form (Girolimetto et al., 2020). At large entheses (patellar tendon origins and Achilles entheses) clinical and US enthesitis have shown an association (Aydin et al., 2020). In contrast tenosynovitis and peri-tendinitis had very low concordance between clinical and US findings (Sun et al., 2019). Although no significant association was found for clinical examination and US enthesitis, these results raise important questions on the pathological representation of TJ/SJ beyond synovitis, including the association with PsA-related microanatomical enthesitis, tendinopathy/peri-tendon inflammation in early PsA. The results derived from this study also challenge the validity of joint tenderness in isolation (without swelling) and question the emphasis attributed to TJC as a marker of synovial disease activity.

The limitations of this study include the concomitant use of NSAIDs, either intermittently or regularly (81/155 patients) which may have affected low levels of inflammation on US, given that US GS/PD could be masked by NSAIDs (Zayat et al., 2011). The majority of patients had no exposure to steroids; only 3/155 within 6 weeks of their assessment. However, the main limitation of this study may have been the focus on the assessment of US detectable synovitis over extra-synovial pathologies. Given that tender non-swollen joints are common in PsA, one further consideration would be the use of enhanced imaging techniques namely high resolution MRI (hrMRI) of small joints for

assessment of digital microanatomical enthesitis including flexor pulleys and bone marrow oedema, to accurately detect active disease in tender non-swollen joints (Tan et al., 2015). These study findings have important implications for basing treatment decisions heavily on synovial US findings alone and question the validity of the clinical TJ/TJC as a proxy for synovial disease activity in PsA in the absence of concomitant joint swelling.

To the best of my knowledge, this is the largest cross-sectional study to evaluate the association between clinical examination (TJ/SJ) and US synovitis in DMARD naïve, early PsA. In summary, although high overall agreement and high negative agreement was present between SJ/TJ and US synovitis, percentage positive agreement was much lower for the different categories of TJ/SJ. Swelling was associated with a higher probability of GS \geq 2 synovitis, unlike tenderness. However, both TJ and SJ were independently associated with higher odds of PD \geq 1. The ROC curve predictive model indicated minimal differences between the AUC for TJ, SJ, TJ&SJ for US synovitis. Swelling performed marginally better as a clinical discriminator for active US synovitis in PsA with very little substantial effect on the AUC when TJ were added to the ROC model. Finally, there was least agreement between tender non-swollen joints and US synovitis, thereby challenging the performance of TJ/TJC as an indicator of synovial disease activity in the absence of swelling. These findings support the use of US for early PsA diagnosis, especially in the presence of tender non-swollen joints. Further research on tender joints may improve the understanding of pathologies in early PsA. Finally, the sensitivity that US offers to clinical practice should be considered for early PsA diagnosis.

5.6 Conclusion

In conclusion, US synovitis was more likely in swollen joints than tender joints with the strongest association observed in joints that were both tender and swollen. The association observed for tender non-swollen joints was weakest, suggesting greater understanding of the relationship between underlying pathologies and this clinical finding is needed. Importantly, this study demonstrates that clinical examination of joints remains limited in comparison to US for identifying synovitis, strengthening the case for US imaging to improve diagnostic accuracy and timely intervention in early PsA.

Key Messages

- This is the largest cross-sectional study evaluating the association between clinical joint examination and synovial US findings in DMARD-naïve early PsA.
- This study confirmed that clinical examination had limited capability to identify synovitis in early PsA in comparison to US which provided greater sensitivity.
- This study also confirmed that swollen joints were more likely to represent synovitis than tender joints, which have a known association with a wider range of pathologies. Therefore, in the absence of swelling, US should be considered for accurate early PsA diagnosis.
- Reappraisal of the tender joint count and further research on tender non-swollen joints may improve the understanding of tender joint pathology in early PsA. The sensitivity that US brings to joint assessment in clinical practice indicates it is an important complementary tool to confirm active synovitis in early PsA.

Chapter 6. Exploring the significance of dactylitis in DMARD-naïve early Psoriatic arthritis: a study of clinical characteristics, ultrasound synovitis and erosion

6.1 Introduction

Dactylitis is defined as a diffuse swelling of a finger or toe, or commonly known due to its appearance as the “sausage digit” and is a hallmark feature of Psoriatic arthritis (PsA). It is a specific lesion typically associated with the Spondyloarthropathies (SpA), but not associated with Rheumatoid arthritis (RA), and has a prevalence of between 33 to 55% in previous PsA cohorts, (Brockbank et al., 2005; C.E. Antoni et al., 2005; Gladman et al., 2013; P. Mease et al., 2017). The majority of dactylitis is often found at presentation (nearly 70%) yet the significance of this lesion is unknown in early PsA. Dactylitis epitomises the pathophysiology of PsA, and is a representation of the multiple underlying pathologies involved, encompassing inflammation to joints (synovitis), tendons/ligaments (enthesitis), including soft tissue and bone oedema. Flexor tenosynovitis, surrounding diffuse peritendinous inflammation and soft tissue oedema are typically responsible for the “sausage” appearance (Olivieri et al., 1996). Synovitis and bone erosion can develop adding to further structural and functional impairment (Kane et al., 1999). Bone marrow oedema and ligamentous enthesitis have also been demonstrated via high resolution magnetic resonance imaging (MRI) (Tan et al., 2015). Superior sensitivities for detecting pathologies in early inflammatory arthritis have also been demonstrated using ultrasonography (US) compared to clinical examination alone (Kane, Balint, et al., 2003). Moreover, the accuracy of US for detecting inflammatory arthritis in PsA is regarded as comparable to MRI, with studies suggesting US may be superior for the assessment of synovitis (Backhaus et al., 1999).

However, direct comparison of PsA with/without dactylitis has not been specifically explored, including the characterisation of clinical, biochemical,

patient reported outcomes and ultrasound imaging outcomes including whether differences exist between these clinical entities at the early stages of PsA. The resultant significance of dactylitis as a unique phenotypical marker in early PsA has not been established in relation to disease status/ severity.

The presence or past history of dactylitis adds to the high sensitivity and specificity towards classifying PsA, and consists of one of the five domains within the CIASsification for Psoriatic ARthritis (CASPAR) criteria. It is associated with greater radiographic damage in chronic established PsA cohorts (Brockbank et al., 2005). Still, direct evaluation of dactylitis as a phenotypical marker of overall disease severity in early PsA has not been elucidated. Improved understanding of this pathognomonic sign, its characterisation, phenotypical significance, and disease burden at the early stages of its onset may further inform clinical practice.

The objective of this study was to determine whether there were differences in the extent of disease severity in PsA patients with dactylitis (dactylitic PsA) compared with PsA patients without dactylitis (non-dactylitic PsA), in terms of clinical, laboratory, patient reported outcomes and US imaging outcomes in an early DMARD naïve PsA cohort based on current dactylitis at/near to diagnosis.

6.2 Hypothesis aims and objectives

6.2.1 Hypothesis

Enthesitis is a significant pathological event in early, new onset spondyloarthritis and may be a biomarker for disease evolution.

6.2.2 Aims and objectives

To explore the significance of dactylitis, as a marker of disease severity in early PsA.

6.3 Methods

6.3.1 Study design

Cross-sectional observational cohort study.

6.3.2 Ethical approval

This study was granted ethics committee approval by the Leeds West Research Ethics Committee (ref: LG03/028).

6.3.3 Patients, clinical details and examination

Between December 2013 and October 2019, 177 consecutive, DMARD naive, early PsA patients attending the Leeds early arthritis clinic were recruited into a prospective observational study: the Leeds Spondyloarthritis Register for Research and Observation (SpARRO). Eligible participants were determined by age (≥ 18 years), meeting $\geq 3/5$ of the CASPAR criteria, and non-exposure to DMARDs (current or past) (Taylor et al., 2006). Patient data was collected on demographics, clinical history and examination, patient reported outcomes, biochemical and serological investigations, and PsA related ultrasound imaging. A thorough clinical history and examination was conducted by experienced and trained rheumatologists.

Examination of individual joints was recorded as per the PsA 78/76 joint count. The PsA cohort was dichotomised based on the presence or absence of dactylitis in patients. Dactylitis was recorded per digit in the hands or feet bilaterally (fingers 1-5, toes 1-5) or absence (no dactylitis) (Clegg et al., 1996). Dactylitis type was also recorded per digit as tender ("hot") or non-tender ("cold"). Individual joint examination was recorded as either tender, swollen, or both. Clinical, laboratory and imaging details were anonymised and recorded into a secure electronic case report form. Written informed consent was received from all patients for study participation in accordance with the declaration of Helsinki.

6.3.4 Ultrasound examination

The US protocol encompassed scanning of 50 joints per patient conducted using the GE Logiq E9 machine and linear ML 15-6 MHz probe or small-footprint linear array 18-8 MHz transducer by trained and experienced ultrasonographers who were blinded to all clinical details including laboratory results and any previous imaging. The US examination followed a protocol driven procedure standardised as per EULAR guidelines (Backhaus et al., 2001).

Patients underwent consent followed by clinical history, examination, and then ultrasound assessment on the same day. US synovitis was graded via semiquantitative GS and PD scores, dichotomised to identify US synovitis ($GS \geq 2$ vs $GS \leq 1$; $PD \geq 1$ vs $PD = 0$). The applied grading for synovitis was $GS \geq 2$, often associated with disease, and US $GS \leq 1$ determined as normal as it may occur frequently in healthy individuals (Padovano et al., 2016). The presence of abnormal PD signal ($PD \geq 1$) was defined as synovitis.

Synovitis was determined via semi-quantitative scoring for grades of GS and PD, recorded individually for each US scanned joint on a 0-3 scale (Szkudlarek et al., 2003). Synovitis was scored in 50 joints: wrist, metacarpophalangeal joints (MCP) 1-5, proximal interphalangeal joints (PIP) 1-5, distal interphalangeal joints (DIP) 2-5, elbows, knees, ankles (tibio-talar joint), subtalar joint (STJ), talonavicular joints (TNJ) and metatarsophalangeal joints (MTP) 1-5 joints. Ultrasonographic evaluation at the wrists encompassed radio-carpal, intercarpal, and ulnar-carpal joints and the highest GS and PD grades achieved were recorded for each wrist. At each knee, the suprapatellar pouch, medial and lateral recesses were evaluated, and the highest GS/PD scores recorded.

Bone erosions at joints were assessed using US given that it has superior sensitivity over conventional radiography in early PsA (Wakefield et al., 2000). Erosions were determined by peri/intra-articular cortical bone discontinuity present in two perpendicular planes (longitudinal/transverse), and scored via semiquantitative grading as defined by outcome measures in rheumatology (OMERACT) (Wakefield et al., 2005). Erosions were scored at 46 joints: wrists, MCP 1-5, PIP 1-5, distal interphalangeal joints DIP 2-5, knees, ankles (tibio-talar joint), TNJ, STJ, and MTP 2-5 joints. MTP 1 was excluded from erosion

scoring because it is a highly frequent site of osteoarthritis. All joints were scanned in longitudinal and transverse planes.

Enthesitis was determined by the OMERACT definitions for elementary lesions and modified Glasgow Ultrasound Enthesitis Severity Score (GUESS) was calculated per patient based on all the available enthesitis domains for each enthesal site (except bursitis at the quadriceps tendon insertion which was not recorded in the study protocol) (Terslev et al., 2014; Balint et al., 2018).

The study sonographers underwent training twice per year to ensure study procedures such as the performance and quality of US scans, image interpretation and the recording of results were maintained to a high and consistent standard and as per study protocol. The US scans were performed and scored by one of four research department sonographers with over 5 years of experience. Clinical examination was also completed by one of four rheumatology doctors with more than 5 years of experience.

6.3.5 Statistical analysis

Statistical tests were two-tailed, statistical significance pre-specified at 5% ($p < 0.05$) with 95% confidence intervals. Differences between mean, medians and proportions were calculated using student's t-test, quantile regression (continuous variables), Chi² test (binary variables), and Kruskal-Wallis (categorical variables) via STATA version 16.1 (StataCorp).

6.4 Results

6.4.1 Clinical patient cohort characteristics

PsA with/without dactylitis

Of 177 PsA patients, PsA with dactylitis (dactylitic PsA) occurred in 81/177 (46%) and PsA without dactylitis (non-dactylitic PsA) in 96 /177 (54%) (Figure 6:1). The mean ages were similar, 43.7 and 44.4 years in dactylitic vs non-dactylitic PsA patients respectively. The characteristics between dactylitic and non-dactylitic PsA groups are shown in Table 6:1.

Table 6:1. Characteristics of the PsA cohort dichotomised by the presence or absence of dactylitis.

Characteristics and outcomes	Non-dactylitic PsA [96/177 (54.2%)]	Dactylitic PsA [81/177 (45.8%)]	Difference/ p value
Clinical			
Age, mean (SD), years	44.4 (12.8)	43.7 (13.3)	0.7 (-3.2 to 4.5)
Male	38.0 (39.6%)	42.0 (51.9%)	p>0.05
Symptom duration, median (IQR), months	18.0 (10.5-36)	12.0 (6.0-24.0)	-6.0 (-13.1 to 1.1)
Duration from diagnosis, median (IQR), months	1.1 (0-2.7)	1.2 (0.3-4.6)	0.03 (-0.9 to 1.0)
Early morning stiffness median (IQR), minutes	50.0 (15.0-90.0)	60.0 (15.0-180.0)	0 (-24.1 to 24.1)
TJC (78), median (IQR)	4.0 (1.0-10)	9.0 (5.0-19.0)	5.0 (2.0 to 8.0)**
SJC (76), median (IQR)	1.0 (0.0-3.0)	7.0 (4.0-13.0)	6.0 (4.3 to 7.6)***
TJC (78) median (IQR) (excluding dactylitis)	4.0 (1.0-10.0)	5.0 (2.0-11.0)	1.0 (-1.4 to 3.4)
SJC (76) median (IQR) (excluding dactylitis)	1.0 (0.0-3.0)	3.0 (1.0-6.0)	2.0 (0.8 to 3.3)**
Current Psoriasis	96/96 (100.0%)	74/81 (91.4%)	p<0.003**
Family history of Psoriasis	52/94 (55.3%)	49/78 (62.8%)	p>0.05
PASI, median (IQR)	2.9 (0.8- 4.9)	1.9 (0.4-4.2)	-1.2 (-2.4 to 0.0)
Psoriatic Nail dystrophy	49/96 (51.0%)	44/81 (54.3%)	p>0.05
mNAPSI, median (IQR)	2.0 (0.0-7.5)	0.0 (0.0-8.0)	-2.0 (-3.7 to -27.9)*
Clinical Enthesitis	34/96 (35.4%)	42/81 (51.9%)	p=0.027*
MASES, median (IQR)	0.0 (0.0-2.0)	1.0 (0.0-2.0)	1.0 (0.4 to 1.6)**
BMI, median (IQR)	28.2 (24.0-32.1)	28.6 (25.0-31.5)	0.3 (-1.7 to 2.4)
Smoking (current)	19.0 (19.8%)	9.0 (11.1%)	p>0.05
Disease phenotype			
Oligoarthritis	83/96 (86.5%)	28/81 (34.6%)	p<0.001***
Polyarthritis	13/96 (13.5%)	53/81 (65.4%)	p<0.001***
DIP joint disease	7/93 (7.5%)	13/77 (16.9%)	p=0.058
Axial disease	17/94 (18.1%)	9/78 (11.5%)	p>0.05
Arthritis Mutilans	0	0	0
Laboratory markers			
CRP (mg/L), median (IQR)	5.0 (5.0-9.3)	8.1 (5.0-18.4)	3.1 (0.9 to 5.3)**
Elevated (>10)	24/96 (25.0%)	36/81 (44.4%)	p=0.006**
ESR, median (IQR)	11.0 (5.0-25.0)	16.5 (7.0-27.0)	7.0 (0.4 to 13.6)*
Patient Reported Outcomes (PROs)			
PsAQoL, median (IQR)	6.0 (0.0-13.0)	6.0 (2.0-12.0)	0.0 (-4.1 to 4.1)
DLQI, median (IQR)	3.0 (1.0-9.0)	2.0 (1.0-6.0)	-1.0 (-3.3 to 1.3)
HAQ, median (IQR)	0.75 (0.25-1.50)	0.75 (0.38-1.38)	0.125 (-0.23 to 0.48)
*p<0.05, **p<0.01, ***p<0.001			

Arthritis characteristics

The median symptom duration was shorter in dactylitic PsA (12 months) compared to non-dactylitic PsA (18 months). Early morning stiffness was longer in patients with dactylitis than without (60 vs 50 minutes). Tender and swollen joint counts were significantly higher in PsA with dactylitis in comparison to PsA without dactylitis [9/7 vs 4/1 respectively ($p < 0.01/p < 0.001$)]. Significantly more patients in the PsA without dactylitis group were oligoarticular in phenotype, compared to polyarticular classification in PsA with dactylitis (86.5% vs 34.6%; $p < 0.001$). Excluding dactylitic joints, dactylitic PsA remained predominantly polyarticular (51/81; 62.9%), with the SJC (but not the TJC) still significantly greater [total/ patients: 326/81 vs 209/96; median 3 vs 1; $p = 0.002$] in this group.

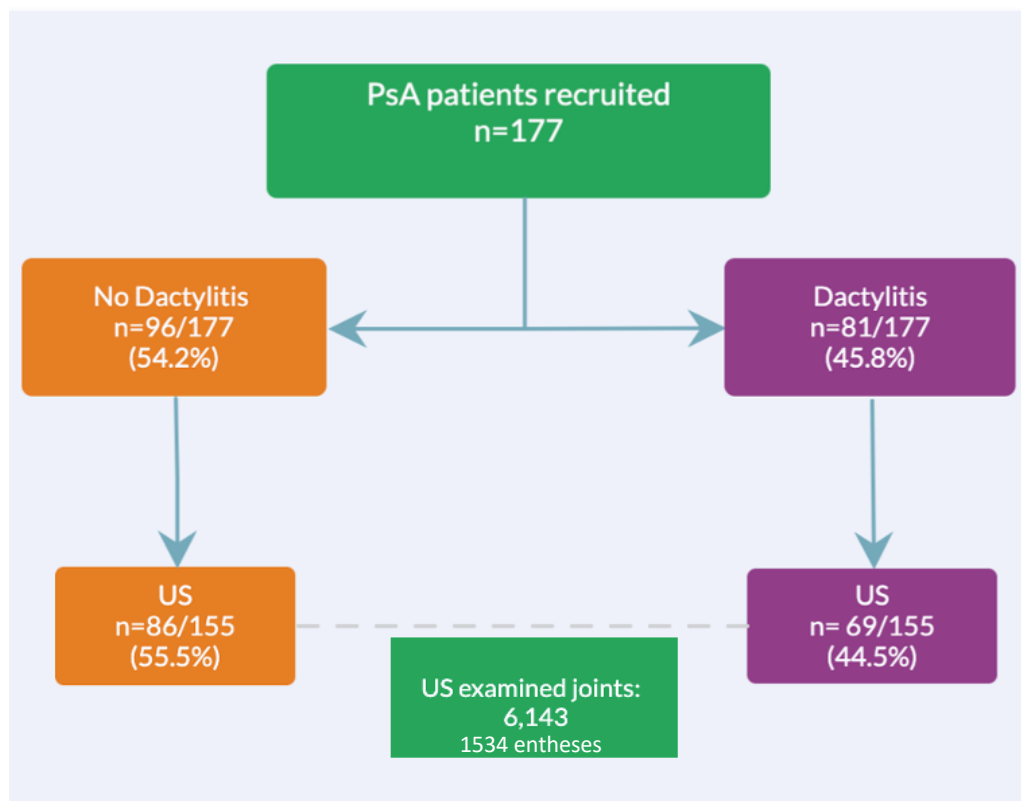


Figure 6:1. The total number of dactylitic and non-dactylitic PsA patients recruited and evaluated by clinical examination followed by US.

Dactylitis

Of 81/177 (45.8%) PsA patients with dactylitis, a total of 214 digits were affected. Multiple digits (>1) were involved in 51/81 (63%) patients with a median of 2 digits (1-3). Hands were involved in 23/81 (28.4%) patients, feet in 40/81 (49.4%) and both in 18/81 (22.2%). The distribution was predominantly asymmetrical in 52/81 (64%) patients. In terms of digits affected, dactylitis was more prevalent in toes (146/214; 68.2%) than fingers (68/214; 31.8%). “Hot” dactylitis was more prevalent affecting 179/214 digits (83.6%) in contrast with “cold” dactylitis presenting in only 35/214 (16.4%). The most frequent sites for “hot” dactylitis were the 2nd finger (23/179; 12.8%) and 4th toe (40/179; 22.3%), and for “cold” dactylitis, 3rd finger (2/35; 5.7%) and 4th toe (10/35; 28.6%) as shown in Figure 6:2.

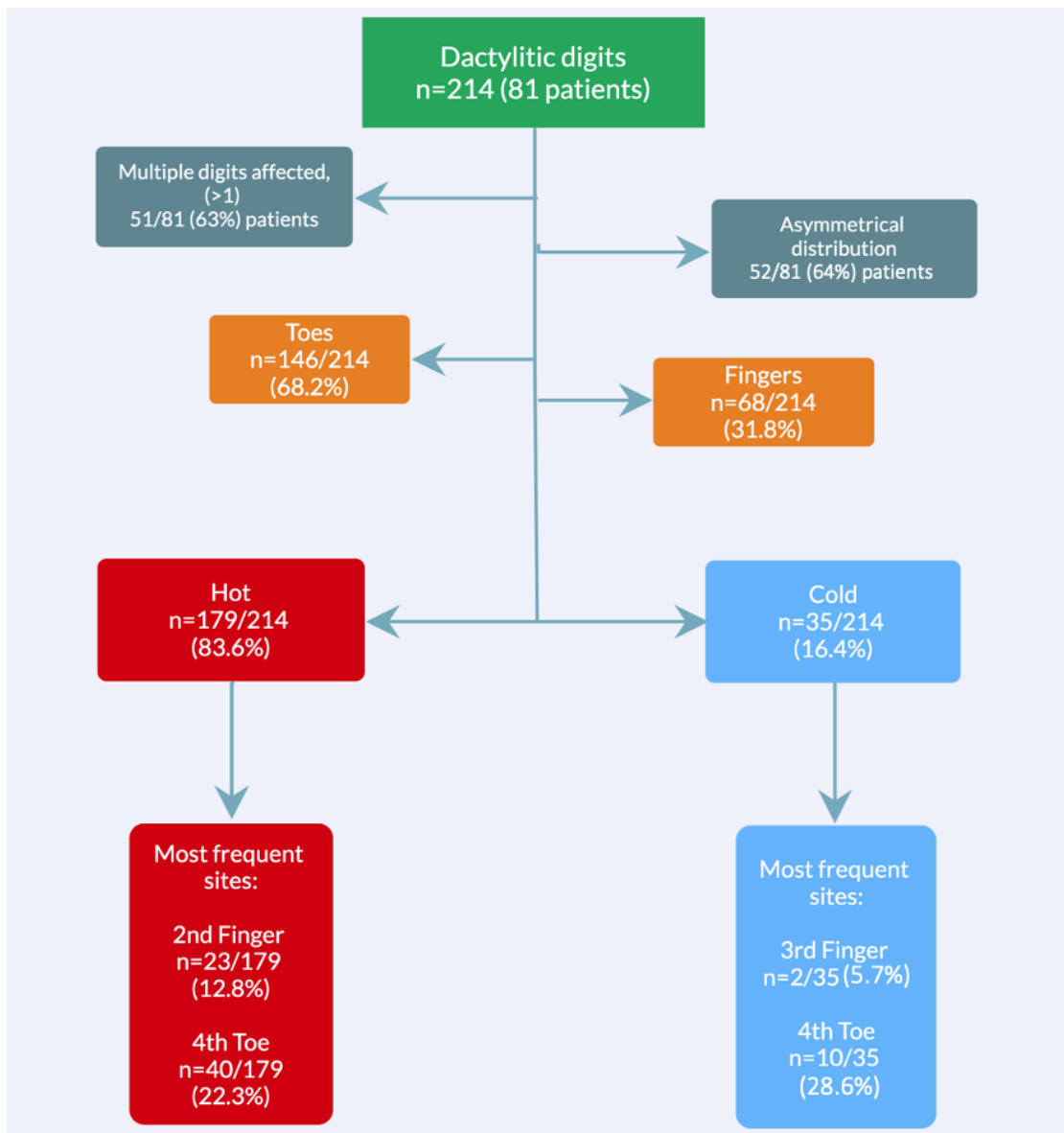


Figure 6:2. Flow diagram illustrating the clinical characteristics of dactylitis.

Cutaneous Psoriasis

The Psoriasis area severity index (PASI) was greater in non-dactylitic patients but was not statistically significant ($p>0.05$) given that the medians were relatively low between groups respectively with overlapping CIs [2.9 (0.8- 4.9) *versus* 1.9 (0.4-4.2)].

Nail Psoriasis

The median modified nail PsO severity index (mNAPSI) was in fact greater in non-dactylitic PsA ($p<0.05$). No differences were observed for the prevalence of nail dystrophy between groups. Of the patients with dactylitis, nail dystrophy occurred in 44/81 (54.3%) and of all nail dystrophy affected patients, 44/93 (47.3%) were dactylitic PsA. No significant association was found between nail dystrophy corresponding to the digit affected by dactylitis.

Clinical Enthesitis

Clinical enthesitis, defined by positive Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), was present in a greater proportion ($p>0.05$; non-significant) of PsA with dactylitis compared to non-dactylitic PsA, 42/81 (52%) vs 34/96 (35%) respectively. The median difference in (MASES) reflected low levels of clinical enthesitis overall but was significantly greater in dactylitic PsA patients [1.0 (0.0-2.0) vs 0.0 (0.0-2.0); ($p<0.01$)].

Inflammatory markers

In contrast to non-dactylitic patients, blood CRP (mg/L) and ESR (mm/hr.) were found to be significantly higher in patients with dactylitis [CRP: 5.0 vs 8.1 ($p<0.01$), ESR: 11 vs 16.5 ($p<0.05$) by median difference].

Composite clinical and patient outcomes

A high disease activity in PsA (DAPSA) state was recorded in a greater proportion of PsA patients with dactylitis, and similarly greater DAPSA scores were recorded but the difference did not meet significance (median 24.4 vs 20.8; $p=0.07$). There were no significant differences in the PsAQoL, HAQ, or the DLQI.

6.4.2 Ultrasonographic examination

Synovitis

In total 155/177 (87.5%) PsA patients underwent US examination of 6143 joints; 69/155 PsA patients with dactylitis; 86/155 without dactylitis. Ultrasound synovitis was significantly more prevalent in the PsA with dactylitis group [GS \geq 2: mean difference -7.5 (-12.0 to -3.0), $p < 0.001$; PD \geq 1: mean difference -4.0 (-8.8 to 0.9), $p < 0.001$] as detailed in Table 6:2 (a). Concomitant GS \geq 2+PD \geq 1 per joint was observed significantly more frequently in dactylitic PsA patients (6.3% vs 2.6%; $p < 0.001$). Compared to non-dactylitic PsA, in dactylitic PsA there was greater prevalence of GS \geq 2 synovitis observed at MCP 2-5, PIP1-3, MTP2-5, and PD \geq 1 synovitis at MCP2, MTP4-5. Figure 6:3 (A) illustrates synovitis in an affected toe (MTP5).

Erosions

Ultrasonographic cortical bone erosions were identified in a significantly greater proportion of dactylitic PsA patients, compared to PsA without dactylitis [22/69 (31.9%) vs 11/86 (12.8%); ($p = 0.004$)]. There was also a significant difference in the total number of erosions detected in dactylitic PsA compared to non-dactylitic PsA patients [33/2557 joints vs 15/3206 joints ($p < 0.001$) as shown in Table 6:2]. The anatomical sites for joints most prone to erosive damage were MCP2 [9/33 (27.3%)] and MTP5 [11/33 (33.3%)].

On exclusion of dactylitic digits from the analysis, US erosions remained proportionally greater in 24/2315 (1.1%) joints in dactylitic PsA vs 15/3206 (0.5%) joints in non-dactylitic PsA ($p = 0.008$). The proportion of patients with US erosions was greater for dactylitic PsA [18/69 (26.1%) vs 11/86 (12.8%) patients ($p = 0.035$)]. Total erosion scores at the patient level were also greater for dactylitic PsA ($p = 0.016$), including when dactylitis was excluded ($p = 0.048$) as shown in Table 6:2 (b)). The appearances of erosions detected in the dactylitic PsA group are illustrated in Figure 6:3 (B,D).

Table 6:2 Ultrasound synovitis and joint erosions in non-dactylitic *versus* dactylitic PsA: a) including dactylitis affected digits; b) excluding dactylitic affected digits.

a) US synovitis and erosions	Non-dactylitic PsA [86/155 (55.5%)]	Dactylitic PsA [69/155 (44.5%)]	Difference
Total GS \geq 2	551/3422 (16.1%)	642/2721 (23.6%)	p<0.001
Total PD \geq 1	114/3422 (3.3%)	198/2721 (7.3%)	p<0.001
Total GS \geq 2+PD>1	89/3422 (2.6%)	171/2721 (6.3%)	p<0.001
Total US erosions	15/3206 (0.5%)	33/2557 (1.3%)	p<0.001
Total erosion score (patient level)	Mean 0.28 (SD 0.87), median 0 (0,0)	Mean 0.72 (SD 1.63), median 0 (0,1)	p=0.016
Total patients US erosive	11/86 (12.8%)	22/69 (31.9%)	p=0.004
b) US synovitis and erosions	Non-dactylitic PsA (same as above (a)) [86/155 (55.5%)]	Dactylitic PsA (dactylitis excluded) [69/155 (44.5%)]	Difference
Total GS \geq 2	551/3422 (16.1%)	507/2466 (20.6%)	p<0.001
Total PD \geq 1	114/3422 (3.3%)	126/2466 (5.1%)	p<0.001
Total GS \geq 2+PD>1	89/3422 (2.6%)	101/2466 (4.1%)	p=0.003
Total US erosions	15/3206 (0.5%)	24/2315 (1.1%)	p=0.008
Total erosion score (patient level)	Mean 0.28 (SD 0.87), median 0 (0,0)	Mean 0.58 (SD 1.52), median 0 (0,1)	p=0.048
Total patients US erosive	11/86 (12.8%)	18/69 (26.1%)	p=0.035

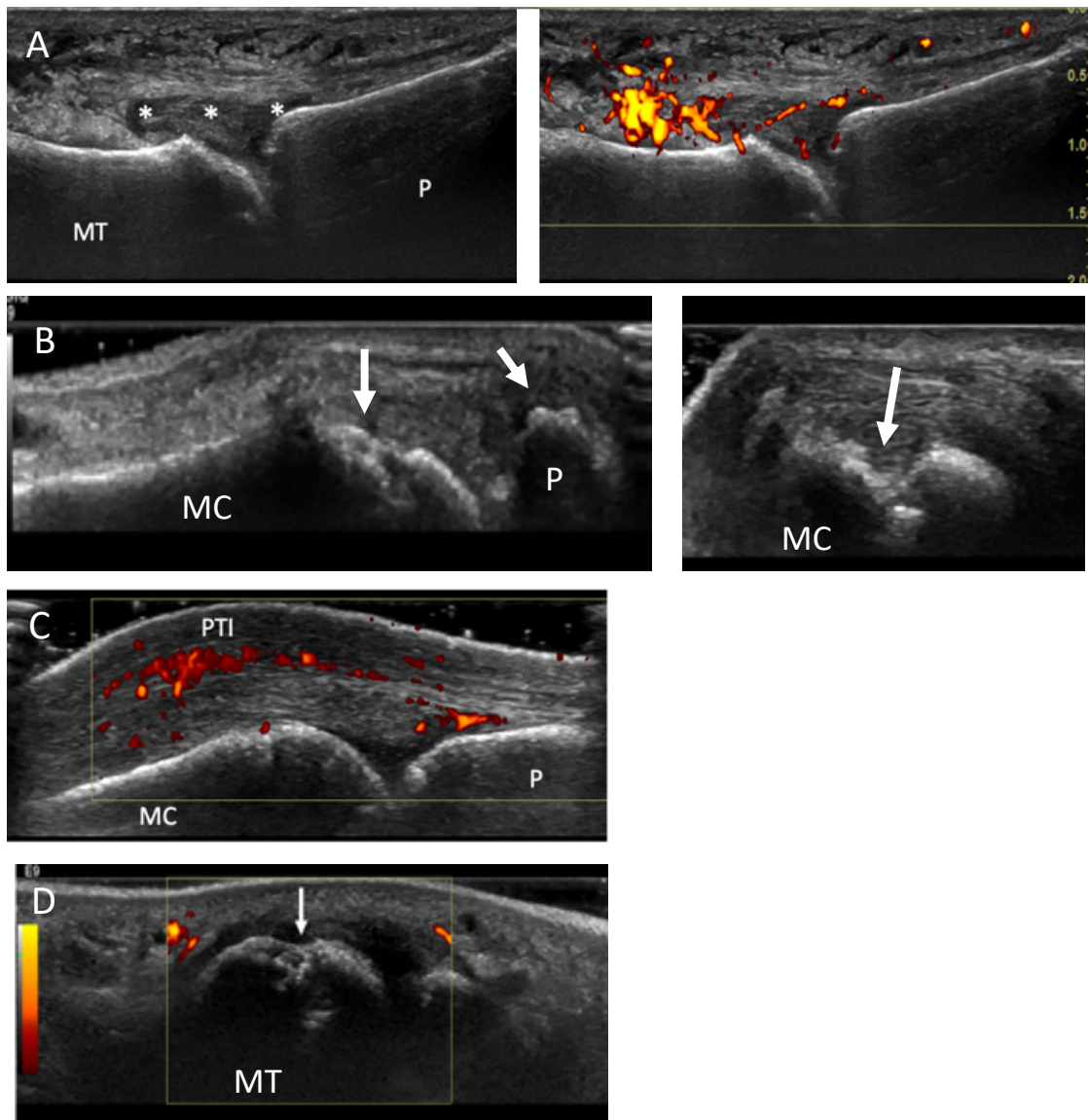


Figure 6:3. Characteristic ultrasound pathologies in early dactylitic PsA.

A: Longitudinal view through the 5th metatarsophalangeal joint (MTP5) illustrating synovitis within a dactylitic toe. There is grey scale synovitis (grade 3) with effusion (*) and abnormal power Doppler signal (grade 2, right image) consistent with 'active' synovitis. MT= metatarsal; P=phalanx. **B:** Periarticular cortical bone irregularity at the 2nd metacarpophalangeal (MCP2) joint confirmed in the longitudinal (left) and transverse planes respectively (right) confirming erosion. A common site of erosion in PsA, and in dactylitis. **C:** Longitudinal view at the metacarpophalangeal (MCP) joint displaying power Doppler signal above the extensor tendon (peri-tendon inflammation (PTI)). **D:** Image in the transverse plane showing the 5th metatarsal head, the most frequent site of erosion in feet, demonstrating peri-articular bone irregularity (arrow). There is also surrounding grey scale synovial hypertrophy (grade 2). Bone irregularity was confirmed further in longitudinal plane to signify erosion.

Dactylitis

In digits affected by dactylitis, US synovitis (GS \geq 2 +/- PD \geq 1) was prevalent in 137/255 (53.7%) joints. A higher prevalence of US synovitis in joints affected by “hot” dactylitis 129/227 (56.8%) was observed compared with the “cold” type [8/28 (28.6%)]. Ultrasound PD synovitis (PD \geq 1 regardless of GS grade) was present in 72/255 (28.2%) of the total joints clinically affected by dactylitis [“hot”: 69/227 (30.4%), and “cold”: 3/28 (10.7%)]. In “hot” dactylitis, erosions occurred in 9/227 (2.6%) of affected joints [4/69 (6%) patients] and none in “cold” dactylitis (0/28).

Enthesitis

A total of 1534 entheses were assessed via US imaging. No significant differences were found between dactylitic PsA and non-dactylitic PsA patients for total modified GUESS scores [median (IQR): 3(2,6) vs 4(1,6), (p=0.91)]. Direct comparison of each OMERACT defined elementary lesion per enthesal site assessed (Achilles tendon enthesis, quadriceps tendon insertion, proximal and distal patellar tendon insertions, plantar fascia) was unremarkable except for significant differences in the detection of bursitis at the Achilles tendon in dactylitic PsA [4/56 vs 0/69 patients; (p<0.038)] and presence of enthesophytes at the quadriceps tendon insertion in non-dactylitic PsA patients [23/80 vs 51/104 patients; (p=0.005)].

6.5 Discussion

This is the first study to examine clinical and ultrasound characteristics of a DMARD-naïve, early PsA cohort based on presence/absence of dactylitis. These study results demonstrated a greater burden of disease in PsA with dactylitis. Independent of dactylitis (i.e. exclusion of digits affected by dactylitis), dactylitic PsA patients still had greater SJC, CRP, prevalence of US synovitis and erosive damage compared to non-dactylitic PsA. The presence of dactylitis can therefore be considered a clinical marker for a more aggressive articular phenotype in early PsA.

Brockbank et al first reported on acute dactylitis with an average disease onset of 8 years, and confirmed that radiographic damage occurred frequently in joints affected by dactylitis and first suggested dactylitis may be associated with PsA disease severity (Brockbank et al., 2005). Healy and colleagues reported a high prevalence of MRI synovitis in joints affected by “hot” dactylitis (69%), nearly matching the prevalence of US synovitis found in this study (56.8%) (Healy et al., 2008). Gladman and colleagues also later reported that dactylitis responded better to biologic DMARDs than conventional synthetic (cs) DMARDs (Gladman et al., 2013). Longitudinal follow-up in PsA showed that development of dactylitis predicted further radiographic joint destruction suggesting it is a poor prognostic factor (Geijer et al., 2015). This study is the first to directly evaluate the presence/absence of dactylitis, to demonstrate that in DMARD untreated early PsA, patients with dactylitis had a higher burden of US synovitis and erosion, not only in dactylitis affected digits, but independently (i.e. excluding dactylitis).

Synovitis and erosion in early PsA are significant pathological findings, affecting management and functional outcomes in the long term. Yet frequently in PsA, CRP/ESR remain low or normal, nonetheless in addition to a higher median CRP ($p < 0.01$), elevated CRP was present in greater proportions of dactylitic PsA (44.4% vs 25%; $p = 0.006$). This study also supports the 2019 EULAR recommendations which regard dactylitis as a poor prognostic factor in early PsA advocating rapid initiation of DMARDs (Gossec et al., 2020). Delays to diagnosis and treatment in early symptomatic PsA lead to poor radiographic and functional outcomes; thus early recognition of dactylitis, often a feature at disease presentation, can facilitate therapeutic stratification leading to better outcomes (Haroon et al., 2015). Why some PsA patients are burdened by dactylitis and others are not remains unclear, despite studies having explored biomechanical factors including the “deep Koebner” phenomenon which may explain the greater prevalence of dactylitis in the feet (Wilkins et al., 2016; Tinazzi et al., 2018).

Tailored therapy specific to PsA phenotypes is increasingly pertinent to avoid bDMARD failure and associated decremental treatment responses, especially relevant given the diverse mode of action therapies available. These study data could further inform a clinical trial of therapy stratification by dactylitis as

a phenotypical sign to improve understanding of differential responses within PsA phenotypes. In summary, this study demonstrated an increased severity of joint disease in early DMARD untreated PsA presenting with dactylitis in line with previous studies in established disease. Dactylitis in early PsA therefore signifies a phenotype of more aggressive disease and may have a role for therapeutic and prognostic stratification.

6.6 Conclusion

This study identifies dactylitis as a clinical indicator for a severe phenotype with a greater burden of articular disease in early DMARD-naive PsA. Although synovitis was prevalent in dactylitis, the increased disease burden in PsA patients was also independent of digits affected by dactylitis. Dactylitis may be a useful discriminator for risk stratification in future PsA management strategies and clinical trials.

Key messages

- Greater SJC, CRP and US synovitis and erosions were found in dactylitic PsA, independent of dactylitis.
- Dactylitis is an indicator of a more severe phenotype with a greater burden of disease and may be used for disease stratification and early intervention approaches.

Chapter 7. Infliximab drug trough levels and anti-infliximab antibody levels as biomarkers of treatment response in Spondyloarthritis

7.1 Introduction

Personalised medicine is the concept of individualised treatment, tailored to each person's characteristics. Attaining management strategies that allow personalisation of care can lead to optimal outcomes for more patients. This approach is more relevant in SpA in recent years with an array of several therapeutic options including the advent of bDMARD monitoring. Infliximab (IFX), is a chimeric monoclonal antibody targeted against TNF α and an efficacious bDMARD for the treatment of enthesal and synovial pathology in SpA, which has led to its widespread use in routine practice (Van Der Heijde et al., 2005; Reich et al., 2005). It is effective for the treatment of several other immune mediated inflammatory diseases (IMIDs) including psoriasis (PsO) and inflammatory bowel disease (IBD) which share common aetiopathogenic associations with SpA. Despite the revolutionary developments in therapeutics, bDMARD inefficacy still occurs in at least 30- 35% of patients with AS or PsA (Saad et al., 2010; Grintborg et al., 2013). Often bDMARDs lose efficacy with time and one of the main reasons for secondary loss of response (LOR) is immunogenicity, the development of human anti-drug antibodies (ADAs) that effectively interfere or neutralise the drug preventing therapeutic efficacy (Schaeffer et al., 2015). Data from axSpA clinical trials indicate that only 50% of patients achieve a meaningful ASAS40 response after 24 weeks of their first bDMARD, signifying that LOR is a highly relevant issue (Navarro-Compán et al., 2017). Subsequent second or third line bDMARDs are associated with a stepwise decremental response in SpA patients many of which have developed immunogenicity.

In clinical practice in SpA, objective biomarkers for monitoring disease are lacking. Inflammatory markers such as the CRP and ESR are frequently normal in at least 50% of PsA and 39% of AS (Dougados et al., 1999; Bogliolo

et al., 2012). There is therefore a reliance on clinical history and examination, and validated questionnaire-based outcomes such as the BASDAI, all of which have elements of subjectivity. Assessment of treatment efficacy could therefore be improved with greater objectivity. Measurement of serum drug trough levels (DLs) can provide a potential opportunity to assess and maintain treatment efficacy via optimisation of therapeutic serum drug concentrations known as therapeutic drug monitoring (TDM), and may involve precise and accurate bDMARD dose/interval adjustment tailored to the individual.

In order to explore whether treatment responses to IFX treated SpA could be rationalised, a clinical evaluation of serum infliximab DLs and ADAs was conducted. This also complemented the SpA service related improvements at the time when bDMARD switching and cost-effectiveness were being evaluated.

7.2 Hypotheses, aims and objectives

7.2.1 Hypothesis

- Measuring drug and antibody levels in IFX treated SpA patients can rationalise treatment non-response.

7.2.2 Aims and objectives

- To explore mechanisms of treatment non-response in SpA patients receiving the monoclonal antibody IFX.
- To rationalise treatment based upon IFX drug level.

7.3 Methods

7.3.1 Study design

A prospective clinical evaluation of IFX treated SpA patients was conducted.

7.3.2 Patients

Patients with SpA receiving IFX were identified via the local biologics register and offered DL and ADA. Eligible patients included only those with a diagnosis of SpA, treated within the Leeds Specialist Spondyloarthritis service, and currently receiving IFX. All patients confirmed his/her consent to have DL and ADA taken and were counselled on the possible implications these additional investigations may have on the treatment regimen such as possible change to dose or interval, or change of bDMARD. Following baseline DL/ADA measurement, the clinical impression from the treating rheumatologist was recorded to identify which SpA patients had loss of response (LOR) to IFX.

7.3.3 Laboratory assay

Blood collection for IFX serum DLs and ADAs was conducted just prior to their IFX infusion (as per drug “trough” level). Serum analysis was conducted by enzyme-linked immunosorbent assay (ELISA) to determine the quantity of free IFX (validated for detecting the IFX bio-originator and biosimilar (CT-P13)). Serum was also analysed using a bridging ELISA assay to measure total free and bound human antibodies to IFX (ADAs).

7.3.4 Statistical methods

Differences between groups were tested using the Mann–Whitney U test and logistic regression modelling was conducted to identify predictors of LOR.

7.4 Results

7.4.1 Patients and baseline characteristics

At baseline, 58 SpA patients were identified (39 axSpA, 19 PsA). Of the axSpA patients, 36/39 had a confirmed diagnosis of AS (including 4 with uveitis, 1

with Crohn's disease (CD)), 3/39 had nr-axSpA (2/3 with PsO). A peripheral PsA phenotype was predominantly present in 19/19 of the remaining patients. The median age (IQR) was 48 years (38-58) in axSpA and 57 years (50-63) in PsA patients. In axSpA, 32/39 (82%) were male compared with 6/19 (32%) in PsA. Disease duration was 19 years (12-30) in axSpA and 17 years (14-23) in PsA. The duration of IFX treatment was 10 (4-14) years and 9 (6-14) years in axSpA and PsA respectively. The mean interval between infusions was 7 weeks and mean dose of 5mg/kg. The median weight of individuals was greater in PsA, 88 kg (65-104) compared with axSpA, 80 kg (71-90). Concomitant csDMARD therapy was taken by 18/39 (46%) of axSpA compared with 17/19 (89%) of PsA. Methotrexate was the most frequent concomitant csDMARD taken by 94% of SpA patients at a median dose of 15mg weekly. There was a previous history of bDMARD in 10/ 58 (17%) patients [5/39 (13%) axSpA; 5/19 (26%) PsA]. Baseline characteristics are outlined in Table 7:1. The baseline median BASDAI was 3.7 (2.1-5.8) for axSpA patients (missing data n=5). In PsA patients the median (IQR) for TJC was 2 (0-12) and for SJC was 0 (0-1), (missing data n=2).

Table 7:1. Baseline characteristics of IFX treated SpA patients

Patient Characteristics	Total SpA (n=58, 100%)	axSpA (n=39, 67%)	PsA (n=19, 33%)
Age, years; median (IQR)	52 (43-59)	48 (38-58)	57 (50-63)
Male: Female	38:20	32:7	6:13
Disease duration, years; median (IQR)	17 (12-28)	19 (12-30)	17 (14-23)
IFX duration, years; median (IQR)	10 (5-14)	10 (4-14)	9 (6-14)
Weight (kg); median (IQR)	81 (70-95)	80 (71-90)	88 (65-104)
Concomitant csDMARD, n (%)	35/58 (60%)	18/39 (46%)	17/19 (89%)
MTX, n (%)	33/35 (94%)	16/18 (89%)	17/17 (100%)
MTX dose/wk; median (IQR)	15mg (10-25)	17.5mg (14-25)	10mg (10-25)
HCQ, 200mg/od, n (%)	2/35 (6%)	2/18 (11%)	0/19 (0%)
Previous bDMARD	10/58 (17%)	5/39 (13%)	5/19 (26%)

7.4.2 Baseline DLs and ADAs

Baseline IFX DLs were proportionately similar at each category for axSpA and PsA patients (Table 7:2). Therapeutic IFX DLs were found in 17/39 (44%) axSpA vs 8/19 (42%) PsA. Low/undetectable DLs were found in 15/39 (38%) axSpA and 8/19 (42%) PsA patients respectively. Infliximab DLs were undetectable in 7/39 (18%) axSpA vs 4/19 (21%) PsA patients and classed as low in 8/39 (20%) axSpA and 4/19 (21%) PsA. High IFX DLs were observed in 7/39 (18%) axSpA vs 3/19 (16%) PsA. A significantly greater median DL was identified in IFX responders compared to non-responders (patients with LOR); 3.4 mcg/ml vs 0.8 mcg/ml ($p < 0.01$ / $p = 0.007$). Figure 7:1 illustrates the higher DLs observed in responders versus lower/undetectable DLs in non-responders.

Positive ADAs were identified in 17/39 (44%) axSpA and 8/19 (42%) PsA patients. High ADAs (>100 AU/ml) were detected in 3/17 (17%) axSpA vs 4/8 (50%) PsA. Of these high ADAs, 6/7 (86%) had concurrent undetectable DLs. In LOR, positive ADAs were present in 7/9 (78%), and negative ADAs in 2/9 (22%). Of the 23/58 (40%) patients with low/undetectable DLs, 15/23 (65%) were ADA positive and 8/23 (35%) were ADA negative. Of the 15/23 ADA positive, 7/15 (47%) had LOR and 8/15 (53%) continued IFX (responders). Figure 7:2 demonstrates the baseline IFX ADAs and corresponding DLs indicating an inverse relationship is present.

Table 7:2. Infliximab drug trough level (DL) and anti-drug antibody (ADA) results

	Baseline (n=58)			Follow-up: 6 -12 months (n=48)		
	SpA n=58 (Total/100%)	axSpA n=39 (67%)	PsA n=19 (33%)	SpA n=48 (Total/100%)	axSpA n=34 (71%)	PsA n=14 (29%)
IFX DL						
High (>6 mg/l)	10/58 (17%)	7/39 (18%)	3/19 (16%)	2/48 (4%)	2/34 (6%)	0/14 (0%)
Therapeutic (2-6 mg/l)	25/58 (43%)	17/39 (44%)	8/19 (42%)	29/48 (60%)	21/34 (62%)	8/14 (57%)
Low (<2mg/l)	12/58 (21%)	8/39 (20%)	4/19 (21%)	7/48 (15%)	4/34 (12%)	3/14 (21%)
Undetectable (<0.8mg/l)	11/58 (19%)	7/39 (18%)	4/19 (21%)	10/48 (21%)	7/34 (21%)	3/14 (21%)
ADA +ve (total)	25/58 (43%)	17/39 (44%)	8/19 (42%)	21/48 (45%)	17/34 (50%)	4/14 (29%)
Low <50 AU/ml	11/25 (44%)	8/17 (47%)	3/8 (38%)	17/21 (81%)	14/17 (82%)	3/4 (75%)
Mod 50 - 100	7/25 (28%)	6/17 (35%)	1/8 (12%)	2/21 (9.5%)	1/17 (6%)	1/4 (25%)
High >100	7/25 (28%)	3/17 (17%)	4/8 (50%)	2/21 (9.5%)	2/17 (12%)	0/4 (0%)
ADA -ve	33/58 (57%)	22/39 (56%)	11/19 (58%)	27/48 (56%)	17/34 (50%)	10/14 (71%)

	Baseline (n=58)			Follow-up: 6 -12 months (n=48)		
	SpA n=58 (Total/100%)	axSpA n=39 (67%)	PsA n=19 (33%)	SpA n=48 (Total/100%)	axSpA n=34 (71%)	PsA n=14 (29%)
ADA+ve (mod/high) and undetectable/low DL*	11/58 (19%)	7/39 (18%)	4/19 (21%)	4/48 (8%)	3/34 (9%)	1/14 (7%)
IDA (n)	4/11 (36%)	3/7 (43%)	1/4 (25%)	1/4 (25%)	0/3 (0%)	1/1 (100%)
IFX discontinued	6/11 (55%)**	3/7 (43%)**	3/4 (75%)**	2/4 (50%)**	2/3 (67%)**	0/1 (0%)
No change	1/11 (9%)	1/7 (14%)	0/4 (0%)	1/4 (25%)	1/3 (33%)	0/0 (0%)
ADA -ve and undetectable/low DL***	8/58 (14%)	6/39 (15%)	2/19 (11%)	7/48 (15%)	4/34 (12%)	3/14 (21%)
IDA (n)	4/8 (50%)	3/6 (50%)	1/2 (50%)	2/7 (29%)	0/4 (0%)	2/3 (67%)
IFX discontinued (n)	1/8 (13%)	1/6 (17%)	0/2 (0%)	0/7 (0%)	0/4 (0%)	0/3 (0%)
No change	3/8 (37%)	2/6 (33%)	1/2 (50%)	5/7 (71%)	4/4 (100%)	1/3 (33%)

IDA= interval or dose adjustment; n= number of patients; +ve=Positive, -ve=Negative; *possible drug neutralisation; **all patients had loss of response (LOR); ***low or undetectable drug suggests review of drug dose/interval is required.

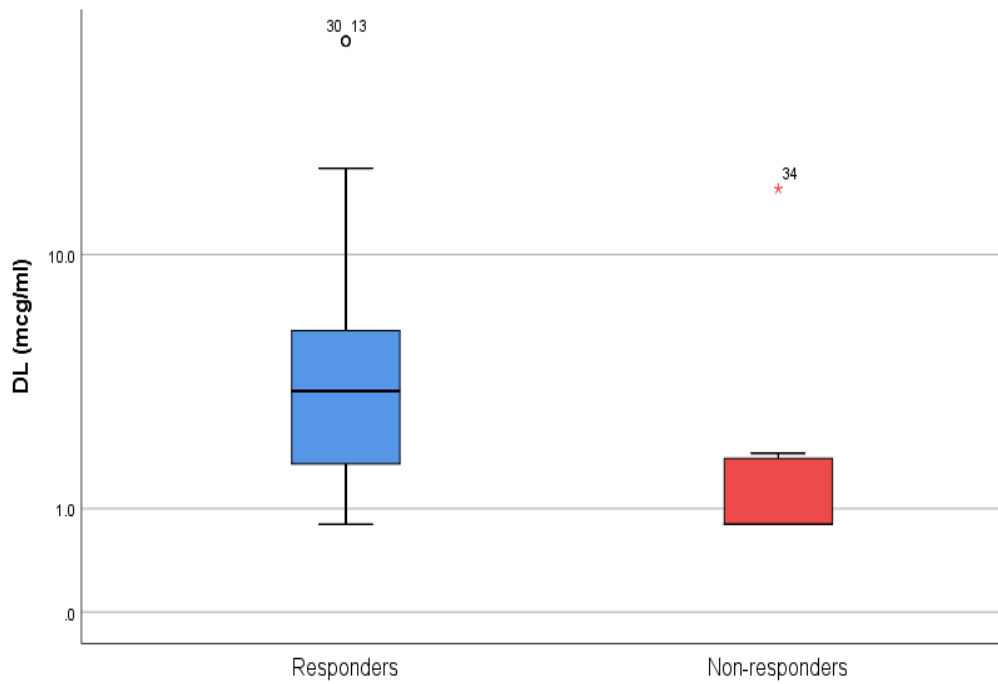


Figure 7:1 Serum infliximab drug trough level (DL) in non-responders (LOR) versus responders.

In SpA patients with LOR there were either undetectable DLs (<0.8 mcg/ml) or low DLs (<2 mcg/ml) found, compared with higher DLs observed in responders ($p=0.007$).

7.4.3 Baseline clinical outcome

At baseline, there were 9/58 (16%) SpA patients deemed to have a clinical loss of response (LOR) to IFX. Low DLs occurred in 8/9 (89%) SpA patients (4/8 AS, 4/8 PsO) with LOR. Of those with LOR, the mean BASDAI was 6.8 (no data 5/9 patients), the mean CRP was 36 mg/L (no data in 3/9), TJC 9 SJC 3 (no data 4/9). Two thirds of LOR [6/9 patients: 4 axSpA, 5 PsA; (67%)] had high/moderate ADAs (70-400AU/ml) and 5/6 (83%) of these patients had corresponding undetectable (<0.8 AU/ml) DLs. The remaining 3/9 patients included 2/3 ADA negative (1/3 high DL, 1/3 low DL) and one patient with low ADA and low DL. Of these 6/9 patients had concomitant MTX prescribed. The clinical outcome was determined by the treating rheumatologist and included 9/9 SpA patients that discontinued IFX, and 8/9 of these switched to an alternative bDMARD. Figure 7:3 illustrates the ADA/DLs in patients identified with clinical LOR to IFX and the subsequent management outcomes.

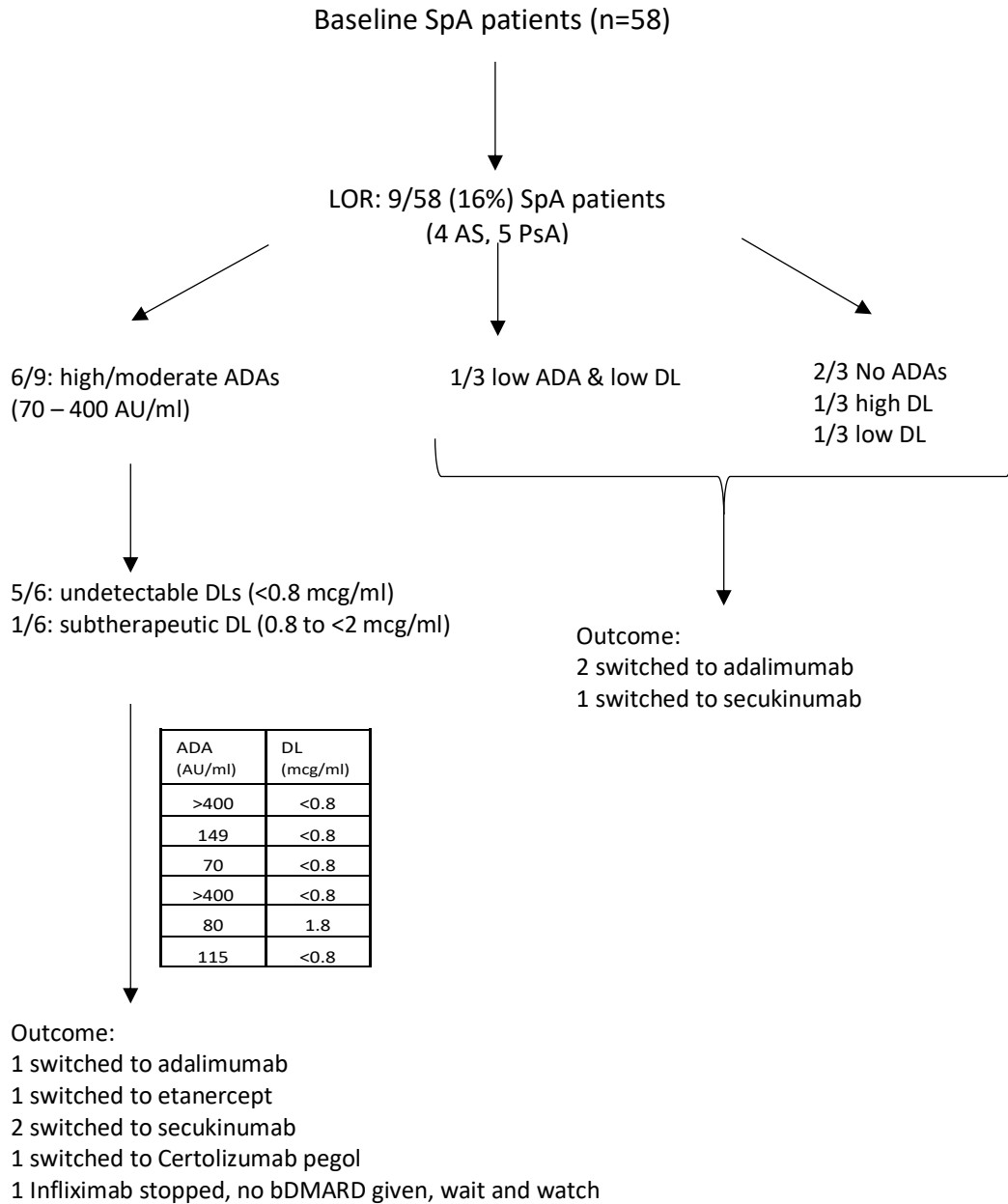


Figure 7:3 Flow diagram outlining ADA/DLs in SpA patients with LOR to infliximab (baseline).

Of those patients with LOR to infliximab, two thirds had high/moderate ADAs and corresponding undetectable or low DLs.

7.4.4 Follow-up IFX DLs and ADAs

Follow up was available in 48/58 patients at baseline. No follow up was available in 10 patients as no further IFX DLs/ADAs were conducted in the 9 patients that stopped IFX and the 1 patient that was lost to follow-up (clinic non-attendance). The remaining IFX treated patients [48/58 (83%)] underwent repeat DL and ADA between 6-12 months from baseline (results as shown in Table 7:2). The proportion of SpA with therapeutic DLs at follow-up was 29/48 (60%), higher than at baseline [25/58 (43%)]. High DLs were less frequent overall 2/48 (4%) [vs 10/58 (17%) at baseline], however a comparable proportion of undetectable DLs remained at follow-up 10/48 (21%) [vs 11/58 (19%) at baseline].

Compared to baseline, a similar proportion of patients at follow-up were ADA negative [27/48 (56%) vs 33/58 (57%) at baseline], and similar proportions were observed for ADA positivity at follow-up and baseline [21/48 (45%) vs 25/58 (43%) respectively]. The presence of high/moderate ADAs and corresponding subtherapeutic/undetectable DLs at follow-up was lower, 3/48 (6%). Interestingly, there were more patients at follow-up with subtherapeutic or undetectable DLs and corresponding negative ADAs, than at baseline [7/48 (15%) vs 2/58 (3%)].

7.4.5 Follow-up clinical outcome (LOR and treatment responders)

Of the baseline responders, 18/48 at follow-up recorded low level ADAs; 3/18 were moderate (50-100 AU/ml), and 3/18 were high (>100 AU/ml). The IFX drug interval was adjusted in 3 of these patients. At follow-up, 2 patients recorded clinical LOR and stopped IFX. Both of these recorded very high ADAs (301, 400 AU/ml) and simultaneous undetectable DLs (<0.8 mcg/ml). Interestingly, both patients had AS and previous positive baseline ADAs (72, 303 AU/ml respectively) with previous corresponding therapeutic/undetectable DL respectively. Infliximab was discontinued in each of the 2/48 (4%) patients; one managed without further bDMARD, and the other initiated onto a different TNFi (golimumab). Of the 6 responders with

moderate/high ADAs, 4 continued IFX, 1 of which received further interval reduction. In total, 4 patients at baseline with positive ADAs developed an increase in their ADA level at follow-up. Very high ADA were present in 2 patients corresponding with loss of treatment response (mean change +90 AU/ml). There were no infusion reactions recorded between baseline and follow-up.

7.4.6 Infliximab dose and interval adjustment (baseline/follow-up)

Measurement of DLs permitted tailoring of the IFX infusion dose or interval if levels were supra/subtherapeutic (i.e. TDM) at the discretion of the treating rheumatologist. Infliximab dose/interval adjustment occurred in 11/58 (19%) patients at baseline and 4/48 (8%) at follow-up. At baseline, the dose of IFX was reduced in 2 SpA (AS) with high DLs. The interval between infusions was adjusted in 9 patients (7 axSpA, 2 PsA); frequency reduced in 6/9 and extended in 3/9 according to clinical response and DL. At follow-up, the frequency of infusions was adjusted in 4 patients; reduced in 3/4 patients and extended in 1/4 patients (Table 7:3).

Table 7:3. Serum infliximab DLs and corresponding number of LOR (a); drug interventions made including interval/dose adjustment (b)

a) DL	Baseline	Follow-up
High	10/58 (17%)	2/48 (4%)
<i>LOR</i>	<i>1/10 (10%)</i>	<i>0/2 (0%)</i>
Low or undetectable	23/58 (40%)	17/48 (36%)
<i>LOR</i>	<i>8/23 (35%)</i>	<i>2/17 (12%)</i>
b) Intervention	Baseline	Follow-up
Dose reduced	2/58 (3%)	0/48 (0%)
Dose increased	0/58 (0%)	0/48 (0%)
Interval reduced	6/58 (10%)	3/48 (6%)
Interval extended	3/58 (5%)	1/48 (2%)
IFX discontinued	9/58 (16%)	2/48 (4%)
IFX continued	49/58 (84%)	46/48 (96%)

7.4.7 Statistical prediction modelling

Logistic regression modelling¹ was conducted to identify predictors of LOR (Table 7:4). Holding all covariates constant, the odds of LOR decreased by a factor of 0.70 ($p=0.032$) for a one-year increase in disease duration (Figure 7:4). The odds of LOR increased by 1.16 times ($p=0.036$) for higher methotrexate doses compared with lower methotrexate doses. Holding drug level, disease duration and methotrexate use at a fixed value, the odds of LOR increased by 1.02 times ($p=0.015$) for a one-unit increase in anti-drug antibody (AU/ml), (Figure 7:5).

Table 7:4. Adjusted odds ratios for predicted LOR

Variables	Odds ratio (CI)	p value
Drug level	0.90 (0.69-1.17)	$p>0.05$
Anti-drug antibody	1.02 (1.00-1.03)	$p=0.015$
Disease duration (years)	0.70 (0.50-0.97)	$p=0.032$
Methotrexate use	1.16 (1.01-1.33)	$p=0.036$

¹Statistical modelling conducted by Dr Oras A Alabas

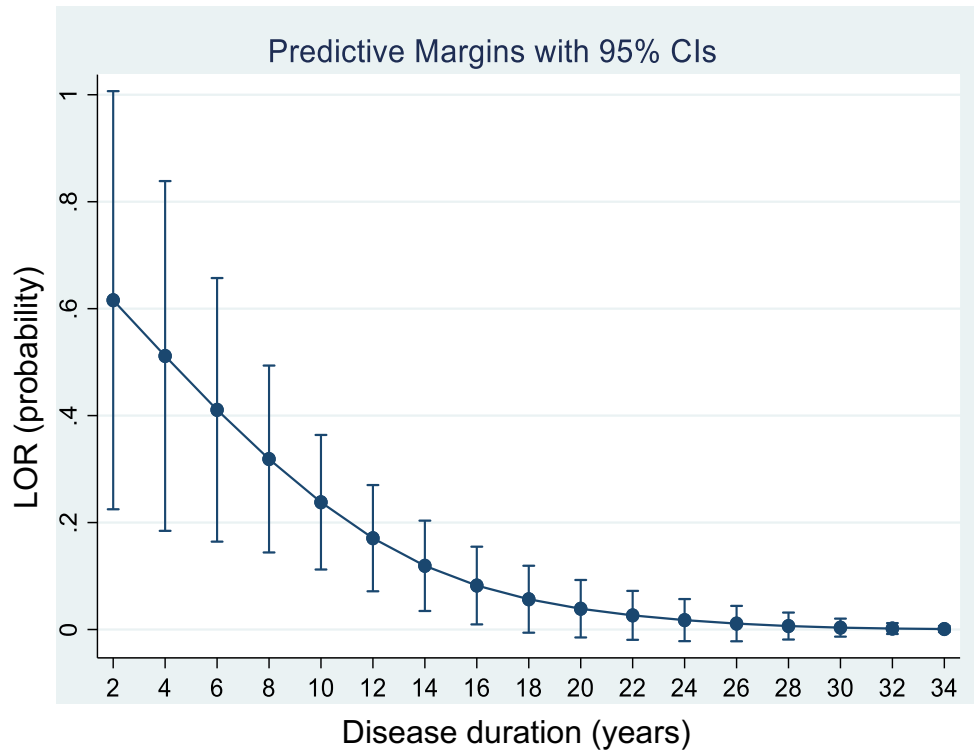


Figure 7:4. Graph of disease duration and probability of loss of response (LOR).

Longer disease duration appeared to lower the probability of LOR.

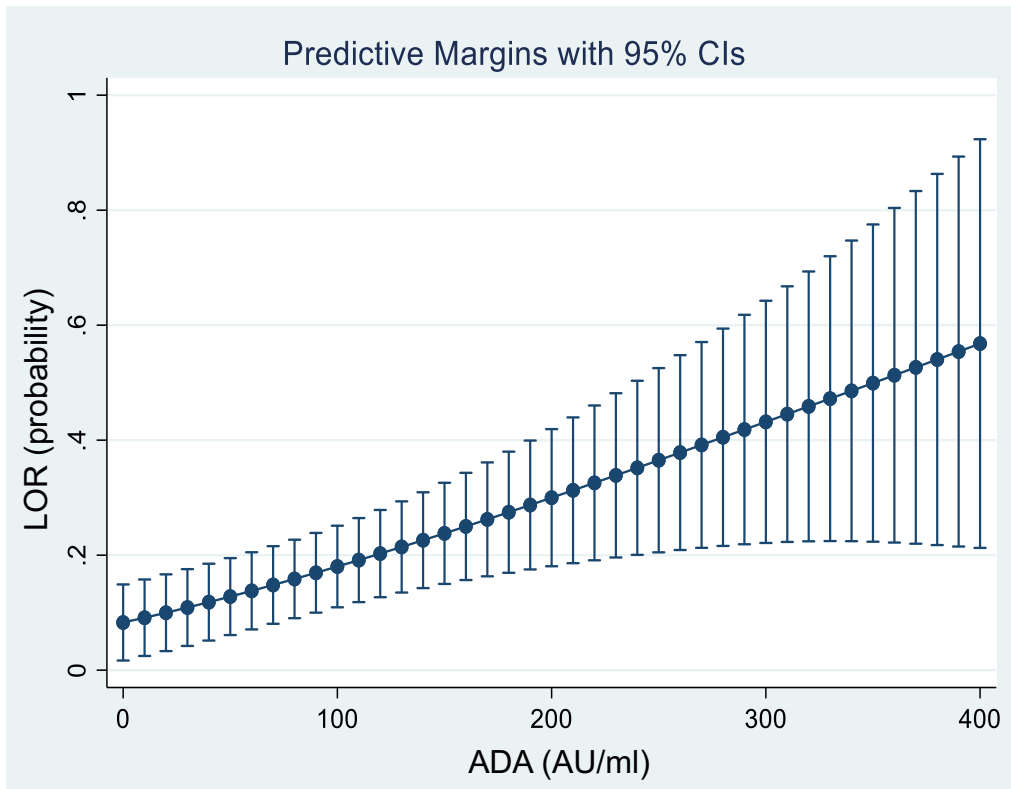


Figure 7:5. Anti-drug antibody and probability of loss of response (LOR).

This graph shows that the greater the ADA, the greater the probability of LOR.

7.5 Discussion

This “real-world” evaluation in a small cohort of SpA patients has shown that measurement of IFX DL/ADAs can assist clinical assessment to rationalise non-response (LOR) as confirmed by low/undetectable DLs and concurrent high/moderate ADAs which were found in 8/11 (73%) patients with LOR [baseline: 6/9, and follow-up: 2/2]. Furthermore, lower IFX DLs were associated with LOR ($p= 0.007$). The measurement of ADAs to IFX was an important and useful test to confirm the aetiology of low/undetectable DLs (immunogenicity/ increased drug clearance), and provided rationale for LOR. In SpA patients with high/therapeutic DLs, LOR occurred in only 1/35 (3%) patients at baseline and 0/31 (0%) at follow-up, which suggested a good relationship between high/therapeutic DLs and efficacious treatment responses in the vast majority.

The results from this study corroborate with several studies on DLs/ADAs. In 38 AS patients, higher serum IFX DLs were associated with clinical response (De Vries et al., 2007). Similarly, IFX DLs and ADAs were found to correlate with the ASDAS disease activity measure in a study of 35 patients (Patil et al., 2019). In fact DLs were reported as a predictor of clinical response to bDMARDs in RA (Chen et al., 2015). Similarly for bDMARDs in various settings, low DLs were found to be associated with LOR and were the main reason to measure ADAs (Jamnitski et al., 2012). Further, in a study of 106 RA patients over 6 months, the development of infliximab ADAs was induced by low DLs (Bendtzen et al., 2006).

In immunogenicity determined LOR (baseline), the median ADA was 115 AU/ml and median DL <0.8 mcg/ml. Moreover, in all SpA patients with ADA >100 AU/ml at baseline, all required a change of therapy or IFX dose/regimen adjustment at either baseline or follow up suggesting therapeutic inefficacy or waning. These median values for DL and ADA may inform clinical management and provide a practical reference point for use of DL/ADAs in IFX treated SpA.

Several longitudinal studies have also reported on the ability to predict bDMARD treatment responses through measurement of ADA. In 103 PsA patients, ADAs to adalimumab were associated with lower DLs and poorer

outcomes at 6 and 12 months (Vogelzang et al., 2014). A larger longitudinal study of 331 RA patients concluded that ADAs and low DLs predict LOR to adalimumab up to 9 months in advance (Jani et al., 2015). In order to facilitate fully integrated decision-making, an algorithm was devised following review of the literature on DLs/ADAs in rheumatic disease, consistent with the most recent evidence-based approach to management (Vincent et al., 2013; Bendtzen, 2015; Strand et al., 2021). This algorithm serves as a guide for the treating rheumatologist to support clinical practice decisions based upon disease activity status and the DL/ADA result as shown in .

Interestingly, both at baseline and follow up in this evaluation, there was a considerable proportion of patients with low or undetectable DLs [23/58 (40%) vs 17/48 (35%) respectively]. This indicated that DL measurement can identify potential for dose/interval optimisation or possible therapy switch in more than one third of patients. This finding could represent a potential risk to therapeutic efficacy in a large proportion of SpA patients given what is known about low TNFi DLs and associated LOR (Kneepkens et al., 2015). Changes to the IFX dose or interval occurred in 15 patients, allowing optimisation according to the DL. Performing DLs has therefore been informative, but whether adjustment of dose and frequency of infliximab prevents further immunogenicity and LOR is still unconfirmed. Regular frequent monitoring of DLs was not assessed in this evaluation, therefore more research on therapeutic drug monitoring may inform on whether intervention on DLs can improve clinical outcomes.

A recent randomised controlled trial (NOR-DRUM) reported that TDM produced no difference in achieving disease remission, but was safer with less adverse events (Syversen et al., 2020). This is somewhat surprising given the literature in CD which has shown superior long term outcomes for TDM with less frequent intestinal surgery or IFX discontinuation (Papamichael et al., 2017; Kamperidis et al., 2019). Indeed, data in IBD showed that higher DLs are associated with clinical and endoscopic evidence of mucosal healing (Zittan et al., 2016). Evidence of improved clinical outcome in active disease led to the American Gastroenterology Association (AGA) recommendations to measure DLs in suspected active IBD, and if DLs are subtherapeutic, to measure ADAs. Given the common aetiopathogenic association between SpA and IBD, there may be further similarities in treatment response to IFX. The

need to assess clinical outcomes in future research on TDM and DL/ADA strategies will be key to achieve recommendations in SpA. Further, the National Institute for Health Clinical Excellence (NICE) advocate assessment of response at 12 weeks from initiation of bDMARD therapy and with the least expensive biologic drug which are currently the biosimilar reference products in the UK (NICE, 2010). Adopting use of DL/ADA may facilitate the assessment at 12 weeks, given the increased costs associated with new therapies. TDM may be one answer towards maximising responses and minimising the development of immunogenicity related bDMARD failure. Finally, the associations between suboptimal DLs/dosing have led to assessment of “proactive” rather than “reactive” dose adjustment to the target therapeutic IFX concentrations, which may be a method to prevent immunisation (ADA formation) (Chaigne and Watier, 2015; Negoescu et al., 2020).

The results of this study should be viewed in light of its limitations such as the small sample size, heterogeneity of SpA phenotypes, and the “real-world” nature of the study. Moreover, IFX is often used because of its high bioavailability via the intravenous route which is important as patients with SpA may also suffer from organ threatening disease (e.g. uveitis, IBD) and therefore DL/ADAs can provide key information in monitoring treatment response. Nonetheless, these data show the advantages of DL/ADA in IFX treated SpA in a practical sense and have potential to inform future clinical research and routine care. These results form part of the step taken towards personalised medicine, moving away from reactive medicine to a proactive approach that includes the future “P4” vision of medicine: predictive, preventative, personalised and participatory (Flores et al., 2013).

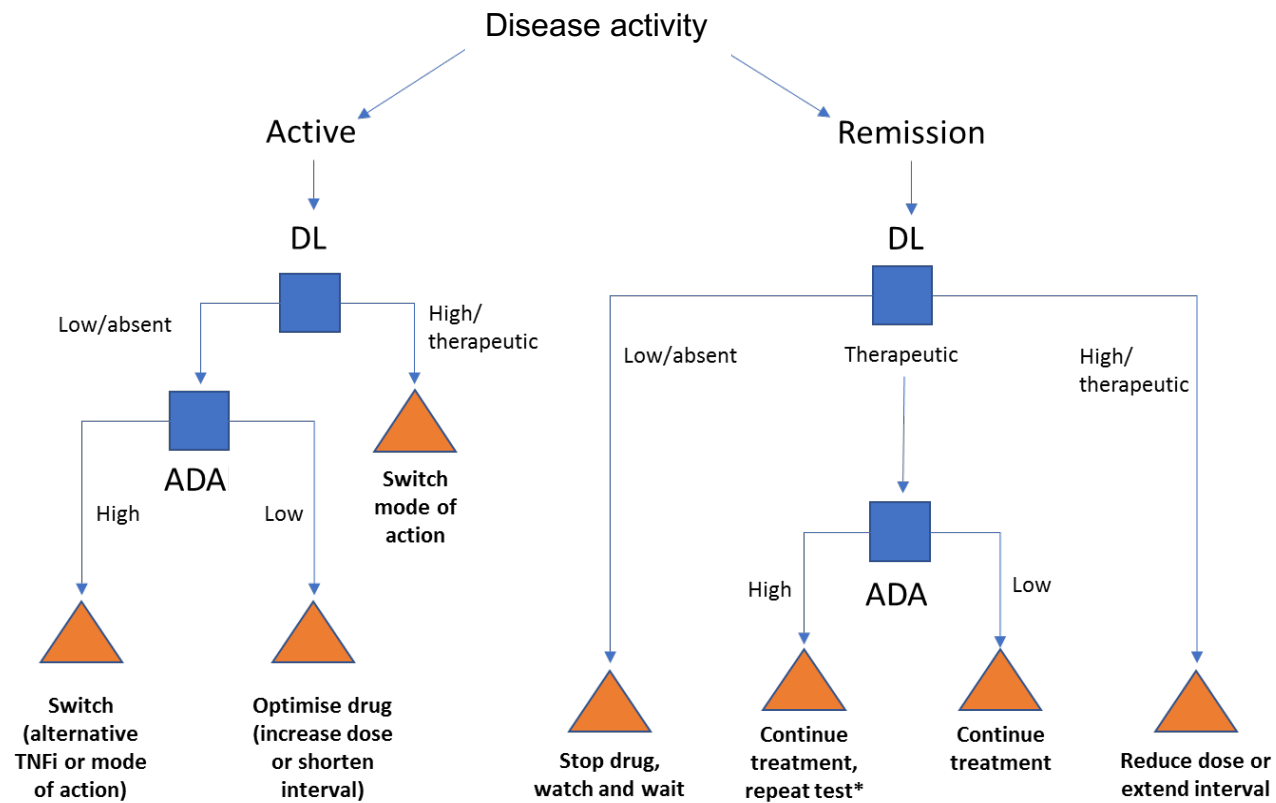


Figure 7:6 Algorithmic guide for treating physician to interpret clinical status with DL and ADA.

*Rising ADAbs and reducing DLs may predict LOR. If LOR is clinically suspected, switch TNFi or mode of action of therapy.

7.6 Conclusion

These data from this small cohort suggest that measuring DLs and ADAs can rationalise treatment response and complement the clinical assessment parameters. This approach can facilitate a tailored treatment regimen for maintaining clinically efficacy in infliximab treated SpA patients. The data from this evaluation can inform future clinical trials and studies using bDMARDs including TDM strategies. This approach opens a window of opportunity within SpA management including in larger cohorts receiving subcutaneous therapies. Utilising DL/ADA in practice unlocks the potential of “personalised medicine”, a step forward towards individualised treatment strategies.

Key messages

- Treatment non-response was rationalised via DL/ADA measurement.
- Infliximab DLs were undetectable/low with corresponding ADAs moderate/high in two thirds of non-responders.
- Low DLs were associated with LOR, and longer disease duration predicted a higher probability of response.
- Treatment regimens may be optimised via DL measurement (TDM) and the devised treatment algorithm.

Chapter 8. Discussion

There have been several advances in science and clinical research in the field of SpA in recent years. These include imaging research using US and MRI for the detection of synovial and enthesal pathology, and the advent of bDMARDs which have been a revolutionary step forward in the management of SpA. The work from this thesis has aimed to contribute further to the knowledge of SpA pathogenesis through clinical research of the axial and peripheral skeleton and imaging research at enthesal and synovial sites in different phenotypes of patients with SpA. In addition to pathogenesis, this thesis has further explored mechanisms for assessment of bDMARD treatment response in SpA through measurement of drug and antibody levels, and how treatment may be rationalised, which may add to the body of accruing literature in these exciting and evolving fields of medicine.

8.1 Discussion of studies conducted

8.1.1 Chapters 1-3: Review of literature, hypothesis and aims

The first aim of this thesis was to identify and understand the current literature in SpA including areas of unknown knowledge and unmet needs which was detailed and achieved in Chapter 2 (background literature review of SpA). This led to the generation of the two main hypotheses (Chapter 3 and below) on pathogenesis (1) and treatment (2). The purpose of this research thesis was to test the following hypotheses:

- 1) Enthesitis is a significant pathological event in early, new onset spondyloarthritis and may be a biomarker for disease evolution.
- 2) Measuring drug and antibody levels in infliximab treated SpA patients can rationalise treatment non-response.

These were addressed by conducting clinical research studies and case series of patients with different phenotypes of SpA, and evaluating the role of assessment of treatment response with drug and antibody monitoring.

8.1.2 Chapter 4: Severe enthesopathy

Acute severe unilateral sacroiliitis with MRI appearances mimicking infection

The second aim of this thesis was to explore the pathogenesis of severe SpA related enthesal pathology at the axial and peripheral skeleton in different SpA phenotypes following acute inflammatory and infective events. The case series conducted reported and identified an extreme SpA phenotype, and discussed the pathogenic relationship between these clinical presentations. Chapter 4 examined the characteristics of severe enthesal inflammation in patients with axial SpA (first case series), and axial and peripheral SpA (second case series). In the first case series, acutely symptomatic patients with severe unilateral sacroiliitis were examined, 50% with extra-articular SpA manifestations (IBD/ PsO), all HLA-B27 negative, and all demonstrating extreme MRI appearances with extensive BMO, adjacent periarticular muscle and/or soft tissue oedema that mimicked the appearances often observed in infection (septic sacroiliitis) (Dubash et al., 2018). Although the most important consideration was infection, no infective causes were isolated and efficacy with NSAIDs indicated that a reactive inflammatory sacroiliitis was considered more likely.

These data highlight the phenotypical heterogeneity of such SpA subsets which pose a diagnostic challenge due to the overlap of clinical features with infection. Indeed infection should be investigated and prioritised first though and could also be the trigger for ReA in these patients. Most importantly in clinical practice, despite some debate, several key features may be helpful to distinguish between infection and inflammation. Periarticular muscle oedema is commonly seen in infectious sacroiliitis, however it has also been observed on MRI in some (5/54) SpA patients (Kang et al., 2015). It is postulated that extensive capsulitis can extend along iliac and sacral periosteum resulting in reactive oedema in periarticular muscles in SpA (Sieper et al., 2009). Typically infectious sacroiliitis is thought to infect the iliac side of the SIJ more severely and show fluid or inflammation in the iliopsoas muscle (Klein et al., 1991). The data from the first case series therefore illustrates how patients with ReA can

present at the boundaries of SpA classification and the considerable overlap present where other conditions are mimicked.

The sacroiliac joint itself embodies the several pathological synovio-entheseal features due to its anatomical make-up, part ligamentous postero-superiorly and part synovial antero-inferiorly. Ligamentous oedema, bony irregularity and BMO, deep to areas of ligament insertions are a common finding in SpA, but a substantial number of young physically active individuals also possess such pathologies from biomechanical stressing including BMO on MRI (Varkas et al., 2018). Stress reactive changes are well documented commonly found in athletes or chronic physical stress, also known as a “stress-riser”, and may lead to stress fracture (Tsoi et al., 2019). Whether biomechanical stress infers a susceptibility for inflammatory or even infective disease to develop at the SIJs is unconfirmed, but is applicable to the case series demographics (three physically active 19 years old males) raise the consideration of biomechanical factors and disease development. It is these predominant entheseal features in SpA that are consistent with the theory that inflammation starts at the enthesis and follows to the synovium. Finally, the presence of all three features, intensive BMO, periarticular spread to soft tissues and muscle (iliacus and gluteus), peri-articular fluid collection (or abscess) are radiologically described as highly suggestive of an infectious origin and screening for infection should be prioritised (Tsoi et al., 2019).

In this small case series the limitations include that greater investigation for infective causes could have been conducted such as greater use of procalcitonin, the biomarker of infection, greater consideration on SIJ biopsy for histopathological tissue diagnosis, and wider screen for infection in some patients. However, these factors should be viewed by the fact that these were real world patients and that the case series was retrospective.

These data are consistent with the fact that in some patients with SpA, autoinflammation components are present which relate to greater presence of innate driven mechanisms. ReA is most relevant of SpA diseases for such mechanisms where antigens can be detected from gastrointestinal or genitourinary infection and are the trigger for immunity. These might explain severe acute clinical presentations, more evident in some SpA patients than others (McGonagle and McDermott, 2006). Secondly, these cases were

mostly young and physically active patients therefore the possibility of biomechanical stressing provoking disease localisation and more severe findings is a consideration given the link with enthesitis (Benjamin and McGonagle, 2001). Finally, the possibilities of infection either as the trigger or sole pathology cannot be entirely dismissed even in the absence of evidence, and there are further considerations into the possibility of pseudo-septic joint as reported in SAPHO that should be present within the differential diagnosis of SIJ infection (Matzaroglou et al., 2009). Ultimately given the successful response to NSAIDs, unconfirmed infective screen, and prompt recovery, a diagnosis of ReA was deemed most likely. The cases demonstrate a phenotypical subset of patients along the spectrum of SpA with severe acute enthesal inflammation. These findings are in keeping with the hypothesis that enthesitis may be a significant event in new onset SpA, and suggest infection may be an important trigger.

Severe spondyloarthropathy related enthesal pathology following successful vedolizumab therapy for inflammatory bowel disease

The second aim of this thesis, also achieved via the second case series of SpA patients, demonstrated severe enthesal and related pathologies following administration of the $\alpha 4\beta 7$ integrin inhibitor, vedolizumab. In this multi-centre case series, severe enthesal inflammation was demonstrated in the axial and peripheral skeleton and the majority of cases were HLA-B27 negative (86% of available data) with de novo SpA (82%). More than a third of patients were hospitalised indicating the severity of their symptoms and the enthesal pathologies observed included sacroiliitis (45%), thoraco-lumbar enthesal-related inflammation (spinal vertebral osteitis, and peri-facetar oedema), peripheral enthesitis (27%) and synovitis (18%). These findings support the hypothesis that enthesitis is indeed a significant pathological event in new onset SpA and support the concept of enthesitis as the likely primary lesion in SpA leading to other related pathologies. However, although enthesitis is likely a biomarker for evolution of pathology (enthesitis leading to osteitis and synovitis), whether it is a marker for progression of disease with time cannot be answered by these cases as there was only limited follow-up. More specifically outcomes at 6 months showed 8/11 (73%) developed improvement in SpA disease, the majority having discontinued VDZ, deemed to have caused induction or flare of SpA. Paradoxical reactions to immunotherapies and are known complications in IMIDs, particularly in SpA where previous administration of a TNFi soluble receptor molecule (etanercept) and IL-17 inhibition resulted in de novo IBD development or flare (Toussirot and Aubin, 2016).

However, whereas discontinuation of the offending drug led to improvement, this may not always be true for all immune-mediated reactions. De novo inflammatory arthritis or colitis has been shown to develop following immune checkpoint inhibitors and may even persist after cessation [anti- PD ligand-1 (anti-PDL1)] (Braaten et al., 2019). These phenomenon are not completely understood, but are evidence confirming that immunomodulators can “switch on” autoimmunity at joints or the gut in individuals with no prior history of disease (Bellaguarda and Hanauer, 2020). Moreover in SpA, where there is a

strong association with intestinal dysbiosis, gut barrier dysfunction is also prevalent which is known to be a significant predisposing factor, and is linked to several other autoimmune diseases (Mu et al., 2017). The intestine is increasingly recognised in early axSpA with incriminating processes that are suggestive of innate immunity. Bacterial molecules (PAMPS) can enter the circulation potentially triggering inflammation at sites of high biomechanical stress via immune activation. Injured tissue cells under stress release molecules called DAMPs (danger-associated molecular patterns) which may activate local innate immune cells to produce pro-inflammatory cytokines and other molecules that may enter the circulation (Sharif et al., 2020). Eventually, activated innate immune cells subsequently circulate towards the entheses and bone as part of the “gut–entheses axis” (Dubash et al., 2019).

In paradoxical events to immunotherapy, what determines the switch of inflammatory disease between phenotypes or organ systems affected is not well understood but may be related to the concept of immune privilege (Forrester et al., 2008). Future registries can provide data to monitor for reactions to new therapies, such as other emerging integrin blockers (e.g. abrilumab, etrolizumab). The limitations of these two-case series include the small sample size, but their strengths include the detailed disease characterisation of SpA phenotypes. These case series confirmed that enthesitis is a significant event at SpA onset and can be severe as shown in these patients. These case series corroborate with the existing literature in SpA, that enthesitis is at the centre point of disease pathogenesis in SpA, and as a pathological entity may be the route for disease evolution.

8.1.3 Chapters 5-6: Synovitis and dactylitis in early PsA

Clinical examination and US synovitis

The third aim of this thesis was to explore baseline clinical and US characteristics of early PsA. This was achieved through a clinical prospective, cross-sectional observational study (SpARRO cohort) of DMARD untreated early PsA patients as described in chapter 5. In this study, synovitis - a key pathology in early SpA, was confirmed via US examination and compared with clinical examination. The presence of US detected synovitis was found to be more likely in swollen than tender joints on clinical examination. The relationship between tender non-swollen joints and US synovitis was weakest, which suggested the wider relationship between tenderness and other causes, was responsible. These study findings also confirm what was found in RA, swollen joints were associated with US synovitis but tender non-swollen joints were not (Hammer et al., 2019). Although these findings suggest less synovitis is represented by tender joints, the study limitations were the focus on detection of synovial pathology. However, in this study US enthesitis was assessed and found to be significantly more prevalent than clinically assessed enthesitis. These study observations are consistent with the majority of literature in SpA where there is a disparity between clinical and US findings (Husic et al., 2014). Most relevant was the greater degree of subclinical synovitis (13.5%) over clinical synovitis (6.9%), which corroborates with the literature in early PsA, and indeed the idea that pathologies in PsA may progress and evolve insidiously in the early phase, with subclinical enthesitis and synovitis being prevalent first (Freeston et al., 2014; Tang et al., 2018). Similarly, a greater number of patients presented with US enthesitis than clinical enthesitis (85.8% vs 45.8%) which supports some level of clinical tolerance of inflammatory pathology before manifesting with tenderness or swelling. The phase between psoriatic arthralgia and development of PsA may represent a transition phase early on in the disease process where pathology develops possibly evolving from synovitis into several PsA related pathologies such as synovitis (Zabotti et al., 2019).

The connection between the enthesis and synovium is justified through the synovial enthesal complex which unites the pathological entities observed in SpA to the enthesis, one common anatomical site of disease origin. Histopathological studies have shown that at least 82% of entheses are associated with a synovial membrane, and some of these were discovered to have invaded sites of enthesal attachment, indicative of the process akin to the invasion of pannus at inflammatory arthritic joints (Benjamin and McGonagle, 2007). These findings substantiated that the enthesis and synovial tissue are intrinsically linked, and that the enthesis organ is dependent upon synovial tissue for its own homeostasis. Hence enthesal inflammation may overspill to synovial tissue.

Sustained clinical swelling and active inflammation in PsA have been shown to cause progressive structural and functional damage in several studies (Gladman et al., 1990; Simon et al., 2012). Given what is known about the treatment of early disease for optimal outcomes to prevent long term damage, it is necessary to translate US pathological outcomes to clinical examination to optimise care. Without use of ultrasound in clinical practice, there is potential to miss disease related pathology and hence possible undertreatment. Conversely, overt emphasis on tender joints to determine diagnosis or disease activity measurements may risk overtreatment or misinterpretation of the underlying cause unless imaging is utilised. Therefore, US is more crucial at the early stage of disease where the window of opportunity to switch off inflammation can lead to better outcomes (Coates et al., 2015).

The findings from this study indicate that enthesitis and synovitis are pathologies linked to onset of SpA, found in early PsA. The results indicate that clinical examination of swollen joints, rather than tender joints, have a higher probability of US synovitis and are therefore the better proxy. These results suggest that enthesitis could represent a biomarker for disease evolution which could be assessed further in longitudinal studies.

Significance of dactylitis

The fourth aim of this thesis was to explore the significance of dactylitis, as a marker of disease severity in early PsA. This was achieved through recruitment of DMARD-naive early PsA patients from the same cohort (SpARRO) as detailed in chapter 6. The PsA cohort was dichotomised, based on the presence or absence of dactylitis, into PsA with dactylitis (dactylitic PsA) or non-dactylitic PsA. Both groups were comparable, with similar numbers of patients, slightly more in non-dactylitic PsA (54.2% vs 45.8%), similar demographics for age and sex, and all patients fulfilled the CASPAR classification criteria on recruitment. These study results showed that the presence of dactylitis in PsA (dactylitic PsA) was associated with greater SJC, CRP, US synovitis and US erosion. Interestingly, analysis by excluding the digits affected by dactylitis confirmed these findings were still significant, i.e. independent of the digits/joints affected by dactylitis. Despite exclusion of the dactylitic digits from the analysis, the dactylitic PsA group was still predominantly polyarticular in phenotype, compared to oligoarticular in non-dactylitic PsA, and US synovitis ($GS \geq 2$ / $PD \geq 1$) and US erosions were still significantly more prevalent. One of the problems in early PsA is the lack of elevated CRP, but dactylitic PsA showed a raised CRP (44% vs 25%) in a much greater proportion of patients. Indeed, these results confirm that dactylitis is a marker of a more severe phenotype, one with an increased disease burden in early PsA.

There is some perception that dactylitis might be linked to nail disease in the corresponding digit, however no differences were found, and there was no difference in the prevalence of nail dystrophy between both groups. The mNAPSI was actually greater in non-dactylitic PsA ($p < 0.05$), as was the PASI but was non-significant. Additionally, dactylitic PsA patients had greater clinical enthesitis but active US enthesitis was greater only for bursitis at the Achilles tendon insertion. These features suggest there is a tendency for a more aggressive polyarticular peripheral PsA phenotype with less aggressive skin/nail PsO.

Synovitis and erosive damage are significant pathological features associated with poorer PsA structural and functional outcomes in the long term (Kane,

Stafford, et al., 2003; Schett et al., 2011). The implications of such have meaningful impact on decisions for the management of PsA such as initiation of DMARDs/ bDMARDs. Greater synovitis and erosion found in dactylitic PsA is therefore of clinical importance for optimal treatment outcomes. Furthermore, US synovitis was confirmed in a high proportion (over 50%) of joints affected by “hot” dactylitis. The knowledge gained from this study may change the perception of psoriatic dactylitis in the routine setting, not only the direct affect it has in affected digits, but the independent association with greater overall PsA disease severity. This is important as longitudinal data from registries have reported that dactylitis is a poor prognostic factor at 5 years (Geijer et al., 2015).

High disease severity in early PsA is also attributed to poor prognosis, especially without prompt and effective treatment (Gladman et al., 2005). In early symptomatic PsA, delays in diagnosis and treatment of beyond 6 months duration are reportedly common and can lead to poor radiographic and functional outcomes; thus early recognition of dactylitis and its significance to associated disease severity can facilitate early rapid treatment of PsA for optimal outcomes (Haroon et al., 2015). Evidence of active and severe disease has also been linked to an increased risk of death from co-morbidities such as cardiovascular disease, with a mortality ratio of 1.62 (Gladman et al., 2005).

A further study reassuringly reported that MTX is effective not only for PsA outcomes but also for treating dactylitis (Appani et al., 2019). Psoriatic dactylitis (GO-DACT), assessed as a primary outcome in an RCT, showed superior responses when bDMARD treatment was added to csDMARDs (Vieira-Sousa et al., 2020).

Dactylitis is a frequent occurrence often easily identifiable and is often the inaugural clinical sign in early PsA, yet it is not always considered a marker for disease severity. Fascinatingly this lesion embodies all key pathologies found within SpA, enthesitis, synovitis, soft tissue and bone oedema and erosion. Often the most common finding, flexor tenosynovitis, unlike synovitis, has not been associated with poor prognosis, but this development may represent a transition phase, where inflammatory enthesopathy spreads via the synovio-entheseal complex evolving to synovitis which was found in the

majority of symptomatic dactylitis in this study. Further, the severity and stage of disease may influence observations between studies. Further studies have confirmed that there is PD enhancement in accessory pulleys in psoriatic dactylitis which supports this idea of significant inflammation at entheses in the initial enthesopathic phase with synovitis developing later often with symptoms (Tinazzi et al., 2019). Other studies have suggested there are more extra-capsular features in acute compared with chronic dactylitis (Girolimetto et al., 2020). Although imaging is helpful for diagnosis and management, dactylitis alone should raise concern to the development of synovitis and erosion. The additional knowledge gained from this study should equip clinicians in routine practice with greater insight into the severity status of disease associated with dactylitis and the “dactylitic PsA” patient.

Previous cohorts reported on dactylitis in PsA after an average disease onset of 8 years, showing an incidence of 48% (Brockbank et al., 2005). Subsequent studies showed that prevalence was greater than 50% (Antoni et al., 2005; Mease et al., 2017; McGonagle et al., 2019). This closely matches the prevalence of 45.8% in this cohort, where patients were of early disease onset. Still, this value represents a relatively high percentage for the prevalence of dactylitis compared with other cohorts, and can be explained by a greater proportion of dactylitis (approximately 70%) occurring at the early stages of disease (McGonagle et al., 2019). The lower prevalence for dactylitis in other studies is explained by their use of a clinical diagnosis of PsA for study eligibility, whereas the CASPAR criteria (which scores a point for dactylitis regardless of presence/absence of psoriasis) permits a homogenised cohort, with one domain dedicated to dactylitis allowing for clinically compatible presentations including PsA *sine* PsO (Taylor et al., 2006). Indeed, the presence of cutaneous PsO was observed in only 91.4% of dactylitic PsA, compared with 100% of those patients with non-dactylitic PsA. These PsA *sine* PsO (8.6%) may present as isolated dactylitis with an initial label of undifferentiated peripheral SpA, possibly resulting in delay to diagnosis and/or early erosive damage. Furthermore, the greater prevalence of lower limb involvement in dactylitis may be explained through enthesal biomechanics and the “deep Koebner” theory given the greater stressing in weight bearing joints. Thickening of accessory pulleys of the hand flexor tendons was

demonstrated in PsA patients with dactylitis compared to PsO, RA, healthy controls (Tinazzi, McGonagle, Aydin, et al., 2018). However, in a small study of only 12 participants in the PsA with dactylitis group, evaluation of plantar pressures between dactylitic and non-dactylitic patients could not identify specific differences (Wilkins et al., 2016).

Perhaps a limitation of this study was that extra-capsular disease was not formerly assessed, but several studies have already reported specifically on this aspect (Olivieri et al., 1996; Healy et al., 2008). Additionally, reliability assessments for clinical and ultrasound examination were not formerly assessed. The strength of this study is that these were real world patients recruited from an early arthritis clinic, DMARD untreated, and all meeting CASPAR criteria, and the dichotomisation of the cohort by presence/absence of dactylitis as the key pathological indicator.

This study suggests that in clinical practice, even in the early stages of disease, PsA patients with dactylitis may be considered a phenotype of greater disease severity than those without dactylitis. Early PsA with dactylitis displayed an increased burden of disease severity at its onset suggesting it is directly associated with overall PsA disease status.

This is the first study to show these findings in a DMARD-naive PsA cohort and adds to the knowledge base on dactylitis in DMARD naive early PsA. In summary, greater SJC, CRP, US synovitis and US erosion was found in dactylitic PsA patients, and was independent of dactylitis. The fact that disease severity was found to be significantly greater, at the early PsA stage is indicative of dactylitis as a clinical marker of disease severity

8.1.4 Chapter 7: Infliximab drug trough and anti-infliximab antibody levels as biomarkers of treatment response in SpA

The fifth and sixth aims of this thesis were to explore mechanisms of treatment non-response in SpA patients receiving the monoclonal antibody infliximab (IFX), and to rationalise treatment based upon IFX drug level. This exercise was originally conducted within the SpA clinical service to rationalise treatment and understand secondary non-response at a time when biologic switching was encouraged and cost-effectiveness under scrutiny.

The detection of low/undetectable DLs and concurrent high/moderate ADAs concurred with 73% of SpA patients with clinically suspected LOR, confirming immunogenicity driven inefficacy. Low and undetectable DLs were associated with LOR which also corroborates with the literature (Thomas et al., 2015) and similar studies (De Vries et al., 2007). In line with the fifth aim, this mechanism was objectively confirmed and will therefore be useful to rationalise LOR in suspected patients in clinical practice.

At baseline and follow up, there were a considerable proportion of patients with either low or undetectable DLs (40% vs 36% respectively). This is an important finding as it indicated that dosing was subtherapeutic in more than one-third of patients. Subsequently, this may pose a potential risk to long term therapeutic responses to IFX, as low DLs predict poorer clinical outcomes, for which the reverse is also true, high DLs reduce the development of ADAs (Ducourau et al., 2011).

As per the sixth aim, the IFX dose/interval was adjusted in 15 patients (following result of the DL) leading to optimisation of treatment dose/interval accordingly. This therapeutic drug monitoring (TDM) approach may be beneficial not only to correct low DLs which have been shown to predict LOR, but to also personalise drug dose/interval specific to each individual (Kiely, 2016). Interestingly, low DLs and poor treatment responses also occur for receptor fusion proteins (e.g. etanercept) which are not associated with neutralising ADAs (Strand et al., 2019). Therefore ensuring DLs are therapeutic may provide the maximal opportunity for successful treatment responses. Finally, the impact of other factors such as smoking, obesity,

metabolic and genetic factors should not be overlooked, and future research may inform further.

As a result of this evaluation, and review of the literature, an algorithmic driven guide for physicians was devised, following which details were presented and disseminated within the Leeds Specialist SpA service to support clinical decisions and treatment personalisation. Such a guide may improve and facilitate therapeutic decision making. Although more longitudinal follow-up and full implementation of the algorithm may permit assessment of outcomes via the therapeutic drug monitoring (TDM) approach in SpA, “reactive” TDM has been shown to be effective in IBD where recommendation for management has been made by the American Gastroenterology Association (AGA) guidelines (Feuerstein et al., 2017). Despite efforts of emerging studies, more data is needed on whether clinical outcomes can be improved via DL or/and ADA measurement before such an approach can be advocated in SpA.

The predictive statistical model conducted found that LOR was less likely with greater disease duration, and given the long duration of disease and age of patients suggests immunosenescence may explain such findings. Interestingly, in a large IFX biosimilar switch study of 802 RA/SpA patients, those with >5 years of IFX treatment were less likely to discontinue therapy suggesting the duration of therapy could also be important (Glintborg et al., 2017). Data from vaccinology suggests lower naive T cell frequencies occur along with failure to trigger an effective adaptive immune response (Cunha et al., 2020). Other literature refers to adequate responses in the elderly, just reduced quantities of antibody formation (Blomberg and Frasca, 2011). However, reports indicate there is much variation in immunogenicity between individuals varying between 10-60% in studies in SpA (Maneiro et al., 2013). There may be considerable difference between biologics also, with greater immunogenicity to infliximab than adalimumab reported at 8 weeks (14% vs 76%) (Levesque et al., 2014). Further considerations include the differences in the sensitivity of assays for the detection of ADAs with electrochemiluminescence (ECL) showing better free drug tolerance and radioimmunoassay (RIA) less likely to produce false positive results (Kim et al., 2015), in comparison to bridging ELISA. However, ADAs are not the only

predictors for increase drug clearance, which is affected by weight, serum CRP, serum albumin and glucose (Eser et al., 2021).

Administration via the intravenous (IV) route is advantageous from the point of high IFX bioavailability but may precipitate infusion reactions. Though no infusion reactions were reported in this cohort, checking for ADAs also informs clinicians on potential risk of such reactions which are higher in ADA positive infliximab/CT-P13 treated individuals (Strand et al., 2017). The literature indicates that MTX may reduce the rate of ADA formation and prolong the response to bDMARD treatment (Ducourau et al., 2020). Though statistical prediction modelling indicated the probability of LOR was greater the higher the ADA, and less likely with longer disease duration, a larger sample size and longitudinal follow up is likely to herald more reliable and accurate results.

Nevertheless, these data have shown that treatment responses can be rationalised via measurement of DLs and ADAs to IFX. Finally, a high rate of LOR to bDMARDs is still a pertinent issue in rheumatology, hence there may be more rationale in attempts to reset differential responses by specific approaches such as TDM to achieve optimise treatment success, prevent ADA formation and achieve personalisation (Schork, 2015).

8.2 Impact of research

The research work undertaken in this thesis has been presented locally, nationally, and internationally, and is important for advancing knowledge through research to benefit the lives of the people with SpA. Through recognition of SpA phenotypes and their pathologies, improvement in understanding of the disease processes can ensue, and their successful management. Since the completion of the research projects, I have developed research interests in various other facets of SpA including PsA and I have developed links with other specialties for collaborative research.

The impact of this research starts at the patient level, where additional use of US for every patient visit has yielded important findings and led to improved care of patients with these diseases. This research has also had an educational impact for myself and many others. Feedback of the findings from

the published research to public and patient partners has enabled dissemination and education

The research articles from this thesis that have been published to date, have been in high impact scientific and rheumatology journals. The VDZ induced SpA (chapter 4) was selected as the “Editor’s choice” article with accompanying editorial (García-Vicuña and Brown, 2019). I have presented aspects of research and educational materials at the patients and public engagement meetings locally at the Leeds biomedical research centre to engage the local community and feedback early findings. I have had the pleasure to present this work at several international meetings (EULAR, ACR, GRAPPA, BSR, Ghent, BritSpA) and speak at about this research work at the ACR and GRAPPA. I have been invited to speak at the BSR meeting regarding work from chapter 6, on the presence of dactylitis in early PsA later this year.

The work in chapter 7 was also presented for a shortlisted BSR award and this work has led to use of DLs and ADAs when required in routine practice in the SpA service. The algorithmic guide to approach these tests has provided support to practising rheumatologists.

Finally, disseminating these research findings and discussion with fellow rheumatologists and scientific colleagues may permit prospects of building collaborative opportunities as well as taking further strides forward in SpA research.

Chapter 9. Future directions

Many clinical and scientific advances have occurred in the field of SpA in recent years. The work encompassed within this thesis, leaves several areas of potential avenues in which to research further.

The detection of SpA pathologies on imaging has been a remarkable diagnostic tool in recent years including MRI for axial enthesal and bone pathology and US for bedside assessment of peripheral synovitis and extra-synovial inflammation. Still, further tools may provide benefit in the study of SpA such as 18F-fluoride PET/CT for the detection of SpA bony pathologies, and assessment of bone formation over time (Bruijnen et al., 2018). It may also have a role in acute/subacute severe pathologies such as aseptic spondylodiscitis (Wendling et al., 2005).

In extreme phenotypes in SpA immune profiling may also be helpful to ascertain the best mode of action therapies (Menegatti et al., 2020; Mauro et al., 2021). Differentiating between infection and inflammation is often a difficult management dilemma, and needs further research.

The work on severe enthesal inflammation will be taken forward further by assessment of expression of integrins and their corresponding ligands in human enthesal tissue. Further, registry recording of paradoxical events to immunotherapy must be recorded in order to accurately recognise and manage such reactions. Given the increasing use of immunotherapies in medical specialities, future research must embrace combining efforts working across specialties for the benefit of patients. Since reporting findings from the two case series, there has been an even stronger relationship working with gastroenterologists for combined management plans for patients with SpA and IBD.

The SpARRO cohort is an observational research study that continues to recruit individuals with SpA and will provide further invaluable longitudinal data with time. Amendments to the protocol will be made to include further outcome measures for future research. Moreover, follow-up of the dactylitic-PsA patients will be fascinating to explore and report on longitudinal findings. Furthermore, the type of therapies and treatment responses in these SpA

phenotypes can be assessed with a view to stratification by dactylitis. This could be achieved via trials within cohorts (TWICs).

Greater understanding of DLs, ADAs to bDMARDs is an important area which may have direct benefits to patients. In order to show whether clinical outcomes are improved by TDM, a larger interventional study can be conducted which could lead to a further piece of research work. Further studies should assess ADAs to bDMARDs in relation to disease duration, IFX duration and age (immunosenescence) -where there is currently limited data on ADAs formation. Despite these opportunities, empirical use of DLs and ADAs can still be practically useful in SpA. There is also an increasing recognition of the need to reduce the health burden and economic burden of ADA formation. Thus studies should now aim to explore the future goal to “predict” and “prevent” LOR (Jullien et al., 2015). Moreover, the associations found from suboptimal dosing have led to proactive dose adjustment studies to the target therapeutic bDMARD concentration which could prevent ADA formation (Negoescu et al., 2020).

Chapter 10. Conclusions

This thesis has added to the scientific and clinical knowledge in SpA, and provides further insight into disease pathogenesis and treatment response in different SpA phenotypes.

- Enthesitis was present in SpA phenotypes at disease onset indicating it is a pivotal pathological feature frequently present in this disease spectrum.
- Severe enthesitis and osteitis were demonstrated in an extreme phenotype mimicking infective sacroiliitis on MRI, likely to resemble ReA.
- De novo severe SpA related enthesitis, osteitis, and synovitis manifested following successful VDZ treated IBD representing a paradoxical reaction, consistent with enthesitis being a significant event in SpA.
- Swollen joints were the better proxy for US synovitis, than tender joints, with greater probability of US synovitis in DMARD-naive, early PsA.
- The presence of dactylitis was associated with a more severe phenotype with greater SJC, CRP, US synovitis and US erosions, independent of digits affected by dactylitis, in DMARD untreated early PsA.
- Measurement of drug trough (DL) and antibody (ADA) levels in IFX treated SpA enabled rationalisation of treatment responses in different SpA phenotypes.

Ultimately, the knowledge acquired from this work will translate into improved management of people affected by these conditions.

Chapter 11. References

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