Improving the Outcome of Psoriatic Arthritis

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The candidate confirms that the work submitted is her 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 Four is based on work from a jointly authored publication by Dr Coates and Dr Freeston. Dr Coates recruited the patients to the study and performed the clinical assessments of enthesitis. Dr Freeston performed the ultrasound scans of the patients. Both authors contributed jointly to the statistical analysis plan and the writing of the paper.

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List of publications/presentations arising from this thesis

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Review articles

Coates LC, Helliwell PS, and members of the GRAPPA imaging subcommittee. Clues to the pathogenesis of psoriasis and psoriatic arthritis from imaging. A literature review. J Rheumatol 2008;35(7):1438-1442.

Coates LC, Helliwell PS. Classification and categorisation of psoriatic arthritis. Clin Rheum 2008; 27:1211-1216.

Original articles

Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis 2009; 69(1): 48-53.

Coates LC, Cook R, Lee KA, Chandran V, Gladman DD. Frequency, predictors and prognosis of sustained minimal disease activity in an observational psoriatic arthritis cohort. Arthritis Care Res 2010; 62(7): 970-6.

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Poster presentations

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Abstract

Psoriatic arthritis (PsA) is recognised to have a significant impact on functional impairment, joint damage and quality of life. The aim of this thesis was to investigate tools for early identification, to develop a clinical target for treatment and to utilise these tools within a clinical trial.

The ClASssification of Psoriatic ARthritis (CASPAR) criteria, previously developed in established PsA, were tested in patients with recent onset inflammatory arthritis (PsA and controls) to test their discriminative ability in early arthritis. The phenotype of early PsA was investigated further with clinical and ultrasound (US) assessment. Clinical criteria for minimal disease activity (MDA) were developed using a questionnaire. These were subsequently tested in an observational cohort and interventional trial dataset. Finally, they are being utilised prospectively in an RCT addressing the benefits of tight control in PsA.

The CASPAR criteria were found to have good sensitivity and specificity for the diagnosis of recent onset PsA. No individual clinical parameters accurately distinguished PsA from other types of inflammatory arthritis, but there was evidence of more oligoarticular disease and enthesitis in PsA compared with rheumatoid arthritis. US imaging showed a small burden of subclinical arthritis and enthesitis but found good correlation between clinical and imaging assessment of disease activity. Criteria for MDA were developed from expert consensus, covering all aspects of psoriatic disease. They were evaluated against the OMERACT filter and have supporting evidence for their validation in terms of truth, discrimination and feasibility. Early unblinded results from the clinical trial indicated that 53% achieved MDA at 12 months.

In summary, the CASPAR criteria can be used for early classification of PsA. In addition, a new composite outcome measure has been developed and validated and is now being utilised in a clinical trial.

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List of Abbreviations

Ab	antibodies
ACR	American College of Rheumatology
ADEPT	ADalimumab Effectiveness in Psoriatic arthritis Trial
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AUC	area under the curve
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
BASMI	Bath ankylosing spondylitis metrology index
BSA	body surface area
CART	classification and regression tree
CASPAR	ClASsification of Psoriatic Arthritis
CCP	anti-cyclic citrillinated peptide
CDAI	clinical disease activity index
CI	confidence interval
CoPSI	Copenhagen Psoriasis Severity Index
CPDAI	Composite PsA Disease Activity Index
CRP	C-reactive protein
DAPSA	Disease Activity in PSoriatic Arthritis
DAREA	Disease Activity in Reactive Arthritis
DAS	Disease Activity Score
DCE-MRI	dynamic contrast enhanced MRI
DIP	distal interphalangeal
DMARD	disease-modifying anti-rheumatic drug
ESR	erythrocyte sedimentation rate
ESSG	European Spondyloarthropathy Study Group
EULAR	European League Against Rheumatism
FT	flexor tenosynovitis

GI	gastrointestinal
GRACE	GRAPPA Composite Exercise
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
GS	grey-scale
HAQ-DI	Health Assessment Questionnaire Disability Index
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRQOL	health-related quality of life
IA	intra-articular
ICC	intra-class coefficient
IL	interleukin
IL2-R	interleukin 2-receptor
IMPACT	Infliximab Multinational Psoriatic Arthritis Controlled Trial
IMPART	International Multicentre Psoriasis and Psoriatic Arthritis Reliability Trial
INSPIRE	International Spondyloarthritis Interobserver Reliability Exercise
IP	interphalangeal
IV	intravenous
JSN	joint space narrowing
LD	laser Doppler
LDF	laser Doppler flowmetry
LDI	Leeds Dactylitis Instrument
LEI	Leeds Enthesitis Index
LS-PGA	Lattice System Physician's Global Assessment
MASES	Maastricht Ankylosing Spondylitis Entheses Score
MCP	metocarpophalangeal
MDA	minimal disease activity
MEI	Mander Enthesitis Index
MHC	major histocompatability complex
mNAPSI	modified NAPSI
MRI	magnetic resonance imaging
mSASSS	modified Stoke Ankylosing Spondylitis Spinal Score
mS-vdH	modified Sharp/van der Heijde score
MTP	metatarsophalangeal
NADPH	nicotinamide adenine dinucleotide phosphate
NAPSI	Nail Psoriasis Severity Index

NOAR	Norfolk Arthritis Register
NOR-DMARD	Norweigian DMARD
NPF	National Psoriasis Foundation
NPF-PS	NPF Psoriasis Score
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
OASIS	Outcome in Ankylosing Spondylitis International Study
OCT	optical coherence tomography
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PABAK	prevalence and bias adjusted Kappa
PAQ	Psoriatic Arthritis Questionnaire
PASDAS	Psoriatic Arthritis Disease Activity Score
PASE	Psoriatic Arthritis Screening and Evaluation tool
PASI	psoriasis area and severity index
PCA	principle component analysis
PD	power Doppler
PD4	phosphodiesterase-4
PEASI	Psoriasis Exact Area and Severity Index
PEST	Psoriasis Epidemiology Screening Tool
PIP	proximal interphalangeal
PLASI	Psoriasis Log-based Area and Severity Index
PNSS	Psoriasis Nail Severity Score
PRESTA	Psoriasis Randomised Etanercept STudy in subjects with Psoriatic Arthritis
PROMs	patient reported outcome measures
PsA	psoriatic arthritis
PsAMRIS	PsA MRI score
PsARC	PsA response criteria
PSORS1	psoriasis susceptibility 1
PsQOL	Psoriatic arthritis Quality Of Life scale
PV	plasma viscosity
RA	rheumatoid arthritis
RAI	Ritchie articular index
RAMRIS	RA MRI score
RCT	randomised controlled trial

RESPOND	REmicade Study in PsA patients Of methotrexate -Naïve Disease
RF	rheumatoid factor
ROC	receiver operator characteristic
SAPASI	self-administered PASI
SAPHO	synovitis/acne/pustulosis/hyperostosis/osteomyelitis
SD	standard deviation
SDAI	simplified disease activity index
SF-36	short form 36
SI	sacroiliac
SIG	special interest group
SJC	swollen joint count
SpA	spondyloarthritides
SPARCC	Spondyloarthritis Research Consortium of Canada
SRM	standardised response mean
STIR	short-tau inversion recovery
SwePsA	Swedish PsA register
TGF	transforming growth factor
TICOPA	TIght COntrol of Psoriatic Arthritis
TICORA	TIght COntrol of Rheumatoid Arthritis
TJC	tender joint count
TNF	tumour necrosis factor
ToPAS	Toronto Psoriatic Arthritis Screening tool
TOPAS	Treatment of Psoriatic Arthritis Study
US	ultrasound
UTE	ultrashort echo time
VAS	visual analogue scale
VAS GH	VAS general health

1 **Introduction**

The aim of this thesis is to improve our understanding of early psoriatic arthritis (PsA) and to investigate tools that can be used to optimise the care of patients with PsA.

PsA is now recognised as a separate disease entity from other inflammatory arthritides, although it is considered as part of the family of spondyloarthropathies. For many years, PsA was dismissed as a mild disease with no long term sequelae and treatment was therefore considered unnecessary. Many observational cohort studies have confirmed a poor long-term outcome of PsA in terms of poor quality of life, functional impairment and radiographic joint damage (Gladman et al. 1987; Sokoll and Helliwell 2001; Bond et al. 2007). Research from the Toronto PsA Clinic has shown that active arthritis (indicated by number of tender and swollen joints) predicts future joint damage suggesting that inflammation in the joints is the key to later damage and resultant disability (Bond et al. 2007). With this recognition of PsA as a potentially damaging and destructive disease came an emphasis on improving management of this disease to optimise outcome.

The first limiting factor in improving care in PsA is an accurate diagnosis early in the course of the disease. PsA is a highly heterogenous disease with variable clinical manifestations, and particularly in the early stages of disease it may be difficult to identify. Typically patients develop skin disease prior to their joint disease, but in up to 20% of early PsA cases, psoriasis may not be present (Kane and Pathare 2005). Typical patterns of radiographic damage that are seen in PsA may be absent at first presentation removing another potential identifying feature. Clearly it would be beneficial if patients can be identified and treated before they develop radiographic joint damage. Some newer, more sensitive imaging techniques such as ultrasound (US) and magnetic resonance imaging (MRI) may be more useful in such early patients. Unfortunately little is currently known about the extent of disease seen on imaging in patients with early PsA.

For three decades, the gold standard classification criteria for PsA were the Moll and Wright criteria (Moll and Wright 1973). Many modifications to these were proposed to try to improve the specificity of the criteria but none have been widely adopted. In 2006, new classification criteria called the ClASsification of Psoriatic ARthritis (CASPAR) criteria were developed using patient derived data. These include characteristic dermatological, clinical and radiological features and have both high sensitivity and specificity for established PsA (Taylor et al. 2006). However less than 10% of the patients had disease duration of less than 2 years, so validation in early disease was not explored. Several groups have attempted to assess the sensitivity of the criteria in identifying patients with recent onset PsA but using only patients with a secure clinical diagnosis and no controls (Chandran et al. 2007b; D'Angelo et al. 2008; Lindqvist et al. 2008; D'Angelo et al. 2009). One group highlighted the low prevalence of radiological criteria in early disease leading to a lower sensitivity to identify PsA (D'Angelo et al. 2009). However, as yet, there have been no properly powered studied addressing the sensitivity and specificity of the CASPAR criteria in early disease and therefore they cannot currently be recommended for use in studies of early PsA.

Once a diagnosis is made, the next issue is that of optimal treatment. The majority of treatment is "borrowed" from rheumatoid arthritis (RA) using similar disease-modifying agents, often without convincing evidence of efficacy in PsA. Although methotrexate is widely used in clinical practice, there is very little evidence to support the use of this treatment in PsA. Newer treatments, such as the Tumour Necrosis Factor (TNF) blocking therapies, have proven efficacy in PsA from large clinical trials but are not available to many patients in the UK (Kay and Griffiths 2006), and are very rarely used as first-line therapy.

The strategy for treatment of RA has been revolutionised in recent years with emphasis on early treatment to effectively control inflammation and prevent joint damage. Empirically, this strategy seems ideal for PsA also given the evidence of the link between inflammation and damage in peripheral joint disease in PsA. However, there are no controlled studies of early treatment in PsA or investigating the concept of "tight control" of inflammation. In the studies in RA, the Disease Activity Score (DAS) definition of low disease activity or remission is routinely used as a target for therapy to allow tight control of inflammation in clinical trials. This is a clinical assessment of disease activity based principally on tender and swollen joint counts. However in PsA there are no criteria defining low disease activity or remission that can be utilised as an important clinical endpoint in such studies.

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) group have agreed a conceptual definition of minimal disease activity which encompasses remission and low disease activity. Criteria for RA have been developed based on this concept but the same approach has not been tried in PsA. Due to the variable phenotype of PsA, any proposed criteria would have to encompass all of the key manifestations of the disease and would have to involve multiple outcome measures. To maximise feasibility of use, it would be advantageous if any potential criteria were based on clinical outcome measures with no specialist imaging or assessment tools required. Investigating the prevalence of sub-clinical disease seen on imaging will allow an evaluation of the accuracy of clinical outcome measures in this population. Any criteria developed will then need validation in both research-orientated interventional settings and real-life clinical observational cohorts. The availability of such validated criteria in PsA would allow future research into tight control of inflammation and would potentially provide an objective target for treatment that could be used in interventional trials and routine clinical practice.

The focus of this thesis is to address the issues discussed above providing insight into early diagnosis, better understanding of disease involvement in early PsA, development of a target for treatment for clinical trials and finally investigating the possible impact on tight control in early PsA. The structure of this thesis can be summarised as follows:

Chapter 2 Review of the literature

This chapter provides an overview of PsA discussing epidemiology, diagnosis, outcome measurement and treatment options. The key issues in the optimal management of PsA, particularly difficulties in early diagnosis and limitations in evidence-based treatment are highlighted.

Chapter 3 The validity of the CASPAR criteria in early PsA

This chapter evaluates the sensitivity and specificity of the CASPAR criteria for PsA in an early inflammatory arthritis clinic setting.

Chapter 4 Imaging in early PsA – the extent of subclinical disease

This chapter investigates whether sub-clinical inflammatory disease (arthritis and enthesitis) exists in patients presenting with a new diagnosis of PsA using grey scale (GS) and power Doppler (PD) US techniques compared with clinical examination.

Chapter 5 Defining Minimal Disease Activity in PsA

This chapter covers the development of new minimal disease activity (MDA) criteria for PsA derived from expert opinion using real-life patient cases.

Chapter 6 Validation of the MDA criteria for PsA

This chapter assesses the validity of the new MDA criteria for PsA according to the OMERACT filter using data from both an observational cohort and from two large randomised interventional trials.

Chapter 7 Tight Control of PsA – preliminary analysis of a large Randomised Controlled Trial (RCT)

This chapter presents a preliminary analysis of the first 40 patients enrolled into the TIght COntrol of Psoriatic Arthritis (TICOPA) study, a randomised controlled single-blind study comparing intensive management of disease with usual clinical care. The analysis addresses the achievement of MDA in this unblinded cohort 48 weeks after starting treatment.

Chapter 8 Conclusions and Future Directions

This chapter examines the conclusions drawn within each chapter and provides a final summary of the work contained within this thesis. Recommendations for improving the outcome of patients with PsA are given and future directions for research are discussed.

2 Literature Review

2.1 Epidemiology of PsA

2.1.1 Introduction

Although inflammatory arthritis associated with psoriasis has been recognised for many years, there was controversy about whether it represented a separate disease entity, or simply the co-existence of RA and psoriasis. PsA was recognised as a separate disease by the American Rheumatism Association (now the American College of Rheumatology) in 1964 (O'Neill and Silman 1994), and it is recognised as one of the forms of seronegative inflammatory spondyloarthritis. PsA was initially defined by Moll and Wright as “an inflammatory arthritis in the presence of psoriasis with a usual absence of rheumatoid factor” (Moll and Wright 1973).

2.1.2 Incidence and Prevalence

A number of studies have attempted to estimate the incidence and prevalence of PsA with significant variation in results. A systematic review of papers published between 1987 and 2006 revealed a median incidence rate of 6 per 100,000 population (range 0.1-23) and a median prevalence of 180 per 100,000 population (range 1-420) (Alamanos et al. 2008). The majority of these studies were published after 2000, and therefore relate to similar periods of time. However there are a few studies published some decades before this (Alamanos et al. 2008), and a recent study has directly compared the trends in epidemiology of PsA over the last 3 decades (Wilson et al. 2009b). This paper and a systematic review of previous epidemiological studies have both shown an increase in the incidence and prevalence of PsA (Alamanos et al. 2008; Wilson et al. 2009b). It is unclear what is causing this increase, but several factors are likely to be at work: Firstly there is likely to be an increased diagnosis of PsA as rheumatologists and dermatologists recognise the condition; secondly there also seems to be an increasing prevalence of psoriasis (Wilson et al. 2009a) which may account for an increase in PsA; and finally there may be other reasons causing an increase in cases. Other causes of increased incidence are likely to relate to environmental causes, as the increasing prevalence over three decades cannot be explained by genetic modification. One study has attempted to address this question by examining incident cases of PsA in a cohort of patients newly diagnosed with psoriasis. They had confirmed the increasing prevalence of psoriasis and PsA, but showed risk of PsA was similar throughout the 30 year study period and was not associated with the year of diagnosis (Wilson et al. 2009a).

Some of the variability between different studies seems to relate to the population studied. Most of the studies were of European or Northern American populations, but marked differences have been seen particularly in Japanese populations. There is only one study of epidemiology of PsA in the Japanese population, and this showed a very low rate of PsA with an annual incidence of 0.1 and a prevalence of 1 per 100,000 population. It has also been noted that Japan has a very low incidence of ankylosing spondylitis (AS) and other spondyloarthritides (SpA). There is a lower prevalence of human leukocyte antigen (HLA)-B27 positivity which may explain the reduction in occurrence of SpA given the strong association between the two (Hukuda et al. 2001). However the association between PsA and HLA-B27 is less clear and there may be other undiscovered genetic or environmental factors that explain the low occurrence of PsA in Japan.

Prior to the publication of the CASPAR criteria (Taylor et al. 2006), there was no consensus on suitable classification criteria, and most of these studies relied either on the European Spondyloarthropathy Study Group (ESSG) criteria (Dougados et al. 1991) or on the coexistence of psoriasis and arthritis. This variation in case definition also increases the variability expected in the results. The ESSG criteria have been shown to have a poor sensitivity in PsA (Taylor et al. 2006) and may underestimate the burden of disease in such studies. The use of psoriasis + arthritis as a case definition has many potential pitfalls, particularly the misdiagnosis of patients with true RA and psoriasis, and the omission of patients with PsA sine psoriasis. A more recent large epidemiological study used the CASPAR criteria to define cases to avoid such problems with misclassification (Wilson et al. 2009b). Reassuringly, the incidence and prevalence reported is not too dissimilar to the median rates reported in the review of previous studies (Alamanos et al. 2008).

2.1.3 Clinical Features

PsA is considered part of the umbrella group of the seronegative SpA. This concept of a group of related disorders was first introduced by Moll and Wright in the 1970s (Helliwell 2004), who documented the common clinical presentations of such disorders. The seronegative SpA include PsA, AS, reactive arthritis, inflammatory bowel disease related arthritis and undifferentiated SpA. Typical features of SpA include absence of rheumatoid factor (RF), asymmetric peripheral oligoarthritis, dactylitis, sacroiliitis, enthesitis, anterior uveitis, psoriasis, inflammatory bowel disease (Crohn’s or ulcerative colitis) and keratoderma blenorrhagica. The identification of this group of disorders was strengthened by the discovery of HLA-B27 (Helliwell 2004), which is linked with SpA, particularly AS. AS is considered as the “prototype” SpA with typical features such as sacroiliitis, a high prevalence of HLA-B27, and only minimal clinical variation. However PsA shows significant clinical heterogeneity and can be harder to classify (see section 2.2.1). The existence of a separate diagnostic entity of PsA, rather than RA with co-existent psoriasis, was a matter for debate until recently.

Although there is a relative paucity of research in this area, it has been suggested by multiple studies that the prevalence of arthritis in patients with psoriasis, particularly those with peripheral inflammatory arthritis is higher than population controls (Fitzgerald and Dougados 2006). In the Norfolk Arthritis Register (NOAR) cohort, the prevalence of psoriasis was 9.5% in patients with new onset arthritis, higher than in the general population (Harrison et al. 1997). Controversy remains concerning how to differentiate seronegative RA with psoriasis and polyarticular PsA. The NOAR cohort showed no significant difference in outcome of polyarthritis between patients with psoriasis and those without at one (Harrison et al. 1997) and five years (Morgan et al. 2007). However analysis of the CASPAR cohort, found that polyarticular PsA had more in common with oligoarticular PsA than with RA. Polyarticular PsA patients had a similar prevalence of RF and anti-cyclic citrillinated peptide (CCP) positivity as well as enthesitis, spinal pain and stiffness. Dactylitis was also seen in a similar proportion of both PsA groups (45-57%) and was uncommon in the RA group (Helliwell et al. 2007).

2.1.4 Natural History

The diagnosis of PsA, particularly in the early stages of disease, is difficult, particularly due to the lack of validated classification criteria for early disease. However a number of studies have attempted to address the initial presentation of such a disease. The majority of patients develop psoriasis prior to the onset of arthritis, even though it may not have been diagnosed by a physician previously. However up to 20% of patients develop arthritis first and are often labelled as undifferentiated SpA until the psoriasis becomes apparent (Kane and Pathare 2005).

Epidemiological studies of cohorts with psoriasis have attempted to identify which patients are more likely to develop PsA. A cohort of 1,633 patients with psoriasis were analysed and approximately 10% of patients were diagnosed with PsA over a 30 year time period. Given the reliance on retrospective review of medical records, the incidence of PsA is likely to be an underestimate. Clinical features associated with the development of PsA were psoriatic nail changes, scalp psoriasis and intergluteal/perianal psoriasis (Wilson et al. 2009a).

There are four main cohorts of early PsA with published data. The NOAR cohort data split their patients according to presence of absence of psoriasis without considering RF status. Although psoriasis patients were less likely to be RF positive, they still had a relatively high prevalence of 13% when compared to the CASPAR cohort (6% of polyarticular PsA were RF positive (Helliwell et al. 2007)). Therefore, there is likely to be some misclassification of patients with RA and coexistent psoriasis. Their clinical presentation was similar across the two groups, although the psoriasis patients were more likely to be male and RF negative. Outcome at one and five years found no obvious clinical differentiators, but the level of radiographic joint damage in those with erosive disease was lower in those patients with psoriasis (Harrison et al. 1997; Morgan et al. 2007)

A small Italian cohort of 66 patients, with PsA of less than one year duration, was followed prospectively for two years. Patients were defined as elderly onset (>60 years) or younger onset PsA, and this study showed a poorer outcome, with more joint destruction in the elderly onset group. This was associated with higher inflammatory markers and higher levels of key inflammatory cytokines. However it must be noted that only 16 patients with elderly onset PsA were included and further studies on this are warranted (Punzi et al. 1999).

A larger cohort of patients with PsA of less than two years duration were followed prospectively in Dublin. Of 1018 patients referred to the early arthritis clinic between 1994 and 2000, 129 (12.7%) were diagnosed with PsA and followed for two years. The mean age at presentation was 41.2 and the mean age at psoriasis onset was 29.8 years. At presentation, 60% of these had polyarticular disease and 40% had oligoarticular PsA. All patients had peripheral synovitis as this was a criterion for referral to the clinic, but in addition to this, nearly 40% had enthesopathy, 30% had dactylitis and 10% had inflammatory back pain. At baseline, 27% of patients had evidence of erosive disease on radiographs, this had increased to 47% of patients at two years (Kane et al. 2003b).

A further study using the Swedish PsA register (SwePsA) studied 183 patients diagnosed with early PsA (<2 years duration) between 2000 and 2007. They showed a similar proportion presented with oligo and polyarticular disease and confirmed the evidence from a previous retrospective study (Jones et al. 1994) which showed that the pattern of disease often changes over time (Lindqvist et al. 2008). The prevalence of radiographic damage at baseline (20%) and two year follow up (32%) was lower than that seen in the Dublin cohort, possibly reflecting more aggressive treatment in later years.

The long term prognosis for patients with PsA has been addressed in the most detail by the Toronto PsA cohort. This cohort includes nearly 800 patients followed prospectively for up to 30 years. An analysis of their first 220 patients identified that polyarthritis was a more common presentation than oligoarthritis and was one of the earliest papers to confirm the high rate of joint damage with 40% of patients suffering with a deforming, erosive arthropathy (Gladman et al. 1987). Detailed analyses of this cohort have identified key prognostic indicators that can be identified at baseline and follow up. Poor prognostic factors for progressive joint damage included high number of active joints, high number of previous medications and high erythrocyte sedimentation rate (ESR) at presentation (Gladman et al. 1995). Analysis of subsequent visits and the progression of joint damage between visits, identified that active joints, poor functional class and current joint damage also predict ongoing damage at future visits (Gladman and Farewell 1999). When looking at predictors for remission (defined as no active joints for >12 months) male sex, fewer active joints and better functional class were independent predictors (Gladman et al. 2001).

2.1.5 Pathogenesis

2.1.5.1 Immunology

Typically, PsA is thought of a seronegative disease and the majority of patients do not have the RF or antibodies to CCP. However a significant minority of patients are positive for one or both of these and this does not exclude a diagnosis of PsA. Some studies have suggested a modification in phenotype seen in sero-positive individuals.

Rheumatoid factor (RF)

Although PsA is typically considered to be sero-negative for RF, RF positivity does occur in PsA. In the 588 patients with PsA recruited to develop the CASPAR criteria, approximately 5% of patients had a positive RF compared to 76% in the RA control group. Interestingly, patients with polyarticular PsA were no more likely to be RF positive than those with oligoarthritis.

Antibodies to Cyclic Citrullinated Peptides (anti-CCP Ab)

The estimates for prevalence of anti-CCP Ab in PsA vary from 6 to 16% in different cross-sectional studies (Bogliolo et al. 2005; Korendowych et al. 2005; Alenius et al. 2006; Shibata et al. 2009). All of the studies with comparative groups have found a trend towards a higher prevalence of CCP Ab in patients with PsA when compared to healthy controls or patients with psoriasis, however the prevalence is significantly lower than that seen in RA (Korendowych et al. 2005; Alenius et al. 2006; Shibata et al. 2009). CCP Ab can also be detected in synovial fluid of affected joints in PsA, but levels are significantly lower than those in RA patients and similar to the levels found in osteoarthritis (OA) patients (Caspi et al. 2006; Spadaro et al. 2007). However the significance of CCP Ab in PsA is uncertain. Nearly all of the studies have shown a significant association between polyarthritis and CCP Ab (Bogliolo et al. 2005; Korendowych et al. 2005; Alenius et al. 2006), but interestingly an analysis of a larger cohort from the CASPAR study (n=588) showed CCP positivity in 7% of polyarticular PsA and 10% of oligoarticular PsA or psoriatic spondylitis (Helliwell et al. 2007). Some have identified an association with erosive disease (Bogliolo et al. 2005; Korendowych et al. 2005) but others did not replicate the findings (Alenius et al. 2006).

2.1.5.2 Genetics

A genetic basis for disease has been investigated in many of the arthritides as the heritability of RA and other autoimmune conditions has been recognised. PsA is known to be a highly heritable disease from family studies with a greater heritability than RA, Sjogrens and other autoimmune disorders. Interestingly the recurrence risk (or ΛS) of PsA is estimated at 27 (Gladman et al. 2003) (risk to siblings/risk in general population) which is also significantly higher than psoriasis (ΛS between 4 and 11) (Bhalerao and Bowcock 1998). A study in Iceland confirmed increased risk ratios for development of PsA in first to fifth-degree relatives of those with PsA. They showed risk ratios of 39, 12, 3.6, 2.3 and 1.2 respectively in first to fifth-degree relatives. There was a significant difference between relatives and controls in the first to fourth degree relatives ($p<0.0001$), with no significant difference ($p=0.236$) seen in fifth-degree relatives (Karason et al. 2009).

The largest proportion of the genetic susceptibility to psoriasis is found in the major histocompatability complex (MHC) class I region with strong associations between the psoriasis susceptibility 1 (PSORS1) gene and HLA-Cw*0602 (Nograles et al. 2009). The frequency of HLA-Cw*0602 is also increased in PsA patients when compared to controls (Gladman et al. 1999). However further analysis has suggested that it is only significantly associated with PsA patients with type I psoriasis and not those with type II psoriasis (Ho et al. 2008). This suggests that its major influence is on the age of onset of psoriasis not with susceptibility to PsA.

HLA-B27, typically associated with AS, is also found to be associated with psoriatic spondylitis although the frequency of B27 positivity is much lower in PsA patients (Queiro-Silva et al. 2004). HLA-B38 and HLA-B39 have been shown to be associated with peripheral PsA, but this may be confounded by the correlation with HLA-Cw*1203 (Nograles et al. 2009). The shared epitope (HLA-DRB1) seen in RA, is also seen in patients with PsA and has been found to be associated with erosive polyarticular disease (Korendowych et al. 2003).

There is a significant association seen with alleles of the interleukin (IL)12B and IL23 receptor gene and susceptibility to both psoriasis (Nograles et al. 2009) and PsA (Liu et al. 2008; Huffmeier et al. 2009) and this has been confirmed in multiple studies (Nograles et al. 2009). Interestingly the same IL23R genes have been found to be associated with inflammatory bowel disease and AS confirming a further genetic link within the seronegative SpA (Nograles et al. 2009).

2.1.5.3 Environmental factors

Whilst the strong heritability seen in PsA suggests underlying genetic causes of the disease, the other risk factors for developing PsA are less clear. The majority of patients have psoriasis prior to developing the arthritis and the average duration of psoriasis is 10 years at the time of diagnosis of PsA (Gladman et al. 2005). Epidemiological studies have sought to answer why PsA develops in genetically susceptible people at certain times, i.e. the triggers of disease.

The most reported trigger of PsA is trauma which seems particularly relevant as psoriasis is also triggered by trauma in the form of the Koebner phenomenon. Two studies suggested that acute physical trauma may be associated with PsA (Scarpa et al. 1992; Punzi et al. 1997), and did not show the same association with RA (Scarpa et al. 1992). A large case-control study looked at multiple potential risk factors and again confirmed the strongest association with trauma, either physical (injury, fracture) or psychological (moving house) (Pattison et al. 2008).

Infection may also be a significant trigger for PsA. In a Zambian clinic population, PsA was seen almost exclusively in patients who were human immunodeficiency virus (HIV) positive (Njobvu and McGill 2000). An association has also been suggested with hepatitis C viral infection where one group found a statistically significant increase in the prevalence of hepatitis C infection in patients with PsA when compared to psoriasis, RA and general population controls (Taglione et al. 1999), but subsequent reports have not shown a significant association (Palazzi et al. 2005). There is a strong link between streptococcal infections of the respiratory tract and skin psoriasis, particularly in its guttate form, probably caused by cross-reactivity between streptococcal antigen and keratinocyte antigens. However there is no evidence of a relationship between such infections and the development of PsA.

Immunomodulatory effects have also been implicated in the triggering of PsA. Thumboo et al showed that patients who developed PsA were more likely to have been prescribed steroids prior to developing arthritis and were less likely to have experienced a recent pregnancy when compared to controls with psoriasis (Thumboo et al. 2002). There is a well documented risk of psoriasis flare on withdrawal of oral corticosteroids (Griffiths 1997), and the authors postulated that a similar mechanism may trigger PsA.

2.1.5.4 Imaging

Much work has been done in the past to determine the nature of PsA using imaging studies. In contrast to the articular disease, imaging of the skin has been relatively neglected, possibly because of the ready availability of the skin for biopsy and histopathological studies. This section will review this literature on what imaging the skin and joints can tell us about the pathology of PsA.

Conventional Radiography

Radiographic changes in PsA are seen more commonly in advancing disease. Damage seen on radiographs is not as severe as patients with RA matched for disease duration (Sokoll and Helliwell 2001) but even early on in the course of disease, it can be significant. At presentation, around 27% have evidence of erosions on x-ray and this increases to 47% at two years despite conventional treatment with disease modifying anti-rheumatic drugs (DMARDs) (Kane et al. 2003b).

In the past literature the key radiographic features of PsA have been defined as joint erosions, joint space narrowing (JSN), bony proliferation, osteolysis (including pencil-in-cup deformity), ankylosis, and new bone formation at entheses, both central and peripheral (Wassenberg et al. 2001). Erosive changes are marginal (similar to RA) but become irregular with disease progression because of new bone formation adjacent to the erosions (Ory et al. 2005). Severe erosions lead to the pencil-in-cup deformity or osteolysis (Gold et al. 1988).

However the CASPAR study, comparing RA with PsA (where radiographs were read blind to diagnosis) found a limited number of unique features. For example, osteolysis at a peripheral joint was not found to discriminate between RA and PsA. Osteolysis was only characteristic of PsA if it occurred at the DIP joint – osteolysis at proximal inter-phalangeal joints and metacarpo-phalangeal joints was seen equally in RA (Taylor et al. 2006). Further, the only distinguishing plain radiographic features of PsA were irregular new bone formation adjacent to small joints of the hand and foot and irregular new bone in the pelvis, particularly at sites of attachment of inguinal ligament, sartorius and rectus femoris muscles to the ilium (Helliwell and Porter 2007).

Axial disease in PsA was first reported by Wright et al who recognised the frequent sacroiliac (SI) changes in patients with PsA compared to rheumatoid controls (Wright 1961). This study of 99 patients with PsA and 90 RA controls showed a significant increased incidence of erosion, sclerosis and ankylosis at the SI joints. Spondylitis is seen in approximately 25% of PsA patients and radiographically looks similar to AS with some important differences. Spinal disease is more often unilateral or asymmetrical and the morphology of syndesmophytes seen also differs from those in AS (McEwen et al. 1971).

Radioisotope Imaging

The majority of studies using bone scintigraphy were published prior to 2000, since when the emphasis has shifted to MRI and US techniques. Most studies have used bone seeking radioisotopes such as bisphosphonates which are ‘taken up’ at sites of increased bone turnover. Scintigraphy thus lacks specificity but it has been used as a surrogate marker of inflammation. Scintigraphy has been used to identify abnormalities before the appearance of plain radiographic features. A study comparing radiographs with standard bone scintigraphy showed that bone scans mirror radiological changes with increased uptake in areas of bony damage (O'Sullivan et al. 1988). It was also apparent that the bone scans were more sensitive than x-ray in detecting clinically active disease.

Scintigraphic studies of patients with skin psoriasis but no clinical arthritis have been particularly interesting in raising the prospect of sub-clinical disease in those with psoriasis. Namey and Rosenthall scanned 12 psoriatic patients and 12 controls showing that all psoriasis patients had markedly abnormal scans with symmetrically increased peri-articular uptake. In contrast, none of the controls had similar findings (Namey and Rosenthall 1976). This is not evidence that all of these patients will go on to develop clinical PsA but raises questions as to the pathological correlate of these changes. Scintigraphic studies in PsA have also shown extra-synovial abnormalities. Increased uptake has been shown in areas adjacent to or even some distance from the synovial joint (Namey and Rosenthall 1976; Hahn et al. 1980; Helliwell et al. 1991).

Scintigraphy has also been used to evaluate sacroiliitis. This allows quantification of inflammation at the SI joints and can demonstrate differential uptake in each side (Szanto and Ruden 1976), but again it is not specific to PsA and therefore cannot aid diagnosis or understanding of pathogenesis.

MRI

The introduction of MRI scanning in the mid 1990s provided better anatomical images of soft-tissue and started to give clues to pathogenesis, particularly in PsA. Although synovitis in PsA and RA is indistinguishable on static or dynamic MRI scanning (Cimmino et al. 2005), features of enthesitis, dactylitis and spondylitis are in accordance with the appearances of the SpA group of disorders and can be used to differentiate the two conditions (McQueen et al. 2006). Bone erosions do not have disease specific appearances but probably progress at a slower rate in PsA than in RA (Savnik et al. 2002). Interestingly, no proof exists to link bone oedema with subsequent development of erosions as in RA (Savnik et al. 2001).

When considering extra-capsular anatomy, the features of PsA on MRI imaging are significantly different to RA and more closely resemble changes seen in other SpAs. Jevtic and co-workers (Jevtic et al. 1995) first described the extensive extra-capsular inflammation seen in PsA. Half of their cases of PsA showed changes similar to those seen in RA with predominantly synovial inflammation. However, the other half of the patients showed inflammation also involving neighbouring structures including thickened collateral ligaments and periarticular soft tissue.

Bone oedema is commonly described as an MRI feature of PsA. This has never been correlated with histopathological changes except in the SI joints of SpA patients (Bollow et al. 2000), where bone oedema was found to correlate with cellular inflammation. Bone oedema is by analogy widely accepted to represent inflammation at other sites. Godfrin et al showed that bone marrow oedema at entheses on MRI correlated with hot spots on radionuclide scanning (Godfrin et al. 2004). Bone oedema has been shown to respond to anti-TNF therapy (Marzo-Ortega et al. 2001; Bongartz et al. 2005) also suggesting that bone oedema represents tissue inflammation and that TNF is an important factor in this. Giovagnoni and colleagues noted bone oedema associated with periarticular oedema of soft tissues in 43% of their patients and described this as a possible "psoriatic pattern" on MRI (Giovagnoni et al. 1995).

Inflammation in tendons and ligaments is viewed well on MRI showing swelling and increased signal. In addition enthesitis is represented by increased signal on STIR images at the tendon/ligament insertion and associated signal change in the underlying bone. McGonagle et al studied enthesitis in knee arthritis associated with new onset SpA (including PsA) and RA (McGonagle et al. 1998). They found increased signal in the patellar tendon, iliotibial band and the posterior capsule of the knee at their insertion into bone. Many of the SpA patients (6/10) also showed bone marrow oedema which was maximal at the site of entheseal insertions (McGonagle et al. 1998). The same group also imaged calcaneal enthesopathy showing a similar increased peri-entheseal signal and bone marrow oedema (McGonagle et al. 2002b).

MRI has also improved our ability to detect axial disease in PsA. Traditionally, the diagnosis of sacroiliitis in all of the SpAs including PsA has relied on radiological evidence of disease. However it can take between one and nine years from the onset of inflammatory back pain for development of radiological sacroiliitis (Braun et al. 2000). In the early 1990s, MRI was investigated as a tool to detect sacroiliitis (Murphey et al. 1991; Docherty et al. 1992; Hanly et al. 1994). It has been shown to demonstrate bone oedema and osteitis seen in the SI joints and in the rest of the spine. Bone oedema adjacent to the SI joints has also been proven to correlate with histopathological evidence of inflammatory disease (Bollow et al. 2000). MRI is now accepted as a diagnostic tool for axial disease in SpA including PsA and has been used as an outcome measure to evaluate treatment with TNF blockers (Marzo-Ortega et al. 2001).

The use of MRI in PsA has expanded rapidly with an explosion of publications over the last 10 years. It’s ability to image soft tissue and bone accurately, and it’s sensitivity for detecting inflammation in synovial tissue, entheses and bone has meant that it has become the “gold standard” when considering imaging of rheumatic conditions.

Further work is also underway exploring the use of MRI in assessing synovitis and the vascularity seen in PsA. As noted above, there is the need to correlate synovial immunohistochemical changes with MRI appearances to validate this approach. The use of software to accurately quantify synovitis, and vascularity in the form of dynamic contrast enhancement has already been explored (Rhodes et al. 2004) and is being further developed. This would then allow further research into the pathology of PsA and the response to treatment such as TNF blockers.

The use of low-field or extremity MRI machines in rheumatology is now expanding as they are practical for use in the outpatient department and are more comfortable for patients. All of the validation studies investigating their use against a gold standard of high field MRI have been in patients with RA. They have been shown in these patients to be equivalent to high field MRI in sensitivity and specificity of detecting bone erosions and synovitis (Ejbjerg et al. 2005). However they are significantly less sensitive when identifying bone marrow oedema (Ejbjerg et al. 2005) and this is of concern when considering their use in the imaging of seronegative conditions.

The only study of low-field MRI scans in PsA was done by Scarpa et al. They scanned 26 PsA patients to look at nail and DIP joint disease (Scarpa et al. 2007) and found similar results to their previous study using high-field MRI (Scarpa et al. 2006). However there have been no studies directly comparing high field and low field MR images to formally validate these machines.

New techniques using high field MRI scanners are also being developed. Ultrashort echo time (UTE) imaging is a novel MR technique which allows the detection of signal from tendons, fibrocartilage and cortical bone. These tissues can be imaged directly, allowing them to be differentiated from each other. Structure within the tendons and fibrocartilage can be appreciated with UTE. Changes which lead to the high signal on conventional images should be seen at an earlier stage using this technique. Using UTE sequences with intravenous (IV) contrast will image tissue vascularity. Abnormalities in enhancement reflecting increased vascularity due to inflammation are likely to precede structural changes. Thus, UTE imaging may allow the detection of early changes at the enthesis, localisation of changes to the fibrocartilage or tendon and visualisation of vascular, oedematous and structural changes. Vascularity may be sensitive to changes in treatment, as it is in the inflamed synovium of RA.

Dynamic contrast enhanced (DCE) MRI of areas of osteitis has the potential to measure inflammatory activity better than conventional MRI of bone marrow oedema. Not only is it more sensitive, it is inherently quantitative and provides information about the vascularity of the inflamed bone. It shows more widespread involvement and increased sensitivity to treatment compared to conventional measures of bone marrow oedema in RA. DCE-MRI of bone marrow may therefore allow early detection of osteitis and quantification of inflammatory activity at the enthesis site.

Computed Tomography

Micro-computed tomography (μCT) has been used to further visualise the bony changes in PsA and has provided additional information regarding the different radiological features when compared to RA. Finzel et al scanned 30 patients with PsA and 58 patients with RA looking in detail at both erosive disease and new bone formation at the MCP joints. Although the number of erosions was similar in both diseases, the extent of erosions was much greater in RA, particularly at the second MCP joint. There was also a significant difference in the shape of erosions identified. 'U'-shaped lesions with a wide cortical break were typical for RA, whereas 'Ω'-shaped lesions with a small cortical break and a large erosion underneath were typical for PsA. Osteophytes were found in all PsA patients, but only 16% of RA patients and large osteophytes (>1mm in diameter) were almost exclusively found in PsA patients. The authors concluded that different pathophysiology may account for these differences, with an increased potential for new bone formation, ie repair, in PsA explaining the different morphology and size of erosions and osteophytes (Finzel et al. 2011).

Ultrasound

Musculoskeletal US has been used in PsA to investigate synovial disease, enthesitis and sacroiliitis. US has helped to characterise the changes seen in PsA and RA particularly in the finger joints. Fournie's group showed that while the synovial membrane of joints and tendon sheaths could be involved in both conditions, extrasynovial abnormalities were only seen in PsA patients. These included abnormalities denoting enthesitis, thickening of soft tissues and Doppler signal from the base of the nail indicating periungual psoriatic involvement (Fournie et al. 2006).

US is used also to investigate enthesitis. Oedema and increased vascularity at the tendon are the characteristic findings (Lehtinen et al. 1994), but more recently, PD has also been used to help distinguish between inflammatory and mechanical enthesitis (D'Agostino et al. 2003).

Dactylitic digits have also been imaged using US which has shown conflicting findings. Kane et al found subcutaneous soft tissue enlargement (pseudotenosynovitis) in all affected digits. After that, flexor tenosynovitis (FT) was the commonest finding (96% of cases) with some related synovitis in around half of the digits (Kane et al. 1999). However Olivieri et al found that all dactylitic digits showed fluid collections surrounding the tendons in keeping with FT but no involvement of the peritendinous soft tissues or the synovial joints (Olivieri et al. 1996).

Enthesitis

Enthesitis has been most commonly imaged using US. Oedema and increased vascularity at the tendon is the characteristic finding. Sonographic evaluation of entheseal insertions has shown a high prevalence of enthesitis in patients with PsA despite many being asymptomatic (Lehtinen et al. 1994).

Another study using PD techniques has shown that entheseal involvement on US imaging affects 98% of patients with SpA including PsA but is far less common in controls with mechanical back pain (44%) or RA (60%). The commonest sites of involvement in PsA were Achilles tendon, patellar tendon, plantar fascia and greater trochanter (D'Agostino et al. 2003). Falsetti et al looked specifically at the calcaneal enthesis using US and plain radiography and compared patients with PsA, RA and OA. There was no significant difference found between the PsA and RA groups but there was a trend towards more Achilles enthesitis and plantar fasciitis in PsA and more erosive disease in patients with RA (Falsetti et al. 2003).

Enthesitis as the Primary Pathology

McGonagle et al have hypothesised the primary role of enthesitis in PsA and a secondary spread of inflammation to the synovium. Most studies involving radionuclide scanning in PsA identified increased uptake adjacent to synovial joints and in some cases, some distance away. No anatomical reason was given for this at the time but it provides confirmation of inflammation distant from the synovium.

Jevtic and co-workers (Jevtic et al. 1995) first described the extensive extra-capsular inflammation seen on MRI scans in PsA. Half of their cases of PsA showed changes similar to those seen in RA with predominantly synovial inflammation. However the other half of the patients showed inflammation also involving neighbouring structures including thickened collateral ligaments and periarticular soft tissue. This extra-capsular inflammation was much greater in the soft tissue seen around dactylitic joints and there was no associated tenosynovitis to explain the uniform swelling of the digit. In one joint, predominant extracapsular inflammation was seen without significant associated synovitis thus raising the possibility that the joint capsule and synovium is not always the primary target in PsA (Jevtic et al. 1995). However not all of their patients showed evidence of extracapsular inflammation. This research suggested that there may be heterogeneity in PsA where some patients have a predominantly synovial disease as in RA and some show a predominantly entheseal driven disease as in SpA. In the latter respect it may be that the somewhat ambiguous criteria suggested by Moll and Wright enabled the authors to include cases of sero-negative RA within their series.

McGonagle et al studied knee synovitis in patients with a recent onset of knee effusions (McGonagle et al. 1998). Ten patients with RA and ten patients with SpA (including three with PsA) were included. The aim of imaging early disease was to try and establish a causal link between the enthesitis and synovitis seen in SpA joints. Focal soft tissue oedema and bone marrow oedema adjacent to the entheseal insertions was common in SpA, despite little clinical evidence of enthesitis. This pattern of inflammation is similar to that seen in peripheral enthesitis and spondylitis suggesting the possibility of a common pathogenesis.

However, as yet, the primary entheseal hypothesis awaits conclusive proof. Enthesitis in PsA is not found universally in imaging studies but this does not detract from the hypothesis – several other explanations might explain this including stage and activity of disease and heterogeneity of disease phenotype.

Distal Interphalangeal Joint Disease

Distal interphalangeal (DIP) joint involvement, although not exclusive to PsA, is certainly one of the characteristic features of this disorder. Nail involvement is more common in PsA than uncomplicated psoriasis and DIP joint involvement is almost never seen in the absence of nail disease. Any clue as to the pathogenesis of this is likely to help us gain a better understanding of the disease. Imaging may have helped in this respect. The changes seen on plain radiography include erosions of the terminal tuft, periarticular new bone formation away from the joint margin, and osteolysis leading to the so-called ‘pencil-in –cup’ deformity.

MRI studies have confirmed the intimate relationship between the nail bed, the distal phalanx, the DIP joint and the insertion of the extensor tendon (Scarpa et al. 2004; Scarpa et al. 2006; Tan et al. 2006; Tan et al. 2007). Histological work has shown that the extensor tendon attaches to the base of the terminal phalanx and then extends distally to connect with the nail root. This can now been visualised on MRI using high-resolution techniques.

Scarpa showed that nail thickening on MRI was extremely common in patients with PsA, even when clinical evidence of onychopathy was lacking, and that all of these patients also showed MRI involvement at the distal phalanx. In the majority of patients without clinical onychopathy, the changes were confined to the nail and distal phalanx with little evidence of DIP joint disease. However involvement of the DIP joint was much more common in those with clinical onychopathy (58% of cases) (Scarpa et al. 2006).

Both Scarpa and McGonagle’s work has raised the possibility of inflammation being transmitted via the enthesis seen around the DIP joint and nail bed. The Leeds group compared OA and PsA patients with DIP joint involvement. This showed that PsA patients have significantly more entheseal and ligament enhancement, extracapsular changes and diffuse bone oedema (Tan et al. 2006). This inflammatory response seemed to be focused around the ligament origins/insertions with almost normality of the ligaments up to the enthesis. Bone oedema was seen diffusely throughout the distal phalanx in 80% of PsA digits but was seen maximally at the insertion of the collateral ligament enthesis (Tan et al. 2006). The inflammation seen was extensive enough in most cases to involve the nail bed, distal phalanx and DIP joint (Tan et al. 2007) providing an explanation for the common association of nail and DIP joint involvement. It seems likely that the inflammation in this region is transmitted via the entheses which extend up to the nail bed and envelop the DIP joint but there has been no way to identify where the primary site of pathology lies.

Another study by Scarpa using radiographs showed that DIP joint involvement was related to duration of onychopathy. He suggested that the involvement of the DIP joint was secondary to that of the distal phalanx which was secondary to the nail changes. However, there is no definite evidence to prove this due to the lack of longitudinal studies. Given the usual scenario in this disease, where skin (and nails) precedes joints then it seems more likely that the nail bed disease is primary. On the other hand the same disease process may be responsible for both manifestations. Longitudinal studies with high resolution MRI may help in this respect.

Dactylitis

Dactylitis, one of the hallmark clinical features of PsA, occurs in 16% to 48% of reported cases. It is often painful, but a chronic, non-tender dactylitic swelling can occur. Further, diffuse swelling of the upper limb has been described and may be a similar manifestation. The pathogenesis of dactylitis is still not fully understood and although FT is a key feature on imaging, other abnormalities are also seen.

Jevtic and co-workers (Jevtic et al. 1995) first described the extensive extra-capsular inflammation seen in dactylitic PsA on MRI. Many of the patients showed inflammation also involving neighbouring structures including thickened collateral ligaments and periarticular soft tissue. This extra-capsular inflammation was much greater in the soft tissue seen around dactylitic joints and there was no associated tenosynovitis to otherwise explain the uniform swelling of the digit.

In contrast, around the same time, Olivieri et al specifically imaged 12 dactylitic fingers using MRI and US and found contrasting results. This first study by Olivieri showed that all dactylitic fingers had a moderate to severe FT but did not see any peritendinous oedema. They initially concluded that dactylitis was due to FT and that the peritendinous soft tissue was not involved (Olivieri et al. 1996). However subsequent work by the same group showed that peritendinous inflammation and oedema was present in a proportion of dactylitic digits (Olivieri et al. 1997; Olivieri et al. 2002; Olivieri et al. 2003). Following this, they suggested that the peritendinous oedema was probably caused by increased capillary permeability secondary to FT.

McGonagle et al proposed the theory that enthesitis was the primary abnormality in PsA but Olivieri's group using MRI in eleven dactylitic fingers found no evidence of bone oedema at the insertions of the extensor or flexor digitorum tendons or in other sites in the phalanges (Olivieri et al. 2002). However, they again found FT in all digits and subcutaneous peritendinous oedema in around half of the cases.

A more recent study by Healy et al., imaging 19 dactylitic digits found soft-tissue oedema and synovitis to be the most frequent abnormalities in 69% of digits. A wide range of other abnormalities were frequently found including FT and bone oedema, the latter in several patterns from discrete areas in a periarticular distribution to abnormalities in the metaphysis of the phalanx (Healy et al. 2008).

Dactylitis has also been imaged using US with similar results seen in MRI studies. US of dactylitic digits has shown subcutaneous soft tissue enlargement, FT and some related synovitis. However studies have differed significantly in the involvement of peritendinous soft tissues (also called pseudotenosynovitis) and synovitis (Olivieri et al. 1996; Kane et al. 1999; Fournie et al. 2006). Fournie suggested that pseudotenosynovitis may play a central role in it's pathogenesis (Fournie et al. 2006), explaining why dactylitis does not occur in RA where inflammation is confined to the synovial membrane of the joint and tendon. The early work of Olivieri showed that at least some of their patients with clinical dactylitis did not have any evidence of soft tissue involvement but the authors have conceded that this may have been due to limitations in the technology at that time (Olivieri et al. and Olivieri personal communication).

Despite the controversy about the site of tissue inflammation in dactylitis it seems clear that virtually all the tissues are involved in an affected digit. Thus MRI scanning has shown us that in acute dactylitis there is synovitis and widespread extra-synovial disease, including soft-tissue involvement (Healy et al. 2008). If dactylitis is considered a paradigm for PsA what does it tell us about the pathology of the disease? In contrast to RA there is inflammation outside the synovial cavity but seemingly localised to certain affected digits.

It has been suggested that dactylitis is a form of the Koebner phenomenon, occurring deep within the tissue of the digit. Given that the commonest affected digits in dactylitis are, in the hand the 2^{nd} and in the foot the 4^{th}, there may be some evidence to support this (Brockbank et al. 2005). It is also clear that repeated minor physical insults to our digital joints and entheses are commonplace providing adequate mechanical stimuli. The tissue response may therefore depend on other factors such as immunogenetic profile and mechanoreceptor response in the target tissues

Axial Disease

Wright et al initially noticed the asymmetry of spinal disease in PsA when they found unilateral changes seen in 21% of those with PsA related sacroiliitis (Wright 1961).

Syndesmophytes are seen less commonly in PsA and are usually single or asymmetrical (Jajic 1968). They are more frequently paramarginal and may not appear in consecutive vertebrae (Ory et al. 2005). The most striking difference between the SpA conditions in the study by McEwen et al was the significant number of non-marginal syndesmophytes in the PsA and reactive arthritis group. They also looked at progression of lesions relative to disease duration to suggest that progression of spondylitis in PsA developed in a random fashion throughout the spine rather than a gradual symmetrical extension of disease (McEwen et al. 1971). A study attempting to replicate this work in 1998 did confirm the differences in severity of involvement, symmetry and morphology of syndesmophytes (Helliwell et al. 1998) although due to the study design they were unable to comment on progression.

As more research has investigated the involvement of the spine in PsA, the prevalence of asymptomatic spinal involvement has been identified. Around one-third of patients have asymptomatic sacroiliitis (Gladman 1994; Gladman 1998; Queiro et al. 2002) and it is more common in women (Queiro et al. 2002). HLA B27 status does not appear to be an independent predictor of spinal involvement and is certainly not a prerequisite for the development of this pathology (Queiro et al. 2002).

The asymmetrical nature of spinal disease in PsA has never been fully explained. It is unclear whether this may represent an important difference in the underlying pathology between axial disease in PsA and AS. Helliwell et al have also raised the possibility that the spinal asymmetry found may be due to other factors rather than a true difference in pathogenesis. They pointed out that symmetry is a function of frequency of joint involvement in peripheral PsA joint disease. Thus the asymmetry may be a function of the paucity of syndesmophytes in the spine, rather than a true difference in pathology (Helliwell et al. 1998).

Suggestions have been made regarding the different morphology of spinal syndesmophytes in PsA whilst compared with AS. The bulkier shape, first depicted by Bywaters (Bywaters and Dixon 1965) and described by Bunim as “tear drop” or “comma shaped”, show significant thickening of one portion (upper or lower) of the syndesmophyte (McEwen et al. 1971). It is known that peripheral PsA is characterised pathologically by intense osteoblastic activity and it may be that this powerful activity produces bulkier syndesmophytes despite a similar initiating pathogenesis (Helliwell et al. 1998). It is also possible that the cytokine profile released in response to inflammation and/or stress in PsA differs from that found in classical AS. Thus a predominance of transforming growth factor (TGF) beta and bone morphogenic proteins may lead to a different pattern of bone deposition. An alternative explanation is that PsA patients do not suffer from the same degree of reduced spinal mobility caused by involvement of the apophyseal joints in AS. Therefore greater mechanical stresses are felt anteriorly resulting in increased inflammation/repair mechanism activation and additional bone formation (de Vlam et al. 1996). Other characteristics of spondylitic PsA include atlantoaxial subluxation, apophyseal joint ankylosis and ligamentous calcification (Salvarani et al. 1992; Wassenberg et al. 2001; Laiho and Kauppi 2002).

Various studies have also investigated radiological changes in the cervical spine and have estimated it to occur in up to 70-75% of patients with PsA (Blau and

Kaufman 1987; Salvarani et al. 1992) making it much more common than sacroiliitis. Disease seen in the cervical spine is particularly interesting as it seems that two distinct pathological types seem to occur. In 1964, Kaplan et al observed that radiological changes in the cervical spine in PsA and skin psoriasis bore a closer resemblance to AS than to RA (Kaplan et al. 1964). Blau and Kaufman went on to describe two separate patterns of cervical spine disease: primarily ankylosing in nature or a rheumatoid-like form of inflammatory cervical involvement (Blau and Kaufman 1987).

This was confirmed in an Italian study some years later where further investigation of these two groups was performed. Unfortunately, despite the strikingly different radiological features, there was no difference found between the two groups in terms of clinical symptoms. Multivariate analysis found that rheumatoid-like disease was associated with B39 and DR4 antigens and with evidence of radiocarpal erosions (Salvarani et al. 1992). Although, it is possible that a small percentage of those patients may have had seronegative RA with co-existing psoriasis, case reports have identified patients with severe erosive peripheral disease inkeeping with arthritis mutilans with coexistant ankylosing-type cervical disease (Ly et al. 2009). A further explanation may be reflected by the contrasting peripheral pattern of disease in PsA with both new bone formation and erosive disease. Synovitis in zygoapophyseal joints and within the atlanto-axial joint could be associated with extensive extra-articular inflammation causing erosion and instability in this region.

Skin and Nail Disease

US has been used to investigate skin psoriasis. Typically 20MHz scanners are used because they offer visualisation of the layers of the skin with a reasonable compromise between resolution and viewing depth. This has allowed assessment of skin thickness within the different layers of the skin. Laser Doppler (LD) imaging (or scanning LD) uses the same principle as Doppler US but uses low-level laser light of a few milliwatts. This is directed onto the skin and penetrates a short distance into the dermis, epidermis and beyond. The penetration depth is dependent upon the tissue imaged and the wavelength of light used. Two methods of imaging can be used – laser Doppler flowmetry (LDF) which measures flow at a single point, or a newer technique of LD imaging which measures blood flow over an area of skin (Murray et al. 2004b).

Imaging of the skin with US and LD imaging has improved our understanding of skin psoriasis. US studies have been able to investigate the changes in psoriatic plaques compared to normal skin. Initial studies found that the average skin thickness is increased within the psoriatic plaque. These changes are due to a dense layer of scaling, a subepidermal low-echogenic band and diffuse enlargement of dermis itself. The thickened echopoor band seen on 20-40MHz US is not present in normal skin. Some have suggested that this may correlate with the sum of acanthosis and the upper dermis with inflammatory infiltrate (Murakami and Miki 1989; Fornage et al. 1993; Hoffmann et al. 1995; Gupta et al. 1996), while others think it represents the papillary dermis (Di Nardo et al. 1992; Stiller et al. 1994; Vaillant et al. 1994). US scanning with 100MHz probes has allowed improved resolution. This meant that a similar thinner echo poor band could be identified in normal skin which seemed to represent the viable epidermis together with the papillary dermis. This band then thickened at the transition from normal to psoriatic skin to around 500 micrometres. This band was also well correlated with histometric thickness of this layer of the skin in related histological specimens. This lends support to the theory that the change in psoriatic skin is that of increased inflammatory infiltrate (El Gammal et al. 1999).

LDF and LD imaging have allowed quantification of the microvascular blood flow in psoriatic plaques using a non-invasive technique and have confirmed the increased blood flow in psoriatic plaques (Hull et al. 1989; Speight et al. 1993; Auer et al. 1994; Hern et al. 1999; Davison et al. 2001). LD imaging has identified an increase in blood flow in psoriatic plaques of around four times that of normal (Speight et al. 1993; Murray et al. 2005) and can differentiate between the advancing and non-advancing edges of the plaque (Hull et al. 1989; Speight et al. 1993; Davison et al. 2001; Murray et al. 2005). Interestingly there is also an increased blood flow observed in clinically non-involved but adjacent skin. This is again maximal near the advancing edge of the plaque and extends for around 4mm beyond the clinically obvious plaque (Hull et al. 1989; Speight et al. 1993; Davison et al. 2001). Auer et al used a 3D reconstruction of LD images to further investigate the increased vascularity. They found that the volume of papillary vessels was twice as large in psoriatic skin and suggested that this may be due to dilation of the blood vessels and increased blood flow (Auer et al. 1994). Hern et al further investigated the perfusion of psoriatic plaques and their response to altered vascular resistance to try and identify the pathological cause of increased blood flow. This showed that vasoconstriction of blood vessels within plaques was intact meaning that the increased blood flow could only be due to more arterioles or a chronic structural widening of the existing arterioles (Hern et al. 1999).

LDF and LD imaging have been used to identify leading edges of plaques to allow directed biopsies to further investigate pathology (Hull et al. 1989; Speight et al. 1993; Davison et al. 2001). Hull et al biopsied this hypervascular area just beyond the advancing edge of the plaque, but found no epidermal changes of T-lymphocyte infiltration when compared with the non-advancing edge (Hull et al. 1989). He therefore concluded that the LD had been able to identify the earliest identifier of evolving plaques in the form of increased blood flow (Hull et al. 1989). This fits with the observation that vascular abnormalities appear before a clinical relapse.

More recently, technological advancements have meant that simultaneous scanning with different wavelengths is possible (Murray et al. 2004b). In psoriasis, this is done with red and green light which can differentiate between superficial and deeper microvascular blood flow. It is believed that green wavelength LD images small capillaries in the superficial dermis and red wavelength LD images larger thermoregulatory vessels of the cutaneous plexus (Murray et al. 2004a), thus allowing better understanding of precisely where the abnormal vascularity is found. Using this dual wavelength LD imaging in psoriasis has shown that although blood flow in both layers of the skin is increased, the increase is far more prominent in deeper larger vessels than superficial capillaries (Murray et al. 2005).

As well as a recognising angiogenesis, Braverman and Yen showed on US that lymphatic capillaries extended high into the papillary dermis (Braverman and Yen 1974). Unfortunately these are difficult to identify on skin biopsies and rely on imaging for further investigation. Cliff et al used a novel method of fluorescence microlymphography to further investigate dermal microlymphatics (Cliff et al. 1999). He found that the lymphatic density and maximum spread of fluorescin tracer was decreased in plaque skin compared to perilesional skin.

After the recognition of possible increased lymphatic capillaries in the dermis on US (Braverman and Yen 1974), it was postulated that abnormal proliferation of lymph vessels occurred alongside blood vessel changes. Investigations with microlymphography however found contrary results, showing fewer lymphatics in the psoriatic skin and a poorer spread of the flourescin tracer (Cliff et al. 1999). The authors suggested three possibilities for this:

1. A reduction in number of dermal lymphatics with abnormal extension into the dermal papillae
2. Lymphangiogenesis does occur but the vessels are functionally abnormal and cannot conduct the tracer used
3. Lymphatics are compressed by angiogenesis as in cancer models and are collapsed and not seen.

The authors felt that there was most likely a structural or functional lymphatic abnormality and this would be in keeping with Ryan's hypothesis that the oedema seen in the dermis of psoriatic plaques results in part from a failure of adequate lymphatic drainage (Ryan 1980).

We are still unclear as to how psoriatic nail disease develops. In seems likely from the work in DIP joint disease that there is a common link between inflammation in the DIP joint, distal phalanx and nail bed and we have an anatomical explanation for that. Nail disease in psoriasis has also been studied using US. Wortsman et al observed a hyperechoic plaque at the ventral plate in psoriatic nails (Wortsman et al. 2004). In severe disease, there was also the appearance of a wavy dorsal plate with loss of definition of the ventral plate. They found no significant differences between normal and psoriatic nail thickness overall but showed an enlarged nail-bone distance in those with psoriatic onychopathy, suggesting that the pathology is deeper than the nail plate itself. This was not seen in patients with skin psoriasis but no clinical nail involvement. This contrasts with MRI work by Scarpa et al which found a significantly increased nail thickness in 95.7% of all PsA patients (100% of those with clinical onychopathy) (Scarpa et al. 2006). However all of Scarpa's patients had PsA, not just skin psoriasis and the vast majority had MRI abnormalities in the distal phalanx.

Novel methods of imaging skin are also currently in development. Optical coherence tomography (OCT) was initially developed for imaging the human eye but is now being evaluated in skin disease. It uses infrared light instead of US to produce two-dimensional images representing the optical inhomogeneities of the tissue scanned (Welzel et al. 2003). This technique allows the visualisation of the epidermis and dermis and provides much better resolution in comparison with US. In psoriasis this has shown a pronounced entrance signal corresponding to the scaling in psoriatic plaques and has visualised the thickening of the epidermis and the ill-defined border between the enlarged papillary dermis and the epidermis (Welzel et al. 2003). OCT is a promising technique that should become of greater interest in dermatology as the resolution of these scans improves. This would allow longitudinal, non-invasive, in-vivo assessment of skin lesions and may improve our understanding of the pathology of skin psoriasis.

Another new method being developed is multi-photon fluorescence microscopy. This allows visualisation of individual cells in the skin. Reflection of light photons and autofluorescence due to naturally occurring fluorescent biomolecules is used in this technique to perform optical imaging of the tissues (Konig and Riemann 2003). It uses high intensity, near-infrared laser pulses that do not damage tissues, but can penetrate the skin with maintenance of image resolution beyond 200 μm (Masters et al. 1997). This allows clear visualisation of individual cells with much better resolution than OCT. Further work may allow functional imaging by autofluorescence detection of nicotinamide adenine dinucleotide phosphate (NADPH) which may allow further investigation of the pathogenesis of psoriasis.

Another novel technique is the use of photoacoustic microscopy which allows visualisation of the microvasculature. This uses short pulses of laser but then detects acoustic waves created by rapid thermoelastic expansion. These are detected and reconstructed to create an image (Zemp et al. 2007). As blood has a significantly larger absorption coefficient, blood vessels can be clearly imaged and this technique has been used in an animal model (Zemp et al. 2007). It allows visualisation to a larger depth than optical microscopy as it does not have the same problems with multiply scattered light. Also, by using multiple optical wavelengths, it will enable the assessment of microvascular oxygenation and angiogenesis (Maslov et al. 2006). At present, there are no reports of its use in psoriasis but its ability to visualise microvascular function and pathology means that it should be a promising future area.

2.2 Diagnosis and Classification

2.2.1 Diagnosis/classification

Diagnosis or classification of PsA has always been a limiting factor in research in this field. It is now recognised that we are researching a unique disease rather than studying a condition where otherwise typical RA is modified by the presence of psoriasis. However, there is no clear cut laboratory or imaging test that can make a certain diagnosis, instead it relies on a combination of clinical, laboratory and imaging features. Unlike RA and AS, which are strongly associated with different antibodies to help clinch the diagnosis, no such tests are available for PsA. Most rheumatologists now recognise typical cases of PsA easily, but there are a number of grey areas which cause problems for diagnosis. In everyday rheumatology practice, physicians without a specialty interest in PsA still have difficulty making the diagnosis (Gorter et al. 2002) and there is even some doubt about the ability of ‘experts’ to agree on the diagnosis in these ‘grey’ cases (Symmons et al. 2006). Common issues regarding the diagnosis of PsA include:

- The diagnosis of psoriasis is sometimes unclear. Patients are often unaware of their psoriasis, particularly if it only affects a small amount of body surface area or is only visible in the nails. The diagnosis of scalp psoriasis is also often confused by seborrheic dermatitis.

- The patient may not have psoriasis. Up to 30% of cases of PsA develop the arthritis prior to psoriasis and therefore there may be a significant delay in diagnosis.
- Patients may present with polyarticular small joint arthritis and psoriasis which may represent PsA or coexistent psoriasis and RA.

2.2.1.1 The importance of classification criteria in PsA

Classification criteria are vital in this disease, particularly for research, as homogeneous populations are needed for clinical studies and therapeutic trials. The ideal characteristics for classification criteria are usually defined according to the planned use of the criteria. The use of the phrase “classification” rather than “diagnostic” implies a certain use and related characteristics required. If criteria are required for diagnosis the aim is to identify as many cases as possible, such as in screening for a particular disease. In this case a high sensitivity (given a population similar to that in which the criteria will be applied) is appropriate. If, however, cases are required for observational research studies or therapeutic trials, then it is necessary to derive criteria with a high specificity to ensure a homogeneous study population. Therefore it is necessary to manipulate the sensitivity and specificity according to the use to which the criteria are likely to be put.

2.2.1.2 Historic classification criteria

Virtually all published studies of PsA to date use the criteria suggested by Moll and Wright in their classic paper published in 1973 (Moll and Wright 1973). The criteria are simple to use and specify three conditions: the presence of psoriasis, an inflammatory arthritis and the usual absence of a positive serological test for RF. In addition to the Moll and Wright criteria several other criteria sets have been proposed including Gladman et al (Gladman et al. 1987), McGonagle (McGonagle et al. 1999), Bennett (Bennett 1979), Vasey & Espinoza (Vasey and Espinoza 1987), ESSG (Dougados et al. 1991) and Fournie et al (Fournie et al. 1999). These other criteria sets represent some modifications to the Moll and Wright criteria, and some entirely new criteria. Until recently, none of these were validated and none of these were founded on patient derived data.

The Moll and Wright criteria focused on sensitivity to detect PsA as diagnostic criteria rather than classification criteria. Although the combination of psoriasis and inflammatory arthritis has been shown subsequently to be relatively sensitive and specific in the CASPAR cohort, they did not include any of the characteristic clinical features of PsA, such as dactylitis and enthesitis, to aid diagnosis. There still remains a difficulty in differentiating seronegative RA with coincidental psoriasis from PsA.

It is likely that Moll and Wright were using some of the characteristic other features of the disease to make their diagnosis rather than rigidly interpreting the criteria. However since their publication, they have been used routinely in research work with a strict interpretation of the criteria. As a result of this, the people classified with PsA by subsequent authors differ significantly from those included by Moll and Wright, particularly with reference to the number of involved joints. The proportion of people with polyarthritis in the Moll and Wright series was 15%, whereas in later series up to 65% had polyarthritis (Gladman et al. 1987; Biondi Oriente et al. 1989; Helliwell et al. 1991; Torre Alonso et al. 1991; Jones et al. 1994).

Due to the interpretation of the third criteria ("usual absence of RF") later series also included patients who were RF positive, in up to 13% in some cases (Gladman et al. 1987). This interpretation of the criteria raised the spectre of cases of RA, even those sero-positive for RF but with coincidental psoriasis, being classified as PsA. It seems from these studies, and from opinions of the authors themselves, that Moll and Wright may have omitted the other defining features of PsA from the published criteria in an effort to simplify them, while still using these additional features in clinical practice.

All of the subsequent modifications to the Moll and Wright criteria and new criteria developed for PsA were designed to add further specificity to the original criteria, usually a feature which is enhanced at the cost of reduced sensitivity. They aimed to produce classification criteria to allow identification of homogeneous cohorts for research purposes. Recently, these criteria sets have been compared, firstly in a retrospective cross-sectional study in two centres and secondly in a prospective multi-centre design (Taylor et al. 2004; Taylor et al. 2006). The specificity of all the criteria sets was found to be high (over 0.9) but the sensitivity varied from 0.42 to 0.98. Further, not all cases could be classified due to missing data. This was particularly true for the Fournie classification which included HLA status among its criteria (Fournie et al. 1999).

2.2.1.3 The CASPAR criteria

The CASPAR study group was established to derive new data driven classification criteria for PsA. Data were collected in 32 centres worldwide by people with acknowledged expertise in this condition. On average each centre contributed 20 cases and 20 controls, the controls being cases of other inflammatory arthritis, with at least half of these having RA. Data was collected to a standard format on consecutive clinic attendees with PsA (total included 588) and the next case of inflammatory arthritis (total 536). Altogether over 100 clinical, radiological and laboratory variables were collected. The new criteria were derived by logistic regression and classification and regression tree (CART) analysis (as a cross check) and the performance of the new criteria compared to the other existing criteria.

The new CASPAR criteria (figure 1) include characteristic dermatological, clinical and radiological features and have both high sensitivity and very high specificity. It is also interesting to note that, with these criteria, it is possible to be RF positive and still have a diagnosis of PsA, providing other characteristic features are present. People with the features described by Moll and Wright are still classifiable as PsA. Dermatological features contribute more to the criteria than the other features: the simple combination of psoriasis and an inflammatory arthritis gave the very respectable figures of 0.96 and 0.97 for sensitivity and specificity respectively (Taylor et al. 2006).

The CASPAR criteria		
Inflammatory articular disease (joint, spine, or entheseal) With 3 or more points from the following:		
1. Evidence of psoriasis (one of a, b, c)	(a) Current psoriasis *	*Psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist*
	(b) Personal history of psoriasis	*A history of psoriasis that may be obtained from patient, family doctor, dermatologist, rheumatologist or other qualified health-care provider*
	(c) Family history of psoriasis	*A history of psoriasis in a first or second degree relative according to patient report*
2. Psoriatic nail dystrophy		*Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination*
3. A negative test for rheumatoid factor		*By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range*
4. Dactylitis (one of a, b)	(a) Current	*Swelling of an entire digit*
	(b) History	*A history of dactylitis recorded by a rheumatologist*
5. Radiological evidence of juxta-articular new bone formation		*Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain xrays of hand or foot*
Specificity 0.987, sensitivity 0.914 * Current psoriasis scores 2 whereas all other items score 1		

Figure 1 – The CASPAR criteria

The main limitation highlighted in the CASPAR paper concerns the applicability of the criteria to early disease as the mean duration of disease of the cases was 12.5 years. Recent research done by the Toronto group attempted to address this issue and evaluated the use of the CASPAR criteria in early disease within their clinic population (Chandran et al. 2007b). They performed a retrospective analysis of patients enrolling into the specialist PsA clinic and found a sensitivity of 99.1% in those patients with disease duration of less than 2.5 years, and a sensitivity of 100% for those with disease duration of less than 12 months (Chandran et al. 2007b). Although important, this study only included patients referred to a specialist tertiary referral clinic and did not evaluate any control population. It seems likely that only patients with secure clinical diagnoses are referred and enrolled into this clinic, possibly leading to an overestimate of the sensitivity of the criteria. As yet, the only evaluations of the CASPAR criteria in new rheumatology referrals at a secondary care level have been studies in Sweden and Italy. In the Swedish early PsA register, 134 of 183 patients fulfilled the CASPAR criteria when compared to consultant diagnosis (Lindqvist et al. 2008). A single centre study in Italy of 44 patients (D'Angelo et al. 2009), found that 34 of the patients met the criteria on their first visit (77.3%) and the majority fulfilled the criteria by having skin psoriasis and being RF negative. Only two patients satisfied the radiological criteria as their disease duration was less than one year. They concluded that the CASPAR criteria are less sensitive in early PsA, mainly because patients are unlikely to have radiological evidence of new bone formation (D'Angelo et al. 2009). There were no controls analysed in either of these studies, so only the sensitivity could be calculated. There is early data from an Italian multicentre PsA study which found a high sensitivity and specificity of 91% and 97.1% respectively (D'Angelo et al. 2008). However, as yet, there have been no properly powered studies addressing the sensitivity and specificity of the CASPAR criteria in early disease and therefore they cannot currently be recommended for use in studies of early PsA.

Perhaps the weakest aspect of the CASPAR criteria is the initial qualification criterion: inflammatory arthritis including spinal, peripheral and entheseal disease. As cases were physician diagnosed and without other stipulation in the selection process, it was impossible to be more precise with this description. In fact the majority of cases had a peripheral arthritis pattern, although 72 had a combined axial/peripheral pattern and 21 did not have any peripheral joint involvement at all. Of these 21, two had pure axial disease, eight dactylitis, 12 enthesitis, and 10 inflammatory spinal pain (in combinations) (Taylor et al. 2006).

A third concern with these criteria is located in the composition of the controls. About 70% of the controls had RA but 13% had AS so the statistical analyses were influenced against selecting spinal features as characteristic of PsA (Taylor et al. 2006). Although it has been suggested that the spondylitis of PsA is qualitatively and quantitatively different from that seen in classical AS, these differences did not appear as discriminating features. Of course, had the controls only consisted of RA cases, it is possible that the spinal features would have appeared in the final criteria set. The criteria derived, and the figures for sensitivity and specificity (and those for post hoc calculations like the likelihood ratios) are therefore very dependent on the control population (non- or alternative disease) used to derive them.

2.2.1.4 Investigations used in diagnosis of PsA

2.2.2 Subtypes of PsA

PsA is a heterogenous disease and there have been multiple attempts to subgroup patients according to their clinical presentation. Wright originally proposed three subgroups for PsA (Wright 1959). These were "DIP joint predominant disease", "severely deforming arthritis" (which included patients with axial disease), and "rheumatoid like disease". Later, Moll and Wright described the five classic sub-groups (monoarthritis, oligoarthritis, DIP-predominant disease, RA-like polyarticular disease and arthritis mutilans) (Moll and Wright 1973). Since then, there have been problems highlighted with these subgroups and minor modifications have been made to the Moll and Wright subgroups by a number of authors (Gladman et al. 1987; Biondi Oriente et al. 1989; Helliwell et al. 1991; Torre Alonso et al. 1991). Rather more drastic modifications have been proposed by Helliwell et al, (with Wright as a senior co-author) and Veale et al (Helliwell et al. 1991; Veale et al. 1994).

Gladman expanded the five subgroups to seven: distal disease (DIP joints only affected), oligoarthritis (less than four joints), polyarthritis, spondylitis only, distal plus spondylitis, oligoarthritis plus spondylitis, polyarthritis plus spondylitis (Gladman et al. 1987). Arthritis mutilans was not seen sufficiently frequently to require its own subgroup and was believed to be an indicator of severity, rather than a distinct group. Torre Alonso removed the category of DIP joint arthritis as it can occur in any subgroup, but retained the other four Moll and Wright categories (Torre Alonso et al. 1991).

Later, Wright used scintigraphy to identify the distribution of both clinically apparent disease and subclinical disease and then created an alternative three subgroup classification: peripheral polyarthritis, spondarthritis, and synovitis/acne/pustulosis/hyperostosis/osteomyelitis (SAPHO) (Helliwell et al.

1991). However, Veale et al felt that the peripheral arthritis group was too broad, combining patients with a symmetrical polyarthritis and an asymmetrical oligoarthritis who may differ significantly. They concluded with the following three group classification: asymmetrical oligoarthritis, symmetrical polyarthritis and predominant spondylitis (Veale et al. 1994).

2.2.2.1 Dividing axial and peripheral disease

The main difficulty in dividing axial and peripheral disease is in accurately diagnosing and defining the axial subgroup. Axial involvement in PsA is particularly hard to study as there is very little research into this subgroup. The majority of evidence is "borrowed" from AS, but this may not be clinically valid. In particular, the definitions used for AS – such as the modified New York criteria – may not be applicable to PsA as spinal changes may develop in the absence of SI disease (Khan et al. 2003; Taylor et al. 2004). Therefore, there is no clear definition of axial involvement in PsA. The diagnosis of proven axial involvement still relies on conventional radiography to detect typical changes in the SI joints and spine. This can take a variable length of time to become apparent and at least partially accounts for the increase in prevalence with longer disease duration.

Like many rheumatological conditions, research in AS is increasingly focusing on the detection of early disease and lessons from this may help our ability to diagnose axial PsA. MRI has been proposed as an ideal tool to demonstrate inflammation in the spine and SI joints, but has its limitations. Research has shown that MRI proven sacroiliitis is not always predictive of future AS. A study by Bennett et al, followed a cohort of patients with a new presentation of early inflammatory back pain and confirmed inflammation in the form of bone oedema confirmed on MRI scan. Eight years after their initial presentation, only 33% (n=13) had progressed to meet a radiographic diagnosis of AS. The key predictor of progression to AS, as diagnosed by the modified New York criteria, was a combination of HLA-B27 positivity and severe sacroiliitis on MRI (Bennett et al. 2008). This study highlights the need for caution when using MRI as a diagnostic tool, particularly if the level of inflammation is low. Finally, axial involvement may be apparent on conventional radiography or MRI when clinically absent (Williamson et al. 2004b). It remains unclear why such changes occur in the absence of symptoms and whether this represents clinically significant disease that should be treated.

Data from genetics studies can also help us to identify axial disease in PsA. Although PsA is classified as one of the spondyloarthropathies, the frequency of HLA antigens varies within the different subgroups (see Table 1). A consistent association between HLA-B27 and spinal involvement has been demonstrated, especially with pure axial disease (Gladman et al. 1986; McHugh et al. 1987).

HLA Type	Spondylitis	Symmetrical polyarthritis resembling RA	DIP predominant disease	Oligoarthritis
B27 (%)	62	15	41	9
B38 (%)	0	12	0	5
CW6 (%)	50	15	18	23
DR4 (%)	25 - 40	61	53	18

Table 1 – Proportion of patients with HLA associations in subgroups of PsA

2.2.2.2 Subgrouping peripheral disease

To be useful from a clinical and prognostic point of view, subgroup classification ought to be stable over time. Particularly when considering patterns of peripheral joint involvement, this does not seem to be the case. Jones et al retrospectively studied a cohort of patients diagnosed with PsA and recorded their sub-group longitudinally. They found frequent changes in sub-group, particularly progression from an oligoarticular pattern at onset to a polyarticular pattern at the final assessment (Jones et al. 1994) and this was further corroborated by Marsal et al (Marsal et al. 1999). Kane's key paper investigating the features of early PsA also found significant movement between sub-groups but in this study, they found polyarthritis common at presentation but not at follow-up. This seemed to be related to the proportion of patients treated with disease modifying therapy (Kane et al. 2003a). It seems that the change between groups is probably particularly marked at the beginning of a disease course as the disease may still be evolving and treatment is changed more frequently.

Subgroup definition may also be a function of the way joint involvement is assessed. Clinical examination is a relatively insensitive way of identifying articular involvement. The use of imaging, in particular colour Doppler US and MRI, suggest that patterns of articular involvement are quantitative rather than qualitative (Backhaus et al. 2002). US in patients with oligoarthritis has shown that many patients would actually be re-classified as polyarthritis once subclinical disease is identified on imaging (Wakefield et al. 2004). In this way, different methods of evaluation will produce different patterns of joint and entheseal involvement.

One of the main reasons to form subgroups is that they might behave differently over time either in terms of natural history or response to treatment. With respect to the first of these points, data from the Toronto group originally found that the number of inflamed joints at presentation was an important predictor variable for long term damage (Gladman et al. 1995). Given the recent availability of highly effective therapies for PsA, but the potential limitation due to the high cost of these drugs, clinicians must target these therapies accurately. Those with polyarticular disease should be targeted for early and intensive therapy to prevent a poor long term outcome. Further work is required to test the efficacy of this practice given that the polyarticular sub-group incorporates a wide range of severity. Since those patients destined to develop arthritis mutilans will almost certainly be in this group, it will be of interest to see if an aggressive treatment strategy will eliminate this devastating condition.

In this respect, therefore, it is of importance to distinguish between oligo- and polyarthritis at onset, even though people change subgroup with time and treatment. With respect to treatment it may be possible to select subgroups by their response to different drugs. It is clear that sulphasalazine and methotrexate work differently for peripheral manifestations compared to axial manifestations in spondyloarthropathies (Clegg et al. 1996), so it is reasonable to at least examine this possibility by separately analysing people with axial disease and peripheral disease. However, the recently introduced anti-TNF drugs seem to be beneficial for all aspects of the disease, including SAPHO, suggesting that, at this level, there is no worth in distinguishing between sub-groups (Mease et al. 2000; Antoni et al. 2005a).

Genetics studies have also helped to identify sub-groups of peripheral joint involvement with a recent interest in class II HLA associations and the more severe forms of polyarthritis. Gladman originally demonstrated an association between DR4 and symmetrical polyarthritis resembling RA, and more recently the Bath group have shown that this is probably a severity marker associated with the shared epitope of DRB1, as in RA (Korendowych et al. 2003). In further studies, it has been confirmed that the frequency of shared epitope is not increased in PsA compared to controls (Ho et al. 2007). Interestingly, the presence of anti-CCP antibodies in PsA is associated with the presence of the shared epitope, disease severity and activity scores (Korendowych et al. 2005). The HLA data therefore support the concept of different types of peripheral disease with the shared epitope acting as a marker for severe, polyarticular disease.

2.2.2.3 Are subgroups clinically relevent?

There is a strong clinical argument for abandoning the concept of subgroups all together in view of the difficulties in defining the groups and the high number of patients who alter sub-group of peripheral disease (Taylor et al. 2005) This would also be consistent with the ‘unifying’ hypothesis that the pathological basis of the disease is enthesitis (McGonagle et al. 1999). However, treatment and HLA data would support the distinction between at least two subgroups – axial and peripheral. If the concept of subgroups is abandoned, as suggested by Taylor et al, classification criteria become simplified but therapeutic trials remain problematic because of the possibility of different treatment responses seen in, for example, axial and peripheral groups.

2.3 Outcome measurement in PsA

2.3.1 Clinical Outcome Measures

Measuring outcomes in research is a key part of any study design. Clinical outcome measures provide an assessment of disease activity, in a particular area of disease, using only simple clinical interventions. Clinical outcome measures are required for both research and clinical use to measure the impact of therapies and the response of patients; both at a group and individual level.

Research in PsA has always lagged behind that in RA and it suffers significant setbacks due to a lack of validated clinical outcome measures. PsA is a multi-faceted disease with involvement in many areas including peripheral joints, skin and nail disease, entheseal involvement, dactylitis and axial disease. There are many different outcome measures available for each of these separate aspects of the disease but most are borrowed from related diseases and only some of these have been validated in PsA. At present, there are no composite outcome measures for PsA that take all of these disease aspects into account.

2.3.1.1 Peripheral Joint Disease

The simplest assessments of peripheral joint activity are joint counts. Joint counts used in PsA studies have included tender joint counts, swollen joint counts, active joint counts and damaged joint counts. When assessing peripheral joints, there are 78 recognised joints for assessment, however reduced joint counts are usually used. It is widely accepted that 68 joint counts are acceptable, as it is difficult clinically to distinguish the DIP joints of the toes. As it is not possible to clinically evaluate the hip for swelling accurately, the hip is excluded from any swollen joint counts, creating the 66/68 joint count.

Peripheral joint disease activity has been most thoroughly researched in RA as patients with RA commonly only have disease in this domain. In addition to simple joint counts, multiple peripheral joint disease activity measures have been proposed. Most of these include results of a joint count, laboratory measures of disease activity and a patient's perspective of disease activity. The two most widely used measures are the American College of Rheumatology (ACR) response criteria and the DAS and its modifications. Some of these developed instruments are response criteria, such as ACR response criteria, where improvement of a certain proportion from baseline is calculated. Some are measures of state, such as the DAS and DAS28, where a cross-sectional disease activity measure is obtained (van der Heijde et al. 1990; Prevoo et al. 1995). Subsequently, response criteria called the European League Against Rheumatism (EULAR) response criteria were developed using the DAS and DAS28 scores (van Gestel et al. 1996; van Gestel et al. 1998).

The ACR response criteria require measurement of the seven core domains in RA which are tender joint count (TJC), swollen joint count (SJC), physician global assessment visual analogue scale (VAS), patient global assessment VAS, patient pain VAS, physical function measured by health assessment questionnaire disability index (HAQ-DI) and laboratory acute phase response. The ACR response criteria include the ACR20, 50 and 70. These require a 20%, 50% or 70% improvement in both of the joint counts as well as the same percentage improvement in three of the other five variables (Felson et al. 1995).

The DAS is calculated using the Ritchie articular index (RAI) based on 53 joints, an assessment of 44 joints for swelling, an ESR value and a patient reported VAS (0-100mm) for general health (VAS GH); as follows (van der Heijde et al. 1990):

$$DAS=(0.54 \times \sqrt{RAI}) + (0.065 \times SJC) + (0.33 \times \ln[ESR]) + (0.007 \times VAS\ GH)$$

DAS28 scores are based on the reduced 28 joint count for both tender and swollen joints as follows (Prevoo et al. 1995):

$$DAS28= (0.56 \times \sqrt{TJC}) + (0.28 \times \sqrt{SJC}) + (0.7 \times \ln[ESR]) + (0.014 \times VAS\ GH)$$

The EULAR response criteria define good response, moderate response and non-response. A good response is defined as achieving a DAS $\leq$2.4 or DAS28 $\leq$3.2 together with an improvement in DAS of >1.2. Moderate response is defined as a reduction of >0.6 with an end DAS of 2.4-3.7 or DAS28 of 3.2-5.1. Non-response is defined as a reduction of $\leq$0.6 or a reduction of $\leq$1.2 with an end DAS of >3.7 or DAS28 of >5.1 (van Gestel et al. 1996; van Gestel et al. 1998).

The ACR response criteria, DAS/DAS28 and EULAR responses have undergone significant reliability testing in RA and are now reported widely in clinical trials. Following the development of these composite measures, they were then “borrowed” for use in therapeutic trials in PsA despite the fact that they were not developed for such use, as there was little research into specific measures developed for PsA.

The only specific outcome measure that was designed for use in PsA was the PsA response criteria (PsARC) which is a response measure. The measures included in the PsARC are the TJC, SJC, patient self assessment of disease activity and physician assessment of disease activity (using 1-5 Likert scales). Treatment response according to the PsARC requires improvement in at least two of the four measures, one of which must be a joint count, and no worsening in the other domains. Improvement/worsening are defined as a decrease/increase of 30% for joint counts and a decrease/increase of one category for global assessments of disease activity (Clegg et al. 1996). However the major drawback of the PsARC criteria is that they were not developed based on patients' data, but were simply stated by a single researcher.

The majority of recent efficacy studies of new agents have used ACR or DAS outcome measures despite a lack of validation. Therefore, subsequent to these trials, retrospective analysis was undertaken using data derived from two phase II randomised controlled clinical trials of TNF inhibitors (Fransen et al. 2006). The aim of this was to analyse the responsiveness of such composite measures in PsA trials and to compare this to the responsiveness of individual variables. The combined data included measurements from 164 patients treated with active drug or placebo. Analysis was reported using the standardised response mean (SRM=mean change/standard deviation (SD) change), effect size (mean change/SD baseline) and t-tests for difference in change between active drug and placebo. In both of the trials, ACR20, EULAR response criteria and PsARC all showed a significant difference between active drug and placebo ($p<0.001$). Importantly, all of the disease activity composite measures demonstrated superior responsiveness to single variables in terms of SRM and effect size (Fransen et al. 2006). This highlights the importance of composite measures for use in clinical trials.

When comparing the different composite measures, it was noted that the EULAR criteria performed slightly better than the ACR criteria, which in turn performed better than the PsARC (Fransen et al. 2006). Most RCTs of TNF blockers have used the ACR20 as a primary outcome measure because of its reasonable responsiveness in early studies. It also shows a lower placebo response rate than the PsARC making it a more stringent measure (Mease et al. 2005a). The good performance of the EULAR criteria in the retrospective analysis was partially due to the relatively high numbers of patients treated with active drug who achieved the low disease activity criterion (Fransen et al. 2006). It is likely that in studies of standard DMARDs, the EULAR and ACR criteria would appear more comparable.

Surprisingly the EULAR response based on DAS28 and the mean change in DAS28 scores performed slightly better than the comparable responses based on full DAS scores. The authors identified that the lower performance of the traditional DAS score is due to the lower discriminitive ability of the RAI. They speculate that this may be related to the relative inaccuracy of grading tenderness scores and the scoring of multiple joints as one unit in the RAI (Fransen et al. 2006). There has been a long-held concern that the DAS28 should not be used in PsA because of the relatively high proportion of patients who have involvement in other joints, such as the feet and DIP joints of the hands, which are not included in this measure. Therefore, DAS28 potentially under represents current disease activity as these joints are not included. Although the DAS28 outcome measures were shown to be responsive in clinical trials there are some important caveats given the problems introduced by the reduced joint count. Firstly, although the measures are responsive at the group level, there is no validation of these in individual patients and the potential underestimation of disease activity should preclude this. Secondly, although the change in DAS28 or EULAR responses may be used, the numerical scores of the DAS are not validated in PsA, therefore cut points such as low disease activity or remission may be inappropriate. The risk of the underestimation of disease is highlighted by the OMERACT PsA group who calculated that 25% of the patients included in these clinical trials of TNF blockers would not have been eligible if the DAS28 was used as an inclusion criteria (Gladman et al. 2007d) despite the fact that 95% of these patients had more than five active joints at the time of recruitment (Fransen et al. 2006).

The other concern is the accuracy of determining disease activity or response in patients with other subtypes of PsA. Although the inclusion criteria for the major TNF blocking studies all required a minimum of three tender and three swollen joints, the mean joint count was far higher and the patients included almost exclusively had a polyarticular joint pattern. These composite measures ‘borrowed’ from RA, have not been accurately evaluated in oligoarticular disease.

One further composite measure of arthritis has subsequently been investigated for use in PsA. The disease activity in reactive arthritis (DAREA) score was developed using patient data from 45 patients with reactive arthritis and is calculated as a simple sum of the TJC, SJC, patient’s pain and global assessment VAS and a C-reactive protein (CRP) (Eberl et al. 2000). Nell-Duxneuner and colleagues collected data on key PsA outcomes in 105 patients and then performed a principle component analysis (PCA) to identify which outcome measures best reflected disease activity. They identified three principal components which reached significance: patient’s pain and global disease activity assessment, tender and swollen joint counts and CRP. A fourth component contained skin assessment but this did not reach significance. After a review of existing measures, the DAREA was thought to be the most relevant composite outcome that encompassed all of these principal components. This group have now renamed the DAREA as the disease activity in psoriatic arthritis (DAPSA) score (Nell-Duxneuner et al. 2010).

The advantage of this analysis in comparison to the validation of DAS and ACR outcomes is that the analysis was based on PCA of a cross-section of PsA patients, rather than being a retrospective analysis of RCTs. The same group have also analysed its sensitivity to change using data from RCTs, providing some support for its use (Schoels et al. 2010). However some similar limitations also apply with this analysis, as for that with the ACR and EULAR outcome measures developed for RA. The analyses are based principally on certain subsets of PsA and may not be generalisable to the whole population. In particular, skin activity was identified as the fourth domain in the PCA but was dropped as it did not quite meet significance. This is likely to be related to the fact that the average psoriasis area and severity index (PASI) in PsA patients identified from rheumatology clinics is low (Helliwell 2009) and it therefore had a lower weighting. However for PsA patients seen in dermatology or combined clinics, psoriasis may have a much more significant impact on their overall disease activity. Although the DAPSA is a composite measure, it is only truly a composite joint disease activity measure and does not reflect changes in other aspects of the disease.

2.3.1.2 Skin and Nail Disease

Many measures have been used to assess disease activity in skin psoriasis. The earliest measure to assess extent of skin involvement was the body surface area (BSA) based on the ‘rule of nines’ used to assess the extent of burns (Wallace 1951). This allows estimation of the extent of skin surface involved assuming that the head represents approximately 10% of the surface area, upper limbs 20%, trunk 30% and lower limbs 40% (Wallace 1951). This estimation of skin surface has been validated in dermatology using volume of ointment required to cover an area as an estimation of area. The areas were similar to those quoted above, with just the head representing a slightly lower percentage of BSA due to the use of ointment only on the face, neck and ears and not on the scalp (Long and Finlay 1991).

In practical assessment of the BSA, an estimation of area is commonly performed using a handprint to represent 1% of BSA. This handprint or palm includes the dorsal aspect of the palm, thumb and all four fingers and has been shown to equate to between 0.51 and 0.91% of the BSA (Long et al. 1992; Rossiter et al. 1996). In the majority of patients, the use of a handprint or palm to assess BSA should therefore result in an overestimation of the extent of psoriasis. This has been confirmed in studies where trained observers overestimate BSA compared to image analysis of whole body photographs and schematic outlines (Ramsay and Lawrence 1991; Tiling-Grosse and Rees 1993). This overestimation is particularly marked when assessing mild psoriasis (Ramsay and Lawrence 1991). Assessing skin psoriasis using BSA has a reasonable intra-observer reliability, but the inter-observer reliability has been reported to show variability (Ramsay and Lawrence 1991; Tiling-Grosse and Rees 1993). In multi-centre studies, this has raised a possible source of bias. However, this can easily be minimised by ensuring that the same assessor measures BSA at each study site within a trial.

The PASI was developed in the 1970s within a clinical trial and is by far the most commonly used outcome measure for psoriasis in clinical trials and studies.

This outcome measure combines assessment of BSA with assessment of disease severity. Disease severity is based on assessments of the plaque’s erythema, induration and desquamation. The head, upper limbs, trunk and legs are assessed separately and then combined into the final score using weightings based on the BSA (head=0.1, upper limbs=0.2, trunk=0.3, lower limbs=0.4). The degree of erythema, induration and desquamation seen within the lesions in each area are graded on a semi-quantitative scale from 0 (no involvement) to 4 (very marked change) and these scores are summed to measure the disease severity. The area of involvement of psoriasis in each body area is graded from 0-6 based on percentage coverage of skin disease (0%=0, <10%=1, 10-29%=2, 30-49%=3, 50-69%=4, 70-89%=5, 90-100%=6) and these body area scores are multiplied by the disease severity score and the weighting for each body area. This gives a total score of between 0-72 (Fredriksson and Pettersson 1978).

The target lesion score uses the same semi-quantitative scoring system for erythema, induration and desquamation but just applies these to a ‘typical’ plaque of psoriasis and does not account for BSA. Therefore the score for this target lesion can vary between 0-12 (Feldman and Krueger 2005). This is ideal to measure change in psoriasis at one site following localised therapy or can be combined with other outcome measures such as a physicians global assessment and quality of life measure to get a measure of the global impact of disease.

The PASI relies heavily on the BSA for components of the score and is therefore subject to the same limitations introduced by the BSA, particularly overestimation with small area plaque psoriasis. The use of subjective scores for erythema, induration and desquamation has been validated comparing single observer subjective scores to objective outcome measures (nitric oxide production, reflectance erythema, US thickness and US entry echo) showing significant correlations individually. When combined as a total score for severity as used in the PASI, this has a higher power to detect change which was comparable to the objective measurements (Ormerod et al. 1997). However, as there was only one observer, the potential for inter-observer variation was not assessed and the subjective scores were found to overestimate the treatment effect compared with the objective measures (Ormerod et al. 1997).

In addition to considering the reliability of assessing BSA and psoriasis severity scores, the validity and sensitivity to change of the PASI also have some recognised shortcomings which must be considered. Criterion validity assesses the ability of the PASI to match up to a “gold standard”. The comparison between subjective and objective measures of the composites of the PASI goes some way to address this, but the lack of a clear gold standard hampers further assessment of this.

To provide face and content validity, the PASI must assess the main aspects of psoriasis and discriminate severity of disease. Clearly the PASI performs better than the BSA in this aspect, as it also includes a subjective score for disease severity as well as area. However it does not include assessment of the most important features of severity as nominated by both dermatologists (systemic symptoms and pustular change) and patients (embarrassment and quality of life) (Baughman and Sobel 1970).

The other major problem is the responsiveness of the scale. There is evidence of general poor responsiveness and of problems at either end of the scale. Anecdotal evidence and retrospective analysis of study data has suggested that the PASI underestimates the degree of clinical improvement assessed by physicians (Carlin et al. 2004) and patients (Jacobson and Kimball 2004). Although the theoretical range of PASI score is 0-72, in practice it is rare to find a PASI score over 40, meaning that nearly half of the score is unused. At the other end of the scale, the PASI has poor sensitivity to change and responsiveness when skin psoriasis is mild. A patient's mild psoriasis may improve but still score the lowest score of 1 for erythema and induration because it is still present, and when there is less than 10% involvement in any body area, the area cannot reduce further from a score of 1 if there is any psoriasis still present.

Several modifications to the PASI have been proposed to try to improve its performance. These attempts have focused on the integration of BSA into the PASI. The Psoriasis Log-based Area and Severity Index (PLASI) still scores area in six categories, but the boundaries for each category are based on a log scale (0%, 1-2%, 3-5%, 6-10%, 11-21%, 22-46%, 47-100%). To allow greater weighting of BSA, the area score is the upper limit of that category (Jacobson and Kimball 2004). These alternative categories allow greater separation of patients with mild psoriasis. This increases the weighting of the BSA within the PLASI as compared to the PASI and improves sensitivity to change particularly among patients with mild disease. However, conversely it reduces the sensitivity to change at the other end of the scale as areas between 47 and 100% will score the same value (Jacobson and Kimball 2004). This is likely to be a less significant problem as only a minority of psoriasis patients have such high BSA values.

The Psoriasis Exact Area and Severity Index (PEASI) was developed by the same team, but uses actual BSA instead of an area score. This is then multiplied by the severity score as in the PASI (Jacobson and Kimball 2004). Again this increases the weighting of the BSA within the total score and improves sensitivity across the scale. In addition, this use of true percentages rather than groups, avoids the problem that a 1% change in BSA at the borders of the groups can significantly alter the score (10% BSA weighted two times higher than 9% in original PASI) (Jacobson and Kimball 2004)

Both the PLASI and the PEASI were analysed using trial data of 40 psoriasis patients during their development. This analysis confirmed an increased percentage improvement in patients using the PLASI and PEASI when compared to the PASI. Both of the new scales also show a greater correlation with the patients' self-assessment of percentage improvement.

The self-administered PASI (SAPASI) has also been developed for patients to assess their disease severity. This uses an anatomical sketch of a person which the patient is asked to shade in to mark their psoriasis. The investigator then scores area on a 0-6 scale as in the PASI. The patient is also asked to score the colour, thickness and scaling of one typical lesion using three VAS. The severity score is calculated by adding the three VAS scores, divided that by the maximum VAS score and multiplying by four. The SAPASI is calculated using the product of the weighted area scores and the severity score (Feldman et al. 1996). Investigations using the SAPASI have shown that it has good intra and inter-rater reliability and correlates well with the PASI (Feldman et al. 1996). The SAPASI was then administered in a multi-centre drug trial involving 182 subjects and correlated with a physician-equivalent PASI scoring erythema, induration, scale and BSA. This showed modest but significant correlations between the two scores and their component parts (Fleischer et al. 1999). The SAPASI was also demonstrated to identify changes in disease severity within a clinical trial (Fleischer et al. 1999).

Comparison of the PASI derived scoring systems has shown good correlation with each other (Henseler and Schmitt-Rau 2008). The SAPASI has very good correlation with PASI and other PASI derived scoring methods, suggesting that it would be valid for use in studies where an investigator is not available (Henseler and Schmitt-Rau 2008). Overall, the analysis concluded that the PLASI is the optimal tool to use in trials. This is due to the fact that it has high sensitivity to change and differentiation, particularly at a lower BSA and it was shown to correlate best with both patient and dermatologist's clinical opinion on improvement (Henseler and Schmitt-Rau 2008).

Due to an ongoing dissatisfaction with the PASI as an outcome measure, other scoring systems have also been developed that are designed differently. However these also use measurements of similar parameters including BSA, erythema, induration and desquamation. The Lattice System Physician's Global Assessment (LS-PGA) requires an assessment of BSA to decide on a category of area involved (0%, 1-3%, 4-9%, 10-20%, 21-29%, 30-50%, 51-100%) and then a factoring in of thickness, erythema and scale from an average plaque. This results in a global assessment from “clear” to “very severe” psoriasis (Langley and Ellis 2004). The LS-PGA has shown good correlation with PASI and BSA which is not surprising as they are based on similar observations. The inter and intra-rater reliability has been shown to be reasonable. In the original study, the LS-PGA had higher intra and inter-rater reliability than PASI and BSA (Langley and Ellis 2004), but in a subsequent study, PASI showed higher reliability than the LS-PGA (Berth-Jones et al. 2006). This scale is clearly much simpler to perform than the PASI, but does still categorise BSA with the resultant limitations. Although the categories are designed to be more responsive in milder disease, there are only three categories for BSA<10% compared to four in the PLASI.

One of the latest instruments developed for use in psoriasis is the Copenhagen Psoriasis Severity Index (CoPSI) developed by the Copenhagen Psoriasis Working Group. This instrument does not involve estimation of BSA, but scores erythema, thickness and scaling each on a scale of 0-3 at 10 sites of the body creating a possible score of 0-90 (Berth-Jones et al. 2008). Testing using 16 patients and 14 raters found a substantial intra and inter-rater reliability (>80%) for the CoPSI and the PASI, as well as good correlation between the two (Berth-Jones et al. 2008). The exclusion of BSA removes the inherent inaccuracies with this evaluation. However the number of sites involved provides some estimation of the extent of disease. The arithmetic required to calculate this score is significantly easier than the PASI and therefore should be less prone to error. The investigators also noted that the range of CoPSI scores extended throughout the theoretical range unlike PASI in which the upper half of the range was largely redundant. The CoPSI also should provide better differentiation at the milder end of psoriasis cases (Berth-Jones et al. 2008).

The National Psoriasis Foundation (NPF) developed an entirely new responder index called the NPF Psoriasis Score (NPF-PS). This combines induration at two target sites, ratio of current BSA to baseline, physician and patient global assessment and patient assessment of itch all scored 0-5. These components are then summed to create a scale from 0-30 (Krueger 1999). This has an advantage as it places more weight on induration which is thought to be more relevant in psoriasis and is less variable depending on temperature and emollient use. It also includes a patient global assessment and assessment of itch which will capture some elements of the impact of psoriasis on quality of life. An initial study of 17 patients compared the NPF-PS to the PASI. The NPF-PS identified a significant change in psoriasis after treatment indicating responsiveness. It also identified this significant improvement at an earlier time point than the PASI, perhaps suggesting that it is more discriminative (Carlin et al. 2003).

Finally, it must be noted that all of the measures discussed above to evaluate psoriasis were designed for use and validated in plaque psoriasis and have not been assessed in other forms of psoriasis.

Nail involvement is a common feature of both skin psoriasis and PsA. It has been estimated to occur in up to 50% of patients with uncomplicated skin psoriasis (Farber and Nall 1992) and is even more prevalent amongst patients with PsA. The frequency of nail involvement in patients with PsA has been reported as between 63% and 83% (Cohen et al. 1999; Elkayam et al. 2000; Salomon et al. 2003; Williamson et al. 2004a).

Psoriatic nail disease can be broadly divided into psoriasis affecting the nail matrix and the nail bed. Involvement in the nail matrix most commonly results in changes to the nail plate which can be seen as the nail grows out. The different areas of the nail matrix are responsible for production of different layers of the nail, with the proximal or dorsal portion of the matrix producing the most superficial layer of the nail plate, and the distal or ventral portion producing the deepest layer of the nail plate adjacent to the nail bed. The commonest change in nail psoriasis is pitting (Tham et al. 1988; Zaias 1990), depressions in the surface of the nail plate resulting from sloughing of abnormal cells laid down when there is involvement in the proximal matrix. If the involvement is in the distal matrix, the abnormality is seen deeper in the nail causing leukonychia. More extensive involvement of the matrix can result in crumbling of the nail plate. Psoriasis affecting the matrix can be viewed directly in the lunula which is a distal extension of the nail matrix. Involvement here results in red spots in the lunula.

Involvement in the nail bed results in distinct patterns of nail disease. Onycholysis and subungual hyperkeratosis are caused by psoriasis affecting the hyponychium, the transitional area between nail bed and normal epidermis at the tip of the digit. Involvement more proximal in the nail bed can be visualised through the nail plate and can result in ‘oil drop change’, salmon spots or splinter haemorrhages.

Clearly assessment of nail disease in PsA must take all of these features into account. Many studies of therapies for nail disease have used subjective measures of nail involvement graded by the investigator as mild/moderate/severe or on a VAS. Prior to the development of any systematic scoring system, therapeutic studies used different grading measures of different features either for the fingernails as a whole or for one target nail.

One of the earliest published nail assessments was developed by the Bath group for use in their 1994 assessment of the outcome of PsA. Jones et al used a predefined scoring system where each fingernail was scored for the presence of pitting, onycholysis, hyperkeratosis and dystrophy. Each of these features scored one point with a maximum score of 40 for the 10 fingernails (Jones et al. 1994). This scoring system was then used and adapted by the Oxford group who used the same scoring system for finger and toenails with a maximum score of 80. This scoring system was labelled as the psoriasis nail severity score (PNSS) (Williamson et al. 2004a).

In 2003, the Nail Psoriasis Severity Index (NAPSI) was devised and published by dermatologists (Rich and Scher 2003). This scored nails by dividing each nail into four quadrants and scoring one point for each quadrant which has any of the features of nail bed psoriasis (onycholysis, oil drop, splinter haemorrhages, nail bed hyperkeratosis) and one point for each quadrant which has any features of nail matrix psoriasis (pitting, leukonychia, red spots in lunula, nail plate crumbling) (Rich and Scher 2003). This results in a score of 0-8 per nail, 0-80 for all fingernails or 0-160 if toenails are included. The advantage of this scoring system is that it does not require scoring for each feature separately which would be more time-consuming. However, it maintains differentiation between nail matrix and nail bed involvement so that sub-analysis could reveal whether treatments affected psoriasis equally in both areas of the nail. A small assessment of the NAPSI using pictures of eight nails shown to 37 dermatologists revealed reasonable reproducibility but no advanced statistical methods were used in the original paper (Rich and Scher 2003). A subsequent study provided evidence of moderate to good interobserver reliability between three dermatologists using the NAPSI scoring system with better reliability in scoring for nail bed features (Aktan et al. 2007). Following on from this, the NAPSI has been used as an outcome measure for both open-label and double-blind trials of biological agents (Reich et al. 2005; Korver et al. 2006; Rigopoulos et al. 2008).

Subsequent to this, the modified NAPSI (mNAPSI) was proposed by rheumatologists working in PsA. They began a study to validate the NAPSI score, but with the aim of modifying the scoring system as required to “enhance its performance characteristics” and create an ideal tool for clinical trials (Cassell et al. 2007). They collected digital photographs of all fingernails of 29 patients with PsA and these were scored by six physicians using the original NAPSI instrument. There was found to be a significant variability in scoring so two focus sessions were held with all of the rating physicians to discuss problems with the scoring instrument. The biggest obstacle found to scoring accurately was the use of quadrants of the nail, which were difficult to quantify precisely. It was also felt that to improve the sensitivity of the score, the individual features of nail matrix and nail bed disease should be considered separately. The only exemption to this was oil drop dyschromia which was considered with onycholysis as they represent the same pathology (Omura 1985). To avoid the use of quadrants, a more quantitative scale for different features of nail disease was introduced, scoring pitting, onycholysis and crumbling as 0-3 depending on the area of the nail involved. The remaining features (splinter haemorrhages, leukonychia, red spots in the lunula and nail bed hyperkeratosis) were scored as either present or absent in each nail. Therefore the possible range of scores is 0-14 per nail, or 0-140 for all fingernails (Cassell et al. 2007).

Regrading of the original photographs by five observers was then performed using the new mNAPSI. Comparison of these mNAPSI scores showed excellent inter-rater reliability and internal consistency as well as strong correlation with physician VAS for nail severity (Cassell et al. 2007). This was confirmed by an independent study of 20 patients with PsA who were assessed by ten rheumatologists and nine dermatologists showing an excellent agreement for the mNAPSI score regardless of speciality (Chandran et al. 2009).

2.3.1.3 Enthesitis

An enthesis is the site of attachment to bone of tendon, ligament or joint capsule (Ball 1971). Enthesitis can cause pain, tenderness and swelling at entheseal sites sometimes with resultant bony damage such as bone spurs at the calcaneum. Enthesitis is recognised as a manifestation of active inflammatory disease in all of the seronegative SpA including PsA, but the majority of outcome measures for enthesitis have been developed and validated in patients with AS.

The first enthesitis index was developed by Mander et al. A list of all entheses easily accessible to clinical examination was created and this was tested on six outpatients with AS on two occasions, once on NSAIDs and once off all treatment. Sites which scored zero in this pilot study were eliminated leaving 66 entheseal sites to be examined for tenderness and graded on a semi-quantitative score from 0 to 3 (Mander et al. 1987). A further study with 19 AS patients showed correlation of the Mander Enthesitis Index (MEI) with pain and stiffness VAS scales and a reduction in the score with non-steroidal anti-inflammatory drug (NSAID) treatment. There was some variability between different examiners performing the MEI, but intra-observer variability was not formally tested (Mander et al. 1987).

Further validation was attempted using the longitudinal outcome in the Outcome in Ankylosing Spondylitis International Study (OASIS) cohort designed to investigate the long term outcome of AS. The authors provided evidence of a correlation between the MEI and other disease activity measures in AS including the Bath ankylosing spondylitis disease activity index (BASDAI). They also tried to simplify the MEI and create a more feasible tool for use in both research and clinical practice. The first step was to remove the tenderness scoring from 0-3 and replace it with a dichotomous 0/1 score for tenderness. This is similar to the modifications made to the RAI in the measurement of peripheral joints. The modified Mander showed similar correlation with other disease activity measures. Then a process of data reduction was performed using the data from patients who had an MEI>0 to try and reduce the number of sites to be assessed. The most commonly involved enthesis was identified and noted, then all patients who reported tenderness at this site were excluded and the process was repeated. This step-wise reduction was performed until 80% of all patients with a positive MEI score were identified. Data was analysed from three timepoints and then all potential sites were combined. After exclusion of entheses difficult to localise or near to other sites, there were 13 sites left for assessment in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) (Heuft-Dorenbosch et al. 2003). Correlation between all of the enthesitis scoring scales and disease activity measures (BASDAI, physician VAS of disease activity and patient VAS of disease activity) were similar with no marked reduction in correlation seen with the shortened MASES (Heuft-Dorenbosch et al. 2003). Other new modifications of the MEI (Gorman et al. 2002) and distinct scoring systems (Braun et al. 2002) have been proposed as enthesitis indices but few have been validated.

In particular, establishing criterion validity for these clinical outcome measures has been difficult because of a lack of gold standard. Ideally a gold standard would have associated evidence of tissue abnormality from histopathological studies. However biopsy of tendons is neither safe nor easy, and there are limited research data available. Histopathological studies in patients with SpA (mostly AS) have shown inflammation in the subchondral bone with bone marrow oedema underlying entheses (Ball 1971; Laloux et al. 2001). A further study identified changes in the fibrous part of the enthesis with increased vascularity and cellular infiltrate (McGonagle et al. 2002a). MRI has been shown to identify bone marrow oedema at tendon insertions and abnormal signal around the enthesis (Marzo-Ortega et al. 2001). US scanning using GS and PD to identify increased vascularisation in and around the enthesis can identify abnormal findings in symptomatic and asymptomatic entheses (D'Agostino et al. 2003). Given that US identified PD signal, and MRI bone marrow oedema have been correlated with tissue evidence of inflammation in other rheumatic manifestations (Appel et al. 2006; Jimenez-Boj et al. 2007; McQueen et al. 2007), it seems likely that imaging is the best “gold standard” available at present.

More recently, the Spondyloarthritis Research Consortium of Canada (SPARCC) created a new outcome measure for enthesitis in AS (Maksymowych et al. 2009) using information from US and MRI studies to decide which entheseal sites should be included. They picked 16 sites which had been identified as commonly involved in imaging studies of SpA patients (D'Agostino et al. 2003; Lambert et al. 2004) and could be clinically identified. Inter-observer reliability was good following a brief specific training session in the scoring system and a substantial correlation was seen between enthesitis score and other disease activity measures. However the reduction in enthesitis score in a sub-group of patients treated in a randomised controlled trial of anti-TNF therapy was not significant after 12 weeks of therapy (Maksymowych et al. 2009). Reduced versions of the SPARCC enthesitis index using more commonly involved sites (SPARCC 8/16 score) and only sites which discriminated between treatment and placebo (SPARCC 6/16 score) showed larger effect sizes and SRMs (Maksymowych et al. 2009).

All of the entheseal outcome measures discussed previously were developed and validated principally for patients with AS. The sites included in the SPARCC score were chosen from studies using a full spectrum of SpA patients, but the validation was only in patients with AS (Maksymowych et al. 2009). The Leeds Enthesitis Index (LEI) is the only measure developed specifically for PsA. The methodology for this study was identical to that of the development of the MASES using dichotomous scoring for pain and then step-wise data reduction to identify and retain only those sites with most common involvement. This resulted in an index with six entheseal sites (bilateral lateral epicondyle, bilateral medial femoral condyle and bilateral Achilles tendon insertion) (Healy and Helliwell 2008). This index was then compared to other entheseal indices including the MEI, MASES and others, in an open-label longitudinal study. The LEI showed closest correlation with other disease activity measures, a large effect size and the smallest floor effect when compared with the MEI. Although the LEI was developed using data from just 28 patients, it is the first tool developed using patients with PsA rather than AS. It has a low floor effect, meaning that it can identify the majority of patients with enthesitis using just six sites, making it far more feasible as an outcome tool (Healy and Helliwell 2008). The reliability of the LEI, MASES, SPARCC and other enthesitis scoring systems was investigated in a reliability study using both AS and PsA patients. Nineteen patients with AS and PsA (n=9 and n=10 respectively) were examined by ten experienced rheumatologists. There was excellent agreement for all patients in all of the indices listed above. In patients with AS, the MASES and SPARCC indices performed better, but in patients with PsA, the LEI and SPARCC showed excellent agreement (Gladman et al. 2007a).

The use of clinical assessment tools for enthesitis has now become widespread in clinical trials despite some of the debate about which particular scoring system is optimal in each disease subtype. However, as alluded to above, there are some crucial problems with the criterion validity of these clinical techniques. Imaging studies have shown changes within tendons and around tendon sheaths at entheses but the correlation with clinically appreciable tenderness or swelling is less convincing (Ibrahim et al. 2009b). In most studies, US has identified more changes at entheses than clinical examination alone (D'Agostino et al. 2003), but the question of the clinical relevance of these subclinical changes has not been answered. In addition to the soft tissue changes visualised with imaging, MRI scanning has identified the involvement of bone with bone marrow oedema adjacent to the enthesis. No studies have addressed whether this deep bony involvement can be clinically identified and whether there is evidence of any correlation with clinical enthesitis counts in these circumstances.

The other limitation of clinical enthesitis counts is the specificity of the findings of tenderness in these areas. Obviously there is an issue regarding training of assessors to ensure inter-observer reliability and there is some difficulty in the anatomical location of some of these sites. However beyond that, there are doubts about the specificity related to enthesitis and whether other pathologies seen in arthritis could cause a false positive result. Many of the entheseal points are relatively near to joints and it is well recognised that inflammation within joints can cause pain in and around the joint. Also many of the entheseal points are located near to accepted fibromyalgia points (Wolfe et al. 1990), raising the possibility that misclassification of enthesitis could occur in patients without active inflammatory lesions. The recognised clinical enthesitis outcome measures try to minimise the possibilities of misclassification by advocating sites that are easily anatomically identified and are distinct from sites of tenderness related to joint inflammation or fibromyalgia. The key to the reliability of these tools in clinical practice is the training provided to assessors in localising the correct points.

2.3.1.4 Dactylitis

Dactylitis describes a uniform swelling of a digit with inflammation causing a "sausage digit" and is one of the key identifying features of PsA. Dactylitis is one of the features used to make a diagnosis of PsA using the recently developed CASPAR classification criteria for PsA (Taylor et al. 2006). Dactylitis can be further characterised as acute/tender dactylitis where the digit is tender to touch and often erythematous and warm to touch, or as chronic/sub-acute/non-tender dactylitis where the digit is swollen but non-tender. It has been hypothesised that the chronic form occurs following an episode of acute dactylitis in some patients but this has not been confirmed in studies. Acute or tender dactylitis has been shown to be a presenting feature of 33.5% of patients at their first visit to the clinic and to occur in 48% of patients at some point in their disease (Brockbank et al. 2005).

Our understanding of dactylitis, its pathogenesis and how to define it is limited. Studies using imaging have confirmed that physical examination can identify pathology in tender dactylitis. Olivieri et al scanned 12 tender dactylitic fingers and their matching contralateral normal digits with both MRI and US. Both scans identified distension of the flexor tendon sheaths and thickening of the flexor tendons, with no involvement in the extensor tendons. Physical examination by one physician identified flexor tendonitis in all of the involved digits with clinically normal extensor tendons (Olivieri et al. 1996). Thus it seems that clinical instruments for assessing dactylitis do have some criterion validity. However this study only assessed 12 obviously swollen digits and the contralateral normal digits. Therefore it seems likely that in normal clinical practice, there will be some variation between observers resulting in lower agreement particularly in “grey” cases, where digits may be slightly swollen or where matching digits on both sides are involved when it is harder to classify as dactylitis. This idea was later confirmed by a reliability study performed in Canada. This showed a moderate agreement (kappa 0.57, 95%CI=0.34, 0.82) between 10 experienced observers for number of digits with dactylitis (Gladman et al. 2004).

Clinical measures of dactylitis have been used as secondary outcome measures in clinical trials but the majority have used non-validated measures. The simplest measure used is a simple count of dactylitic digits, although some have counted only acute/tender dactylitis (Salvarani et al. 2003) and some have included both tender and non-tender digits (Clegg et al. 1996). Other large RCTs of new therapies have attempted to grade dactylitis by physician-rated severity in addition to counting affected digits (Kaltwasser et al. 2004; Antoni et al. 2005b) but none of these measures were validated prior to their inclusion in studies.

The Leeds Dactylitis Instrument (LDI) was developed in response to this need for a clinical, objective, validated outcome measure for dactylitis. This also provided the first numerical definition of dactylitis as an increase in circumference of the digit of more than 10% compared to the contralateral non-affected digit (Helliwell et al. 2005). This was based on the evaluation of the median difference in digital circumference between dactylitic digits and control digits.

The aim of the LDI is to provide a quantification of both the size of the swollen digit and the tenderness so that the score can differentiate between tender and non-tender dactylitis. The LDI tool is a circumferometer which is used to measure the circumference of the affected digit as near to the web space as possible.

This is compared to the contralateral unaffected digit as a ratio. If the contralateral digit is also dactylitic, then normative values based on population averages are provided. The tenderness scoring can be based on the RAI with tenderness scored from 0-3 (LDI scoring) or can be simplified to a dichotomous score of 0 for non-tender and 1 for tender (LDI basic) (Helliwell et al. 2005).

The first study of this instrument tested its reliability, investigating inter- and intraobserver agreement. A cross-sectional examination of seven patients by five examiners using the tool was performed. This showed a relatively poor interobserver reliability for identifying tender dactylitis and a poor agreement on non-tender dactylitis. This was improved significantly by using the LDI scoring system. Inter and intraobserver reliability for the LDI score was good, but was increased further using the LDI basic, suggesting that some of the variability was due to the inaccuracy of grading tenderness (Helliwell et al. 2005).

A longitudinal study was then performed to further investigate the use of this clinical tool and to compare it to other methods used previously. This study recruited 28 patients with dactylitis who were having a change in treatment for their PsA. All five available measures for dactylitis (tender dactylitis count (Salvarani et al. 2003), all dactylitis count (Clegg et al. 1996), IMPACT1 (Antoni et al. 2005b), LDI (Helliwell et al. 2005), LDI basic (Helliwell et al. 2005)) were performed at baseline and then regularly following the change in therapy. All measures showed a change with treatment after three and six months with a reasonable effect size for the variety of treatments used. The majority of these correlated with other clinical disease activity measures such as joint counts and VAS for disease activity (Healy and Helliwell 2007). Only the count of all dactylitic digits performed badly probably due to the inclusion of non-tender dactylitis which may not be thought to represent disease activity in patients' and physicians' opinions.

A subgroup of patients in the above study also had MRI scans performed at baseline and six months to assess the inflammation in the dactylitic digits. Similar to the Olivieri study (Olivieri et al. 1996), this showed that clinically tender dactylitic digits had significant MRI abnormalities compared to non-involved digits or non-tender dactylitis. However the correlation between the level of inflammation on MRI and clinical evaluation was moderate at best (0.37 for LDI local score and MRI score) (Healy et al. 2008). The identification of more inflammation on MRI when compared to a clinical score is unsurprising given the poor sensitivity of clinical examination compared to MRI as seen in other aspects of inflammatory arthritis (Szkudlarek et al. 2004; Szkudlarek et al. 2006).

Although the LDI and LDI basic measures do take longer to perform, particularly if multiple digits are involved, these measures perform better in terms of both truth and discrimination when considering the tool in the context of the OMERACT filter (Healy and Helliwell 2007). Thus, it is the most validated clinical outcome measure available for dactylitis.

2.3.1.5 Axial Disease

Just as peripheral joint assessment tools have been borrowed from RA, measures of axial disease activity have been used in PsA that were initially designed for use in AS. The most commonly used outcomes in AS are the Bath measures including the BASDAI, the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Bath Ankylosing Spondylitis Metrology Index (BASMI). The BASDAI is a patient completed questionnaire with a series of six 100 mm VAS scales asking about fatigue, pain and early morning stiffness (Garrett et al. 1994). This is well validated in AS and has been used as the primary outcome in the vast majority of clinical trials in AS. The BASDAI provides a static measure of disease activity and cut points have been devised to define active disease. It is also routinely used as a response measure. Responses can require a reduction of a certain number of units or a reduction of a certain percentage such as a BASDAI50 which describes a reduction in BASDAI of at least 50%.

The BASDAI has been evaluated in a cohort of PsA patients to assess its use in this condition. This showed a high correlation between BASDAI scores and a self-reported VAS of current overall arthritis activity, suggesting that it is a good representation of patient's perception of disease activity in PsA (Taylor and Harrison 2004). However this correlation was very similar in those with axial disease and those with peripheral disease suggesting that the BASDAI does not differentiate between axial and peripheral disease activity (Taylor and Harrison 2004). No other assessment tools of axial disease activity have been evaluated in PsA.

Related to the BASDAI is the BASFI, a measure of functional ability validated and used in AS (Calin et al. 1994). Like the BASDAI, this is based on a series of 0-100 mm VAS scales where patients rate their ability to perform everyday tasks from easy to impossible. There are limited data concerning the use of the BASFI in PsA. One study of the BASFI showed a correlation with other functional indices in PsA patients but again it shows no difference in responses between patients with axial or peripheral disease (Leung et al. 2008). Therefore there is no obvious benefit to using the BASFI in preference over more established and validated tools such as the HAQ-DI and SF-36.

The BASMI is a combination of five clinical measurements of axial mobility developed from an assessment of twenty different measures in AS (Jenkinson et al. 1994). This shortened metrology index provides an assessment of spinal mobility including the cervical and lumbar spine. These measures have been assessed in PsA patients with axial disease using multiple observers. The International Spondyloarthritis Interobserver Reliability Exercise (INSPIRE) study showed that the intraclass correlation coefficients for patients with AS and axial PsA were similar and were excellent (ICC 0.89) (Gladman et al. 2007b). A further study tested the correlation between spinal mobility measures and radiographic evidence of spinal damage in both AS and PsA. This only used 19 patients (taken from the INSPIRE study) but did show a high correlation between the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) and measures of spinal mobility (Chandran et al. 2007a). This provides some limited evidence of truth in the form of criterion validity.

Increasingly, composite measures including some of the Bath scales are being used to assess axial response in clinical trials in AS. The Assessment of SpondyloArthritis Society (ASAS) response measures were developed in 2001 using data from RCTs comparing NSAIDs versus placebo (Anderson et al. 2001). The authors initially included the five core outcomes established by the ASAS group (physical function, pain, spinal mobility, spinal stiffness/inflammation and the patient’s global assessment), but spinal mobility was excluded as there was no evidence of responsiveness to treatment. Multiple candidate definitions of improvement were tested looking for a low placebo response (<25%) and a significant difference between groups. The best criteria were the ASAS20 response criteria (see table 2) (Anderson et al. 2001).

These were then revised in 2004, following the advent of new therapies. TNF-inhibitors had proven efficacy in improving spinal mobility and acute phase reactants, which had been excluded from the previous response measures. When the original methodology was repeated using data from the RCTs of TNF inhibitors, the new ASAS20 (5 of 6 criteria) and a modification of the original ASAS response criteria using a 40% improvement were shown to be the best discriminators (see table 2) (Brandt et al. 2004).

<table>
<tr><td colspan="2">ASAS criteria for response 2001 (Anderson et al. 2001)</td></tr>
<tr><td colspan="2">Improvement of ≥20% and absolute improvement of ≥10 units in ≥3 of the following 4 domains:
• Patient global assessment (VAS global assessment scale)
• Pain (pain VAS)
• Function (BASFI)
• Inflammation (mean of questions 5&6 from the BASDAI)

with no deterioration, defined as a deterioration of ≥20% and net worsening of ≥10 units in the remaining domain.</td></tr>
<tr><td colspan="2">ASAS response criteria 2004 (Brandt et al. 2004)</td></tr>
<tr><td>ASAS 20 (5 of 6 criteria)</td><td>ASAS 40</td></tr>
<tr><td>Improvement of ≥20% in five of the following six domains</td><td>Improvement of ≥40% and absolute improvement of ≥20 units in ≥3 of the following 4 domains:</td></tr>
<tr><td>• Patient global assessment (VAS global assessment scale)
• Pain (pain VAS)
• Function (BASFI)
• Inflammation (mean of questions 5&6 from the BASDAI)
• Spinal mobility (BASMI)
• Acute phase reactant (CRP)</td><td>• Patient global assessment (VAS global assessment scale)
• Pain (pain VAS)
• Function (BASFI)
• Inflammation (mean of questions 5&6 from the BASDAI)</td></tr>
</table>

Table 2 - The ASAS response criteria 2001 and 2004

More recently, a new composite disease activity score has been developed by the ASAS group to provide a composite measure that could reflect disease activity in AS (Lukas et al. 2009). The Ankylosing Spondylitis Disease Activity Score (ASDAS) was developed from 12 candidate variables selected by ASAS experts. Data from 708 patients were used to develop the ASDAS. First, principal component analysis was used to identify sets of correlated variables to remove redundant outcome measures, then discriminant function analysis was used to investigate the contribution of the different factors in the separation of high and low disease activity. Finally, linear regression analysis was performed to provide a weighting for each of the discriminant variables. This analysis was used to produce four draft ASDAS formulae (see table 3) for future analysis. Cross validation was performed in a second cohort confirming similar discriminatory ability. The discriminatory ability, as measured by the standardised mean difference, was considerably higher for all four ASDAS when compared with any of the single variables (Lukas et al. 2009).

A=	0.122 x back pain	+	0.061 x duration morning stiffness	+	0.119 x patient global	+	0.210 x √(ESR)	+	0.383 x Ln(CRP+1)
B=	0.079 x back pain	+	0.069 x duration morning stiffness	+	0.113 x patient global	+	0.086 x peripheral pain/swelling	+	0.293 x √(ESR)
C=	0.121 x back pain	+	0.058 x duration morning stiffness	+	0.110 x patient global	+	0.073 x peripheral pain/swelling	+	0.579 x Ln(CRP+1)
D=	0.152 x back pain	+	0.069 x duration morning stiffness	+	0.078 x fatigue	+	0.224 x √(ESR)	+	0.400 x Ln(CRP+1)

Table 3 - The ASDAS draft formulae

Further validation work has continued following this initial publication. Analyses in two further independent cohorts again showed that all four draft ASDAS were highly discriminatory (van der Heijde et al. 2009). Discussion within the ASAS group was used to decide on the final ASDAS formula to be recommended. It was decided that the ASDAS with CRP (ASDAS C in table 3) should be the preferred ASDAS score with an alternative ASDAS including ESR (ASDAS B in table 3) to be used if CRP is not available (van der Heijde et al. 2009). A further external validation study showed responsiveness to change and concurrent validity in patients with axial SpA treated with TNF blockers (Pedersen et al. 2010). Preliminary cut-points have also been proposed for different levels of disease activity and responses, although these need further investigation and validation before they are proven.

Unfortunately these composite measures (both ASAS response measures and the ASDAS) have not been assessed in PsA. Given the limitations of the BASDAI in PsA, there are justifiable concerns about their use; however the inclusion of other outcome measures may mean that these composite indices can be helpful in axial PsA. Ideally, studies with newer effective therapies are required in axial PsA to address this issue and to compare these different outcome measures.

2.3.1.6 Composite Outcome Measures

As discussed in previous sections, the majority of outcome measures used in PsA research have been “borrowed” from other diseases and have only been validated in subsets of disease. Recently, there have been increasing efforts in the development of a validated composite outcome measure which reflects disease activity in all of the domains in PsA and can be used in a variety of subsets of disease.

In recent years, work has been underway on two key composite measure initiatives, both led by members of Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Professor Fitzgerald and colleagues proposed a composite outcome measure based on the GRAPPA treatment grid published by Ritchlin and Kavanaugh (Ritchlin et al. 2009). The Composite PsA Disease Activity Index (CPDAI) assigns a score of 0-3 to each of the five domains of PsA based on disease activity and impact of disease for this domain. These scores can then be added together to give a total score of 0-15 with an overall assessment of disease severity based on this total score (Mumtaz et al. 2010). One concern raised during the development of this measure was that patients with severe disease activity in only one domain may be disadvantaged by a relatively low total score. Two solutions have been proposed for this. The first is that anyone with a single domain scored as severe would also be classified as severe overall. The second solution was the proposal of a modified CPDAI, with the total score being divided by the number of domains involved to give a mean CPDAI score.

Both of these CPDAI scores have undergone preliminary validation using data from observational cohorts and datasets from RCTs. Data from patients followed in rheumatology clinics in both Dublin and Leeds were used to relate CPDAI scores to patient and physician global disease activity VAS and to treatment decisions. The CPDAI score showed an excellent correlation with both patient and physician VAS and in multiple analyses, higher scores were found to be associated with treatment changes (Mumtaz et al. 2010).

A second initiative was started by GRAPPA following their annual meeting in 2008. In an attempt to develop an inclusive composite outcome measure based on real patient data, the GRAPPA Composite Exercise (GRACE) project was developed (Coates et al. 2010c). Based on the development of other composite outcome measures for both RA and AS (the DAS and ASDAS), observational longitudinal data are being collected on a large cohort of PsA patients across the world. Individual outcomes assessing disease activity in all of the domains of PsA, as well as patient reported outcome measures (PROMs) are being collected. Patients are classified by their treating physician in two groups: those requiring a treatment change (i.e. active disease) and those not (assumed to have a low disease activity). In this way, the two groups can be compared to see where significant differences exist between the two groups and which individual outcome measures account for this difference. To date, cross-sectional data has been collected on over 400 patients and these patients continue in follow up.

At the OMERACT10 meeting in 2010, the PsA working group (composed of key members of the GRAPPA group) presented a summary of the existing composite scores for PsA and preliminary work from the GRACE initiative. Professor FitzGerald presented data from the psoriasis randomised study in subjects with psoriatic arthritis (Psoriasis Randomised Etanercept STudy in subjects with Psoriatic Arthritis or PRESTA study) investigating the responsiveness of the CPDAI and other proposed indices including the DAREA or DAPSA. This study is particularly interesting as it is the only large RCT to include only patients with both significant joint disease activity and skin disease activity. The study compared standard dose etanercept (50 mg once weekly) with a higher dose of 50mg twice weekly to evaluate if higher doses were more effective in PsA. There was a significant difference seen between the treatment groups in terms of skin disease, but similar improvements were seen in joint disease activity (Sterry et al. 2010).

This differential response makes this database ideal for analysing proposed composite measures. The analysis showed that all measures performed well at discriminating between baseline and the primary endpoint, but none found a significant difference between the treatment groups related to the differential response in skin disease. Interestingly, the mean CPDAI score did show a trend between the two groups, possibly influenced by the skin disease activity but this did not reach significance.

Finally at OMERACT10, preliminary data were presented from the GRACE analysis. When considering individual domains of PsA, there was a clear differentiation between the two groups identified in the GRACE data collection for all outcome measures except those measuring nail psoriasis (mNAPSI), enthesitis (MASES), ESR and BASMI. The lack of a significant difference for these parameters is likely to be related to different factors. In some cases, particularly the nail disease, there is a relatively low prevalence of these features in the patient data. This lack of difference may also suggest that these features are less important to physicians when considering disease activity and potential changes in therapy. A PCA was performed for all variables included in disease activity measures with log transformation for PASI, LEI, dactylitis, joint counts and CRP, to identify which outcome measures best identified the variability in the data. The PCA identified five significant factors that were best represented by

1. Global disease activity VAS
2. Skin disease activity (BSA and PASI)
3. TJC and enthesitis count
4. SJC and dactylitis count
5. CRP

Regression analysis was then applied showing that nearly 80% of the variability (adjusted R^2) was contributed by the global disease activity VAS, and over 90% of the variance can be summarised with just three VAS scores (patient global, patient skin, and physician global). Therefore the PsA disease activity score (PASDAS) was proposed as a composite of three VAS scales (Coates et al. 2010c).

A preliminary analysis of a modular approach to disease assessment rating each domain (peripheral arthritis, skin, dactylitis, enthesitis and spine) in terms of an intention to treat was also presented at the OMERACT 10 conference. Each domain would be rated from A to E on a five point scale where E represents no involvement of that domain and A severe involvement requiring DMARD therapy.

This method of using PCA and regression analysis was used in the development of both the RA DAS and the ASDAS. However, precisely because of the nature of PsA, this methodology has some disadvantages. The most significant issue is that any potential formula is based on a particular sample of patients' data, and their disease pattern influences the resulting formula. For example, the majority of the GRACE participants were recruited from rheumatology clinics where skin disease is usually mild. Therefore skin disease may have less of an impact in these patients on their total disease activity. However patients seen in dermatology clinics are likely to have greater skin disease activity, and the disease activity score may not accurately reflect their pattern of disease. In a more homogenous condition, this is less of an issue as the sample is likely to be representative of most of the patients it will be utilised in. However in PsA, basing disease activity scores on "average" rheumatology patients may severely disadvantage those with other patterns of disease.

2.3.1.7 Defining "state" in PsA

There are no definitions of high or low disease activity states available in PsA. In RA, there are continuous composite outcome measures such as the DAS, for which cutpoints for different disease severities ranging from remission to high disease activity have been defined. The availability of these definitions in RA has provided a different outcome measure for clinical trials. They allow identification of patients who achieve a desired state, rather than a significant reduction in disease activity that may still represent a considerable burden of disease. Despite validation of the DAS scoring system in PsA which showed that it could discriminate well between active treatment and placebo, there are no validated cutpoints for different disease severities of peripheral joint activity in PsA.

The availability of these cutpoints for disease has also meant that they can be used in clinical trials to guide therapy. In particular, the TIght COntrol of Rheumatoid Arthritis (TICORA) study demonstrated that tight control of disease utilising pre-defined activity levels to guide therapeutic changes (escalation of treatment if DAS >2.4), resulted in significantly better clinical and radiographic outcomes compared to routine care with no formal therapeutic protocol (Grigor et al. 2004). Many recent RA studies have used similar objective measures (usually the DAS) to guide therapy (Goekoop-Ruiterman et al. 2005) and this is now beginning to be translated into routine clinical practice.

Remission is clearly the ultimate goal of therapy in PsA as in other inflammatory arthritides, and a definition proposed by Kavanaugh et al suggested that remission in PsA should be characterised by “a complete absence of disease activity, with no signs or symptoms of active disease” (Kavanaugh and Fransen 2006). However, this paper also recognised that remission was not only difficult to achieve and maintain, but that, in some patients, mild disease activity in one domain can be acceptable. Given this, they concluded that “near remission” or “low disease activity” could be an appropriate goal for individual patient’s treatment (Kavanaugh and Fransen 2006).

The need for a definition of MDA was first recognised in the RA research community and was developed within OMERACT. It was recognised that the most important target was achieving a desired state rather than simply a reduction in disease activity that may leave patients with significant ongoing disease. Remission or an absence of disease activity was felt to be an unrealistic goal in many patients, therefore MDA aimed to encompass both remission and “near remission” or “low disease activity” as acceptable targets for therapy. The development of a concept of MDA was done through an OMERACT working group with involvement of rheumatologists, methodologists and patients (Wells et al. 2003).

It was discussed that for physicians, low disease activity state was linked to treatment decisions and to prognosis. For patients, low disease activity state was linked to satisfaction with current symptoms and also to adaptation since a ‘cure’ is not currently possible. The concept of a usual target of treatment was developed based on the example set by the group who developed the RA DAS. They reasoned that a disease activity score should reflect real-life clinical practice and related low and high disease activity to the decision of a physician to initiate or escalate treatment. It was also noted that any definition should be limited in time as treatment options and expectations of both patients and physicians are likely to evolve over time (Boers et al. 2003a).

The conceptual definition of MDA was agreed at the OMERACT 6 conference as “that state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations” (Boers et al. 2003b). This definition is designed to reflect clinical practice and for the rheumatologist is linked to treatment decisions. For the patient, this should be linked to a satisfactory symptomatic state. Following on from the agreement of this conceptual definition, the OMERACT working group went on to create a set of MDA criteria for RA (Wells et al. 2005) based on the ACR core set and the DAS scoring system. Researchers in other rheumatic diseases are now starting to develop disease specific criteria for MDA (Magni-Manzoni et al. 2008).

Discussion regarding remission in PsA has also occurred and this has been investigated in a number of cohort studies. However all of these definitions are different and were not based on patient-derived data (Gladman et al. 2001; Cantini et al. 2008; Lindqvist et al. 2008). Interesting, the majority only assess peripheral joint activity and do not take other aspects of the disease into account (Gladman et al. 2001; Lindqvist et al. 2008).

Any criteria for disease activity in PsA must assess many aspects of this complex disease and a core set of measures for future PsA research was agreed at OMERACT 8 in 2006. The six core measures agreed were peripheral joint activity, skin activity, pain, patient global assessment, physical function and health-related quality of life (HRQOL) (Gladman et al. 2007d). Other important domains included spinal disease, dactylitis, enthesitis, fatigue, nail disease, radiography, physician global assessment and acute-phase reactants (Gladman et al. 2007d). If states of disease activity are to be defined, these core and important measures must be taken into account to ensure that a holistic view of the patient is considered.

2.3.2 Imaging

2.3.2.1 Conventional radiography

Conventional radiography is considered the "gold standard" in measuring progression of joint damage. The importance of assessing radiographic evidence of joint damage in clinical trials is becoming apparent with the advent of newer biological treatments that can impact on the natural progression of disease.

Initially, research into scoring systems for plain radiographs concentrated on RA, and many of the scoring systems developed for PsA are adaptations of these. The majority of radiographic scoring systems for RA assess JSN and erosions. While these features are seen in PsA, additional typical features must be considered. In PsA, particularly in the mutilans subtype, extensive erosions may be seen extending to osteolysis of both joints and phalanges. One of the typical features of PsA, the "pencil-in-cup" deformity, results from marked erosive changes on the proximal side of a joint with new bone formation around the distal side of the joint. This demonstrates the co-existence of bone erosion and new bone formation in PsA. This bone formation can occur adjacent to the joints and the shafts of the bones and may even extend to ankylosis of a joint. Most adaptations of radiographic scoring methods attempt to identify both bone destruction and bone formation in key joints.

At the Toronto PsA Clinic, a modification of the Steinbrocker technique has been used to evaluate the radiographic outcome over time. The original Steinbrocker technique was developed for use in RA in 1949 and scored a patient according to their worst joint on a scale of 0-4 (table 4) (Steinbrocker et al. 1949). There was a concern that just scoring one joint would not be sensitive to change and therefore a modified Steinbrocker is used for monitoring in the clinic. The modification scores 42 joints according to that scale including all joints on the hands (wrist = 1 joint), all metatarsophalangeal (MTP) joints and the interphalangeal (IP) joint of the big toes (Rahman et al. 1998b). This modification has been validated within the Toronto cohort and has shown good inter and intra-observer reliability as well as confirming sensitivity to change over time (Rahman et al. 1998b).

The Toronto validation study also analysed the use of the Larsen score in PsA. This is a similar method where each joint is given a global semi-quantitative score and was also originally developed for use in RA (Larsen et al. 1977). The Toronto group used Larsen's method as modified by Rau and Hehborn (table 5) (Rau and Herborn 1995) and adapted the score to include the same joints as their modified Steinbroker scoring system (Rahman et al. 1998b). This study confirmed similar validity of the Larsen scoring system in PsA with similar inter and intra-observer variability and similar sensitivity to change to the modified Steinbrocker score used routinely in the clinic (Rahman et al. 1998b).

Although both the Larsen and Steinbrocker techniques have been validated in PsA, they both simply assess each joint with a global score. There is no differentiation between different pathologies, and no identification of typical PsA features such as the pencil-in-cup deformity. Three more detailed scoring systems have also been outlined for use in PsA, two of these are based on the Sharp method for scoring RA radiographs and the final method is a score specifically developed for PsA.

The most widely used detailed scoring system for radiographic damage in RA is the Sharp method (Sharp et al. 1971). A modification to this was made in 1989 by van der Heijde to include joints in the feet in addition to those in the hands (van der Heijde et al. 1989). Although more time consuming than the scores which utilise a global score for each joint, such as the Steinbrocker and Larsen scores, the Sharp scores do provide a higher reliability and sensitivity to change due to the detail included in the assessment.

Score	Definition
0	Normal
1	Juxta-articular osteopenia or soft tissue swelling
2	Erosion
3	Erosion and JSN
4	Total joint destruction, either lysis or ankylosis

Table 4 – Steinbrocker scores for joint radiographs

Score	Definition
0	Normal
1	Soft tissue swelling, osteoporosis, slight JSN
2	Erosion with destruction of joint surface (DJS) < 25%
3	Erosion with DJS 26-50%
4	Erosion with DJS 51-75%
5	Erosion with DJS >75%

Table 5 – Larsen's scoring method as modified by Rau and Hehborn

The first modification of the Sharp scoring method was developed for use in trials of anti-TNF therapies. A similar range of joints were assessed as in the standard Sharp RA method (Sharp et al. 1985), except that the DIP joints were assessed in addition for both erosions and JSN. Erosions and JSN are scored using a similar scoring system to that in RA (Sharp et al. 1985), but with additional scores for specific PsA features (table 6). The presence or absence of pencil-in-cup deformity is scored for all lesions of grade 6 or 7 and these additional specific PsA features (grade 6 erosion, grade 7 erosion, pencil-in-cup deformity, grade 5 widening) are not added in the final score but are kept separate to it. Other radiographic features of PsA (including periostitis, tuft resorption) were also scored separately, when this system was first trialled. However once this data was analysed, the system showed sensitivity to change based on the erosion and JSN scores (Mease et al. 2004) and scoring of additional features did not provide any additional improvement in differentiation between treatment groups (van der Heijde et al. 2005a).

A second modification based on the Sharp-van der Heijde method, was developed later for further RCTs of biologic therapies. Again, a similar range of joints is scored with addition of the DIPs (van der Heijde et al. 2005b). Joints are scored for erosions, JSN, subluxation and ankylosis using the table below (table 7). The maximum score for erosions is 5 in the joints of the hand and 10 in the joints of the feet. Gross osteolysis and pencil-in-cup are scored separately; and any joints found to have these abnormalities are given the maximum score for both erosions and JSN.

Erosion scores	
Score	Definition
0	No erosion
1	One discrete erosion of involvement of <21% of the joint area by erosion
2	Two discrete erosions or involvement of 21-40% of the joint
3	Three discrete erosions or involvement of 41-60% fo the joint
4	Four discrete erosions or involvement of 61-80% of the joint
5	Extensive destruction involving more than 80% of the joint
6	More extensive osteolysis
7	Gross osteolysis
Pencil-in-cup	Present or absent
Joint space narrowing scores	
Score	Definition
0	Normal joint
1	Asymmetrical and or minimal narrowing
2	Definite narrowing with loss of up to 50% of the normal space
3	Definite narrowing with loss of 51-99% of the normal space
4	Absence of a joint space, presumptive evidence of ankylosis
5	Widening

Table 6 – modified Sharp scoring system for PsA with inclusion of typical features

Erosion scores	
Score	Definition
0	No erosion
1	Discrete erosion
2	Large erosion not passing the mid-line
3	Large erosion passing the mid-line
Joint space narrowing scores	
Score	Definiton
0	Normal joint
1	Asymmetrical and or minimal narrowing up to a maximum of 25%
2	Definite narrowing with loss of up to 50% of the normal space
3	Definite narrowing with loss of 51-99% of the normal space or subluxation
4	Absence of a joint space, presumptive evidence of ankylosis, or complete luxation

Table 7 – modified Sharp-van der Heijde scoring method for PsA

This scoring system was utilised in the IMPACT and IMPACT2 studies of infliximab therapy in PsA. These analyses found relatively high kappa scores showing good agreement between readers. It also identified a reduction in joint damage progression with infliximab therapy, using the total modified Sharp/van der Heijde (mS-vdH) score, the erosion score and the JSN score. The additional PsA specific features of pencil-in-cup and gross osteolysis occurred infrequently and did not show any change over time (Kavanaugh et al. 2006; van der Heijde et al. 2007). Therefore, it was suggested that these may not be needed, and that the RA scoring system can be utilised with the addition of the DIP joints only.

The Ratingen score is the only radiographic scoring system developed specifically for PsA. The authors recognised the co-existence of bone destruction and bone proliferation in PsA and devised a score for each of these aspects individually (table 8) (Wassenberg et al. 2001). A similar number of joints are scored to that of the modified Steinbrocker, except that the 1st MTP joints are excluded leaving a joint count of 40. The validity of this method was assessed using 20 pairs of radiographs from patients with PsA taken three years apart. Inter and intra-reader reliability and sensitivity to change were found to be comparable to results in RA studies using the Larsen, Ratingen and mS-vdH scoring methods (Wassenberg et al. 2001). Interestingly, although both bone destruction and bone proliferation progressed over the study period, there was little correlation between the amount of progression in bone proliferation and bone destruction scores (Wassenberg et al. 2001). This confirms the independence of these two pathological processes and highlights the importance of such a scoring system where each feature is assessed independently.

Bone Destruction Score (DS)	
Score	Definition
0	Normal
1	One or more definite erosions with an interruption of the cortical plate of >1mm but destruction of less than 10% of the total joint surface
2	Destruction of 11-25%
3	Destruction of 26-50%
4	Destruction of 51-75%
5	Destruction of >75% of joint surface
Bone Proliferation Score (PS)	
Score	Definition
0	Normal
1	Bony proliferation measured from the original bone surface of 1-2mm, or, if the margins of the proliferation cannot be distinguished from the original bone surface, clearly identifiable bone growth not exceeding 25% of the original diameter of the bone
2	Bony proliferation of 2-3mm or bone growth between 25-50%
3	Bone proliferation of >3mm or bone growth >50%
4	Bony ankylosis

Table 8 – Ratingen scoring system for PsA

2.3.2.2 Ultrasound

US is an expanding area of interest in rheumatology clinical trials. The use of US as an objective quantitative outcome measure has been expanding, particularly in RA clinical trials. US allows real time image acquisition of multiple joints to assess both bony changes (erosion) and inflammation. Definitions of pathologies (bone erosion, synovial fluid, synovial hypertrophy, tenosynovitis and enthesopathy) seen on US have been agreed by the US special interest group (SIG) at OMERACT 7 for use in future studies. The majority of studies using US have utilised these definitions and a semi-quantitative 0-3 scoring system where 0=normal, 1=mild, 2=moderate and 3=severe pathology. Erosions can be scored using a binary present/absent system or a 0-3 semi-quantitative score (Szkudlarek et al. 2003).

One of the key questions raised by the use of US as an outcome measure is the question of how many joints should be scanned. Obviously scanning many joints provides additional information, but US is still relatively time-consuming when multiple joints must be assessed, and feasibility is a key issue. Early work has begun in RA to identify reduced joint combinations that can still accurately identify pathology and both seven and 12 joint scores have been proposed (Naredo et al. 2008; Backhaus et al. 2009). Similar work in PsA has yet to be done, and this is likely to be more challenging given the heterogeneity of clinical presentation in PsA.

2.3.2.3 MRI

While MRI has been used since its development as a research tool to investigate pathogenesis in arthritis, it has less commonly been used as an outcome measure for disease activity and joint damage. However increasingly, studies are looking for objective methods of measuring disease activity and MRI is able to visualise all of the structures in and around the joint. MRI also has major advantages over conventional radiography in terms of its sensitivity to change when investigating progression of joint damage.

The OMERACT MRI in inflammatory arthritis group decided to develop a scoring system for PsA, following on from the development of the RA MRI score (RAMRIS). The first step was a literature review of PsA MRI studies to identify typical pathologies that would need inclusion into a scoring system (McQueen et al. 2006).

Synovitis, bone oedema and bone erosions have been identified using MRI in both RA and PsA. Despite the fact that synovial tissue samples have suggested a difference in the histopathology of PsA and RA tissue (Reece et al. 1999), and MRI studies have shown more extensive synovitis in RA compared to PsA (Marzo-

Ortega et al. 2009), the synovitis is indistinguishable, when matched for disease activity (Cimmino et al. 2005). Similarly, although bone erosions are seen at different sites in the two diseases, the appearance of the erosions is non-specific. In both diseases, a break in the bone surface can be visualised on MRI (Ostergaard et al. 2003). This may be filled with inflammatory tissue which will enhance with gadolinium or with fibrous tissue which is non-enhancing. Similarly, the appearance of bone oedema across the arthritides is similar on MRI. Images show an increased signal within the bone on short-tau inversion recovery (STIR) imaging, T2 weighted films with fat saturation and post contrast T1 weighted images (Ostergaard et al. 2003). Similar to the situation regarding bone erosion, the differences seen between RA and PsA relate to the sites of bone oedema and the severity of disease.

The possibility of a different pattern of involvement in PsA was first raised in 1995 in two papers investigating MRI in PsA (Giovagnoni et al. 1995; Jevtic et al. 1995). Both of these papers showed extensive inflammation in the periarticular tissue extending beyond the joint capsule and into the surrounding subcutaneous tissue in patients with PsA whereas in patients with RA, the inflammation was confined to the joint capsule in most cases. Where periarticular oedema was seen in RA patients, it did not extend to the subcutaneous tissue. These papers highlight the additional features seen on MR imaging in PsA and it was recognised that these must be included in a potential scoring system.

The PsA MRI score (PsAMRIS) system has been developed for scoring hand MRIs in PsA. The RAMRIS scores the wrist joints and the metocarpophalangeal (MCP) joints of fingers 2-5. There was a concern about excluding the proximal interphalangeal (PIP) and DIP joints in a potential PsA scoring system given the increased involvement typically in the DIP joints. It was also felt that there was less involvement seen in the wrists in patients with PsA. Therefore the joints scored in the PsAMRIS are MCP, PIP and DIP of fingers 2-5. These joint regions were divided by the midpoints of the phalangeal bones and were then subdivided at the joint space line to give three joint regions and six sub-regions (see figure 2) (Ostergaard et al. 2009).

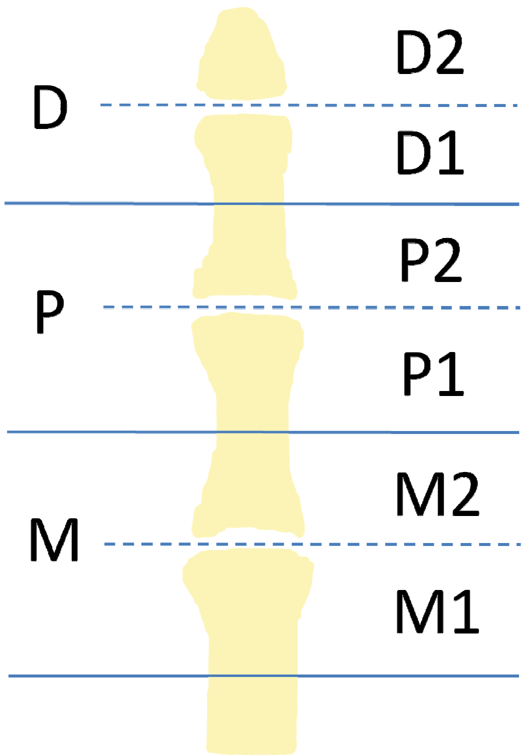

Figure 2 – Scoring regions for the PsAMRIS scoring system

Given that synovitis, bone erosions and bone oedema appear similar to that of RA, the semi-quantitative scoring system used in the RAMRIS was adopted (Ostergaard et al. 2009). Following this system, synovitis is scored in each joint region from 0-3, bone erosions are scored at each articular surface on a scale of 0-10 dependent on the percentage of bone loss and bone oedema is scored from 0-3 for each sub-region. In addition to this, other key features were defined and added to the scoring system. Tenosynovitis is assessed in each joint region in each of the four flexor tendons on a scale of 0-3 depending on the thickness of enhancing or bright signal within the tendon. Periarticular inflammation is scored as present or absent adjacent to each joint region on the dorsal and palmar aspect of the finger. Bone proliferation, defined as “abnormal bone formation in the periarticular region, such as at the entheses (enthesophytes) and across the joint (ankylosis)” (Ostergaard et al. 2009), is also scored as present or absent in each joint region.

Following on from the development of the scoring system, it has been tested in multiple validation exercises. The first exercise was cross-sectional and involved four experienced RAMRIS readers scoring 10 MRI scans of patients with PsA using the proposed PsAMRIS. This showed good to moderate inter-reader reliability for bone erosion and bone oedema, but low inter-reader reliability for the other features (McQueen et al. 2009). Difficulty assessing PIP and DIP joints was reported by the readers as the image resolution was poor at the extremes of the field of view. Also at this stage, readers were asked to record patterns of bone oedema as “subchondral”, “entheseal” or “diaphyseal”. This was felt to be too difficult to distinguish and was removed from later versions of the scoring system. Also, following on from this exercise, further definitions were created to improve inter-reader reliability in scoring (Ostergaard et al. 2009).

A second cross-sectional validation exercise utilised a further 10 MRI scans of patients with PsA and 2 healthy controls. These were scored by eight readers and found an improved intra-class coefficient (ICC) between readers of 0.84-0.91 except for the scoring of periarticular inflammation which was low (McQueen et al. 2009). This provides evidence for an increased reliability following clear definitions of pathologies and a removal of some features.

A longitudinal validation exercise was then performed by eight readers. They scored paired scans taken prior to treatment and at six weeks following treatment with anti-TNF therapy (adalimumab). This confirmed good reliability and sensitivity to change in synovitis, tenosynovitis and periarticular inflammation (McQueen et al. 2009). However given that the scans were only six weeks apart, there was not enough change in the bony features (bone erosion, bone oedema) to accurately assess the validity of scoring these features in a longitudinal study.

Further longitudinal validation exercises are required with a longer time interval between scans.

2.4 Treatment of PsA

2.4.1 Current treatment options

2.4.1.1 Non-steroidal anti-inflammatory drugs

The use of NSAIDs to treat PsA has been recommended for many years, and in mild cases, they are often recommended as the only therapy (Cuellar et al. 1994). However there is a lack of randomised trials to support their use. Only one RCT has compared a standard NSAID (nimesulide) to placebo showing reduce pain, stiffness and active joint counts (Sarzi-Puttini et al. 2001). However this drug has caused many cases of hepatotoxicity and is not licensed for use in most countries (Soriano and McHugh 2006). There have been four RCTs comparing different NSAIDs (Lassus 1976; Lonauer and Wirth 1980; Leatham et al. 1982; Hopkins et al. 1985), but none of them have shown a clear superiority of a particular drug (Soriano and McHugh 2006).

In addition to the standard concerns about gastrointestinal (GI) toxicity caused by NSAIDs and their risks in renal impairment, there is a concern about NSAIDs worsening skin psoriasis. The potential for this flare of skin lesions was highlighted by dermatologists in case reports (Griffiths 1997). However in the five RCTs discussed above, there was no evidence of an effect on psoriasis (Soriano and McHugh 2006).

More recently, one RCT comparing celecoxib to placebo in 608 patients with PsA has been published. This study evaluated the use of celecoxib in PsA flare, therefore all patients had their NSAID and analgesic therapy withdrawn at screening and had to demonstrate a flare in their disease in the ensuing week. Celecoxib treatment resulted in a significant number of patients achieving an improvement in disease activity (ACR20 response) at week two, but further improvements in the placebo arm by week 12 meant that there was no significant difference between the groups at the end of the 12 week study. There was no significant difference in the proportions of patients achieving ACR50 or 70 responses. Importantly celecoxib was well tolerated with less than 3% of patients stopping therapy due to GI side effects. Only two patients experienced a worsening of their skin psoriasis and stopped therapy, while change in PASI scores showed no difference between treatment or placebo (Kivitz et al. 2007).

2.4.1.2 Steroids – systemic

The use of systemic steroids (either given orally or intramuscularly) in PsA has always been controversial. There are no studies assessing the efficacy of corticosteroids in PsA, but they have been widely used in the past and continue to be used today. A multicentre study of 10 rheumatology centres in Italy between 1990 and 1992 revealed that 24% of PsA patients were treated with average daily doses of 5mg methylprednisolone. Interestingly there was a wide range between different centres from none to 55% of patients reflecting a large variation in treatment (Grassi et al. 1998). This variation is likely to represent the uncertainty over the best treatment for patients with PsA and the lack of evidence for standard treatments at that time.

Obviously, the long term side effects of steroids are well recognised and therefore prolonged use is not recommended. In patients with PsA, there may be additional concerns. The concern from colleagues in dermatology is that systemic corticosteroids can cause a flare of skin psoriasis when they are withdrawn. Dermatologists have argued that systemic corticosteroids should not be used in PsA, and have blamed their use for an increase in the incidence of treatment-resistant skin psoriasis and pustular psoriasis (Griffiths 1997). However, there is a lack of prospective studies in PsA assessing the use of corticosteroids and further research is required to evaluate the risk/benefit ratio in PsA.

2.4.1.3 Steroids – local

Despite widespread use, there is little data to support the use of intra-articular (IA) steroids in PsA. Expert opinion is that IA glucocorticoid injections may be used in persistent mono or oligoarthritis with good clinical results (Soriano and McHugh 2006). Evidence from studies in a range of oligoarthritic patients have shown a benefit with IA steroid treatment but only a small proportion of the populations had PsA (Green et al. 2001; Marzo-Ortega et al. 2007).

An analysis of the observational Toronto PsA cohort has also attempted to address the issue of efficacy of IA steroids. They reviewed the notes of 220 patients who received 579 IA steroid injections, particularly to finger, knee and wrist joints. They found that the probability of remission in that particular joint at three months follow up was 41%, and a third of these relapsed within 12 months (Eder et al. 2010). Unfortunately, as this data was collected from the clinic database retrospectively, most patients only have data recorded at their regular clinic visits every 3-6 months. This study was unable to address the response rate in the shorter term and cannot differentiate how many of the 60% who did not achieve remission had no response to steroids, and how many had responded and relapsed quickly.

While these data do suggest a role for IA steroids, they also highlight the need for additional therapy to treat active arthritis and prevent relapse.

2.4.1.4 Disease-modifying anti-rheumatic drugs

Methotrexate

Interest in methotrexate for the treatment of PsA evolved following its use in RA. However, the evidence from RCTs has always been lacking. Only two RCTs have ever been published on this topic and they have evaluated entirely different regimes (Black et al. 1964; Willkens et al. 1984). The first, published in 1964, investigated the use of IV pulsed methotrexate. Despite an improvement seen with treatment versus placebo, the side effects of this high dose IV regime were high. In particular, one patient died of marrow aplasia and several other adverse events were reported (Black et al. 1964).

The second study evaluated low dose oral methotrexate with a weekly dose of 7.5-15mg spread over three consecutive days. This did show a superior response with methotrexate in terms of a physicians assessment of arthritis activity and the BSA of psoriasis (Willkens et al. 1984). A few uncontrolled studies have shown improvement in a variety of outcomes. Espinoza et al described the use of oral methotrexate in 40 patients for a mean period of 34 months. The majority (n=38) were reported to have shown an excellent or good response, with just two non-responders. Despite significant numbers of patients developing liver test abnormalities, the incidence of cirrhosis or liver inflammation was low (Espinoza et al. 1992). A later Cochrane review calculated a moderate effect size of 0.65 based on both patients and physicians global assessments but the confidence intervals did just overlap zero (Jones et al. 2000). This systematic review also highlighted the improvement seen in the placebo groups of all RCTs in PsA. There is a similar improvement seen in all placebo groups over the time of the study, and the magnitude of improvement is similar to that seen in RA (Jones et al. 2000). They therefore guard against the use of evidence from uncontrolled trials in PsA.

Later studies have compared methotrexate to other DMARDs. A controlled trial of methotrexate vs cyclosporin A showed comparable efficacy in most outcome measures, and a superior effect of methotrexate on ESR. They also saw a significant increase in liver enzymes with methotrexate, but persistence of methotrexate therapy was better than cyclosporin (72.2% vs 58.8% at one year) (Spadaro et al. 1995). A retrospective case note review comparing IM gold and methotrexate also showed superior effects with methotrexate therapy. Patients were nearly nine times more likely to respond to methotrexate than gold (response defined as ≥50% reduction in active joint count) and were five times more likely to persevere with methotrexate therapy (Lacaille et al. 2000). Patients with a longer disease duration were less likely to respond to either drug, suggesting a possible benefit in early treatment.

A case-control study utilising the Toronto PsA database in 1995, compared 38 patients treated with methotrexate and their matched controls. The analysis revealed no significant benefit in terms of clinical response (45% showed improvement of ≥40% in active joint counts) or radiographic damage compared to controls, even after two years of therapy (Abu-Shakra et al. 1995). A further analysis was undertaken using the same cohort, but including patients treated with methotrexate between 1994 and 2004. Comparison to the earlier 1995 study showed that patients were being treated with methotrexate earlier in the course of their disease and using higher doses. The clinical response rate (using the same definition as above) was 68% and there was a trend towards a reduced rate of radiographic joint damage progression. However the differences between the cohorts were not found to be significant, probably due to the small numbers in the original study (Chandran et al. 2008).

The increasing emphasis on earlier treatment, led to a trial of immediate vs delayed methotrexate in early psoriatic oligoarthritis. Patients were randomised to methotrexate for six months or to NSAID therapy for three months, followed by methotrexate therapy from month three to six. Although both groups showed a significant improvement in disease activity from baseline, the improvement in both tender and swollen joint count was significantly better at three months in those treated with methotrexate compared to NSAID. There was a similar improvement in other measures of disease activity, such as inflammatory blood tests and pain VAS when comparing NSAID to methotrexate at three months. The authors suggest that this may be due to an incomplete response to methotrexate with partial control of disease (Scarpa et al. 2008b).

To assess effectiveness of methotrexate and anti-TNF therapies, an analysis of the Norwegian DMARD (NOR-DMARD) register was carried out. They identified 526 cases treated with methotrexate (n=380) or anti-TNF +/- methotrexate (n=146). Due to selection bias, patients treated with anti-TNF therapies had a generally more active and severe disease compared to patients in the methotrexate group. Although the adjusted changes in the group receiving anti-TNF therapies were significantly higher than those in the methotrexate group for inflammatory blood results, patients derived outcomes and quality of life, those patients in the methotrexate group did show a similar improvement in both tender and swollen joint counts. The drug adherence rates at six months were similar in both groups, with adverse event being the commonest reason for withdrawal in both groups (Heiberg et al. 2007).

Sulfasalazine

Sulfasalazine is probably the most studied standard DMARD in PsA with multiple RCTs. A meta-analysis performed as part of a Cochrane review assessed six RCTs (Farr et al. 1990; Fraser et al. 1993; Dougados et al. 1995; Gupta et al. 1995; Clegg et al. 1996; Combe et al. 1996), and found a significant benefit of sulfasalazine over placebo (Jones et al. 2000) although effect sizes were small (Soriano and McHugh 2006). Five of these studies were specific to PsA, but one included patients with a mixture of spondyloarthropathies of whom 136 had PsA (Dougados et al. 1995). They found that sulfasalazine appeared to be more effective in patients with PsA than in those with reactive arthritis (Dougados et al. 1995).

Later studies have been open-label in design and have looked at efficacy in daily practice. A more randomised controlled trial used three arms to compare sulfasalazine, cyclosporin and standard treatment (NSAIDs, analgesics and/or low dose prednisolone). This study did not show any significant differences associated with sulfasalazine therapy when compared to standard treatment with regard to arthritis activity or global assessments (Salvarani et al. 2001). However the study only included a total of 99 patients and may have been underpowered.

Data from the Toronto observational database has also been used to investigate the use of sulfasalazine. They identified 36 patients treated with sulfasalazine, but only 20 of them continued treatment for over three months. Fourteen of the 16 who discontinued therapy did so due to adverse events. The 20 patients treated with sulfasalazine for over three months were compared to 20 matched controls who were not treated with sulfasalazine. There was no significant difference in disease activity or radiographic score between the two groups (Rahman et al. 1998a). This is the only study that has attempted to assess the impact of sulfasalazine on radiographic damage, therefore there is no evidence that sulfasalazine slows or stops the progression of radiographic joint damage.

Leflunomide

Leflunomide was approved for use in RA in 2000 and interest grew in whether this could be an effective treatment for PsA. An early open label study with just 12 PsA patients using leflunomide either alone or in combination with other DMARDs, suggested a role for leflunomide and the need for further trials. Despite the small numbers there were significant improvements in TJC, grip strengths and patient's global assessments. Other outcomes showed a trend towards improvement but without statistical significance (Liang and Barr 2001). A case report in 2002 (Reich et al. 2002) highlighted the use of leflunomide in a patient with PsA and pustular psoriasis. Following addition of leflunomide, there was a striking improvement seen in her arthritis activity and in the pustular skin lesions. This patient had stable liver function throughout treatment despite previous hepatic toxicity with methotrexate (Reich et al. 2002).

A further small open label study in psoriasis patients (n=10) confirmed a mild-moderate improvement in joint swelling, pain and physical activity in patients with PsA (n=3) but did not show any significant improvement in plaque or pustular psoriasis (Thami and Garg 2004).

Following on from this selection of positive case reports and small open-label studies, a large multinational randomised trial was conducted comparing leflunomide and placebo (Treatment of Psoriatic Arthritis Study or TOPAS). One hundred and ninety patients with active psoriasis and PsA were randomised to either leflunomide (100mg/day loading dose for three days, then 20mg daily) or placebo for 24 weeks. There was a significant benefit in arthritis activity (PsARC and ACR20 responses), skin disease activity (PASI50), function and quality of life seen with leflunomide treatment (Kaltwasser et al. 2004). However the effect sizes in most of these outcomes were relatively small (Soriano and McHugh 2006), indicating that although leflunomide is significantly better than placebo, the benefit seen with treatment is not that large.

A high number of patients withdrew from the study early (leflunomide n=38, placebo n=51) and the majority withdrew due to lack of efficacy. Unsurprisingly more of patients withdrew due to lack of efficacy in the placebo group and more patients withdrew due to adverse events in the treatment group (Kaltwasser et al. 2004). The commonest adverse event reported was diarrhoea (23/92 patients on leflunomide), which is a recognised side effect of leflunomide, particularly precipitated by the initial three day loading regime. An increase in liver transaminases was seen in 12 of the leflunomide treated patients compared to five of the placebo treated patients. All five of the patients on placebo had only mild elevations of ALT. In the leflunomide group, three patients were withdrawn due to raised transaminases, and all of these elevations were found to be reversible. There were no cases of severe liver toxicity (Kaltwasser et al. 2004).

A further 24 week open label study was completed following this to further evaluate the efficacy and safety of leflunomide in daily clinical practice (Behrens et al. 2007). The treatment regime was identical to that of the TOPAS study (Kaltwasser et al. 2004) with a three day loading dose initially. This study confirmed a significant PsARC response rate of 78.1%, higher than the double-blind RCT. They also showed significant differences between pre and post-treatment measures of pain, dactylitis, skin disease and fatigue although many non-validated outcome measures were used in these analyses. Again, the commonest adverse event was diarrhoea, with a very low rate of hepatic toxicity (Behrens et al. 2007).

One of the major limitations of the TOPAS study is that there was no assessment of radiographic outcomes to analyse the ability of leflunomide to impact on joint damage progression (Kaltwasser et al. 2004). A case report of a patient with PsA treated with leflunomide suggested that leflunomide may have an impact on structural damage progression (Cuchacovich and Soto 2002). This particular patient had evidence of erosive disease on plain radiographs of the feet prior to treatment with leflunomide. After one year of treatment, there were no new erosions and partial filling of a subchondral cyst seen on repeat radiographs. Clearly although this suggests a role for leflunomide in radiographic progression, this does not provide substantial evidence that leflunomide can reduce erosive progression. Further investigations, preferably in controlled trials are required to answer this question.

Cyclosporin

At the time of analysis (2004), there were no studies to be included in the Cochrane review and there have been no RCTs comparing cyclosporin to placebo (Jones et al. 2000). However a number of studies have compared cyclosporin with other DMARDs either alone or in combination.

In 1995, the effectiveness and toxicity of cyclosporin was compared with methotrexate in a small RCT of 35 patients. Both cyclosporin (3-5mg/kg/day) and methotrexate (7.5-15mg/week) showed a significant improvement in measurements of disease activity. The changes in laboratory tests were similar in both groups, except for a significant increase in liver enzymes in the methotrexate group. After one year of therapy, 41% of patients had stopped cyclosporin with a trend towards better persistence in the methotrexate group (Spadaro et al. 1995). Although this study showed a benefit associated with cyclosporin, the study was not placebo controlled and the numbers are too small to assess which treatment is better.

An open-label comparison of cyclosporin, sulfasalazine and standard therapy was undertaken in 99 PsA patients. The cyclosporin arm showed a significant improvement in joint counts, pain scores, global assessments and CRP when compared with the standard therapy arm, and improvement in pain scores was also significantly better than sulfasalazine. In this study, cyclosporin was well tolerated despite development of a mild, reversible kidney dysfunction in a minority of patients (Salvarani et al. 2001).

The final RCT using cyclosporin assessed the benefit of adding cyclosporin into the treatment regime of methotrexate partial responders. Patients continued on a stable dose of methotrexate and were randomised to receive cyclosporin or placebo in addition to this. In addition to clinical outcomes, a sub-group of patients were also assessed using high resolution US to look for synovitis. Although both groups showed a significant reduction in joint tenderness, the methotrexate/cyclosporin group also showed a significant reduction in SJC, CRP and PASI. When comparing the two groups, significant differences were noted in the PASI score and US detected synovitis, in favour of combination treatment. Although the patients treated with cyclosporin had a very slight increase in blood pressure and serum urea, there were no significant differences between the two groups in these measures. In keeping with results from the previous studies, a number of patients discontinued therapy due to adverse events (13/38 in the cyclosporin arm) (Fraser et al. 2005).

None of the RCTs discussed above included radiographic measures of joint damage. One small open-label study (n=15) did assess the change in radiographic scores over a two year treatment period, but there was no control group. Macchioni et al found an increase in the number of joints with radiographic erosions over the time period, but some patients developed far less joint damage than others (Macchioni et al. 1998). Nine patients developed ≤1 new eroded joint while the remaining six patients had five or more new eroded joints. The progression of erosion was correlated with levels of serum soluble interleukin 2-receptor (IL2-R) which is inhibited by cyclosporin. This study therefore suggested that cyclosporin could partially control the progression of joint damage based on these results (Macchioni et al. 1998). However the sample size is small with no control group. It is well known that PsA is a heterogenous disease and there is great variation between natural disease progression in different cases. There is certainly no significant evidence to confirm that cyclosporin is truly disease-modifying.

2.4.1.5 Biologics

Tumour Necrosis Factor Inhibitors

TNF is a key pro-inflammatory cytokine, and blockade of TNF in-vitro causes a down regulation of multiple pro-inflammatory cytokines. TNF and TNF receptor were shown to be present in joint tissue in RA using immunohistochemistry, and studies using TNF blockade were initially performed in mouse models (Feldmann et al. 2005). Early clinical trials in RA showed impressive clinical benefit with TNF blocking agents (Elliott et al. 1993) and led on to large randomised clinical trials. Research in PsA found high levels of TNF in both psoriatic plaques in the skin and in synovial fluid taken from active arthritic joints (Partsch et al. 1997), providing a rationale for treatment of PsA with this class of drugs. A summary of the results from the key trials of TNF blockers is shown in table 9.

Table 9 – Summary of results from key anti-TNF therapy RCTs

Drug	N	Inclusion	Baseline TJC	Baseline SJC	PsARC	ACR20	ACR50	ACR70
Adalimumab 40mg eow (Genovese et al. 2007)	100	_3 TJC and _3 SJC	25.3	18.2	51	39	25	14
Adalimumab 40mg eow (Mease et al. 2005b)	313	_3 TJC and _3 SJC	23.9	14.3	62	52	36	20
Etanercept 25mg biw (Mease et al. 2000)	60	_3 TJC and _3 SJC	20 (median)	14 (median)	87	73	50	13
Etanercept 25mg biw (Mease et al. 2004)	205	_3 TJC and _3 SJC	20.4	15.9	72	59	38	11
Golimumab 50/100mg monthly (Kavanaugh et al. 2009b)	405	_3 TJC and _3 SJC	22.5	12	73/72	51/45	30/28	12/17
Infliximab 5mg/kg 8 weekly (Antoni et al. 2005b)	104	_5 TJC and _5 SJC	23.7	14.6	75	65	46	29
Infliximab 5mg/kg 8 weekly (Antoni et al. 2005a)	200	_5 TJC and _5 SJC	24.6	13.9	77	58	36	15

Etanercept

Etanercept was the first anti-TNF therapy to be tested in a randomised trial in patients with PsA. The first study was published in 2000 and included 60 patients with active PsA and psoriasis who were randomised to receive etanercept (25mg subcutaneous injections twice a week) or placebo. This showed an impressive response to treatment with 87% of etanercept-treated patients achieving a PsARC response compared with 23% of placebo-treated patients. There was also a significant improvement in patient-reported disability (as measured by the HAQ-DI) following treatment with etanercept and those patients with substantial skin psoriasis also showed a significant improvement in PASI scores. The safety profile seemed acceptable with no significant increase in adverse events (Mease et al. 2000). The major issue with this publication was the lack of a clear case definition for PsA. Patients all had psoriasis, but the high number of active joints at baseline (mean TJC 20, mean SJC 14) raised the concern that some of these patients may have RA with coexistant psoriasis (Marzo-Ortega et al. 2000; Taylor et al. 2000). Mease et al later stated that all recruiting doctors were aware of the Moll and Wright criteria (Moll and Wright 1973) and the Gladman modification (Gladman et al. 1987) to these (Marzo-Ortega et al. 2000; Taylor et al. 2000), but it has not been clearly stated that all patients fulfilled these criteria at study entry.

Following on from this phase II study, a larger phase III study involving 205 patients was published in 2004. In addition to confirming the articular and cutaneous response to etanercept, this study also evaluated its effect on joint damage. Radiographic disease progression at 12 months was halted by etanercept treatment (mean annualized rate of change in mTSS was -0.03 compared to +1.00 in the placebo group). Again etanercept was well tolerated with similar low rates of adverse events in both treatment and placebo groups (Mease et al. 2004). A follow-up of these patients, with an open label treatment extension, also confirmed the long term inhibition of joint damage. Patients treated with etanercept throughout the study showed no damage progression over the 2 year period. Patients initially treated with placebo developed progressive joint damage over the first year, but this damage was halted when they switched to open label etanercept (Mease et al. 2006).

Infliximab

Following on from successful trials of infliximab in the treatment of psoriasis, a phase II study of infliximab in PsA (Infliximab Multinational Psoriatic Arthritis Controlled Trial or IMPACT) was published in 2005. This recruited 104 patients with PsA who had double-blind placebo-controlled treatment for 14 weeks followed by an open label extension up to one year. The outcomes at 14 weeks showed a significant benefit with infliximab therapy in terms of ACR and PsARC responses, HAQ-DI, PASI scores, enthesitis and dactylitis (Antoni et al. 2005b). Again the case definition for PsA was not clarified ("established diagnosis of PsA of six months duration or longer"), but all patients were required to be RF negative. The outcome measures used for dactylitis and enthesitis were not stated in the paper and are not validated scoring systems.

Further analysis on this trial examined the effect of infliximab on radiographic progression. This showed a halt in radiographic progression with infliximab therapy over the 12 month treatment time, but there was no direct comparison with a placebo group as placebo patients had the option of switching to open label therapy at from 16 weeks. They estimated a projected annual rate of progression of 5.8 mS-vdH points per year by dividing the baseline xray score by the disease duration (Kavanaugh et al. 2006). This method may not be an accurate representation of the potential damage, without treatment, as there is no evidence that damage progression is linear in PsA.

Following on from the success of the IMPACT study, a larger phase III study (IMPACT 2) was performed. This recruited 200 patients with active PsA. Although specific classification criteria were not stated, all patients had to have "active plaque psoriasis" and "a negative test for RF in their serum", therefore they all would have met the Moll and Wright criteria (Moll and Wright 1973) and the later CASPAR criteria (Taylor et al. 2006). This study confirmed the efficacy of infliximab in terms of improving peripheral joint disease, skin psoriasis, dactylitis, enthesitis and physical and mental function (as measured by the short form 36 or SF-36) compared to placebo (Antoni et al. 2005a). Again the outcome measures for dactylitis and enthesitis were non-validated, using a simple count of dactylitic digits and an assessment of enthesitis only in the feet. This larger group also allowed a more thorough assessment of safety. The overall incidence of adverse events was similar in both groups, although a higher rate of liver function test abnormalities was seen in the infliximab group (Antoni et al. 2005a).

The analysis of joint damage for the IMPACT 2 study was more robust than the previous IMPACT study and used analysis of radiographs at baseline, week 24 (prior to cross-over) and week 54. These showed a significant reduction in radiographic damage in the infliximab group compared to placebo between baseline and week 24. This is despite the fact that nearly half of the placebo-treated patients actually entered an "early escape" arm at week 16 and will have received eight weeks treatment with infliximab at this timepoint (Antoni et al. 2005a). Repeat radiographs at week 54 showed continued inhibition of joint damage in the infliximab/infliximab group and no further damage in the placebo/infliximab crossover patients (van der Heijde et al. 2007).

Adalimumab

Adalimumab has also been tested in PsA following the publication of the above trials. The first study was a placebo-controlled RCT of 100 patients with active PsA. This study only included patients who had failed DMARD therapy, in comparison with other anti-TNF trials which usually include NSAID failures. The study did show a significant difference in favour of adalimumab, but the proportions of patients achieving PsARC and ACR outcomes was lower than in other anti-TNF trials (Genovese et al. 2007). The ADalimumab Effectiveness in Psoriatic arthritis Trial (ADEPT) was a 24 week double-blind placebo-controlled study of 315 patients with active PsA with an open label extension phase beyond week 24. Patients were required to have either active skin psoriasis or a documented history of psoriasis. A positive RF was not included in the exclusion criteria for the study, and around 10% of the patients did have a positive RF at baseline. However this paper did report the sub-type of PsA within their patient population, and around 25% of patients did have a typical asymmetrical oligoarthritis. A significant improvement with adalimumab was noted in peripheral joint disease, skin disease, HAQ-DI, SF-36 and fatigue scores. They also confirmed the inhibition of joint damage seen with anti-TNF treatment, showing a halt in radiographic progression as measured by the mS-vdH score. The safety profile of adalimumab was also similar to other anti-TNF therapies with similar numbers of adverse events in both groups, but a small increase in liver enzymes seen with adalimumab-treated patients (Mease et al. 2005b). Subsequent analyses, after week 48 and 144 of the open-label extension study, showed continued inhibition of disease activity and joint damage as well as sustained improvements in assessments of disability (Gladman et al. 2007c; Mease et al. 2009c).

Golimumab

Golimumab is a newer anti-TNF agent recently licensed for PsA. It is a human monoclonal antibody which can be given by IV infusion or by four weekly subcutaneous injection. A large phase III study (called GO-REVEAL) recruited 405 patients with active PsA to receive placebo or golimumab in doses of 50 or 100mg. All patients fulfilled the Moll and Wright and the CASPAR criteria as they had to have active skin psoriasis and a negative RF. Patients had active disease and were either NSAID or DMARD non-responders. Around half of the population were on concomitant methotrexate. At week 14, 48% of golimumab treated patients achieved an ACR20 compared to 9% of placebo treated patients ($p<0.001$). There was no statistical difference dependent on whether patients were taking methotrexate and there was no marked difference between the two golimumab doses. In addition to improvement in function and quality of life, there was also an improvement in enthesitis (measured at the MASES sites plus bilateral plantar fascia), the dactylitis score (measured by the IMPACT semi-quantitative scoring system), and the NAPSI score for nail psoriasis (Kavanaugh et al. 2009b).

Ongoing analysis from this study has shown impressive clinical responses up to week 104 (Kavanaugh et al. 2009c) and has confirmed a reduction in radiographic progression in the one year data for golimumab (Kavanaugh et al. 2009d). Additional analyses have investigated the effect of golimumab treatment in health economic terms showing benefit even in the short placebo-controlled phase of the GO-REVEAL study (Kavanaugh et al. 2009a).

Ustekinumab

Ustekinumab is a human monoclonal antibody that binds to the p40 subunit present on both human interleukin 12 and 23. It therefore prevents binding of these interleukins to the interleukin 12Rβ1 receptor blocking this signalling pathway. Studies in skin psoriasis have shown a significant response to ustekinumab (Papp et al. 2008), and therefore trials in PsA were conducted.

The phase II trial of ustekinumab in PsA recruited 146 patients to a double-blind crossover design randomised trial where they were randomised into two groups. Patients in the group one received weekly infusions of ustekinumab for four weeks only (weeks 0, 1, 2 and 3) and were then monitored for response. At week 12, patients “crossed over” to the other arm and group one then received placebo infusions. Group two were given four placebo infusions at weeks 0, 1, 2, and 3, but were then treated with two infusions of ustekinumab, given at week 12 and week 16 (Gottlieb et al. 2009).

At week 12, a greater proportion of patients in group one (who had received ustekinumab) achieved the ACR20, 50 and 70 response measures (table 10). Although all patients had to have skin psoriasis to enter the study, PASI responses were analysed for only those patients who had a BSA of at least 3%. PASI responses were also significant for both PASI75 and PASI90. The proportion meeting these response criteria peaked at weeks 12-16 and then showed a very gradual decline to week 36. At week 24, after the cross-over, patients in group two showed similar ACR20 responses following 2 doses of ustekinumab to those in group one.

Endpoint	Group 1 (ustekinumab)	Group 2 (placebo)	P value
ACR20 n (%)	32 (42%)	10 (14%)	0.0002
ACR50 n (%)	19 (25%)	5 (7%)	0.0038
ACR70 n (%)	8 (11%)	0 (0%)	0.0055
PASI75 n (%)	33/63 (52%)	3/55 (5%)	<0.0001

Table 10 – Results of ustekinumab study at week 12

In addition to these responses, improvement was also seen in patients with enthesitis (measured at the plantar fascia and Achilles tendons) and dactylitis (measured with a non-validated semi-quantitative 0-3 score). Significant improvement in function, as measured by the HAQ-DI, was also seen following treatment with ustekinumab. Ustekinumab also seemed to be well tolerated in this short study. Rates of adverse events and infections were similar in both groups, although it was noteworthy that three patients developed abnormal fasting blood glucose levels during the study (Gottlieb et al. 2009). This may be a reflection of the high rate of metabolic syndrome seen in patients with psoriasis and PsA but it does require further evaluation in larger prospective studies.

Phase III trials of ustekinumab are planned to further evaluate optimal dosing regimens and safety in PsA. This is the first biological drug to show efficacy in PsA that is not a TNF blocker. Although TNF blocking agents are remarkably effective in PsA, there is a subgroup of patients who seem to be resistant to these drugs or who lose efficacy over time. Newer therapies such as ustekinumab with different modes of action may help us to treat these patients with resistant disease. However as newer modes of action become available, research must help clinicians to evaluate which therapies should be used first-line and subsequently. From this study, it seems possible that ustekinumab may be less effective in treating PsA than the TNF blockers, however this is a small study and the populations in all of the individual RCTs differ significantly. At present, no head to head trials exist comparing biological therapies in PsA meaning that decisions about which therapies to use have a poor evidence base.

Abatacept

Abatacept (CTLA4Ig) is a selective T-cell co-stimulation modulator. A phase II study investigating its use in PsA has recently been presented. One-hundred and seventy patients with PsA and active skin psoriasis were recruited and randomised 1:1:1:1 to placebo, abatacept 3mg/kg, abatacept 10mg/kg or abatacept 30/10mg/kg. The final group received two loading doses of 30mg/kg abatacept followed by subsequent 10mg/kg doses for the rest of the study. The drug was well tolerated with only 17 discontinuations for inefficacy (n=7) or adverse events (n=10) by the six month timepoint. At six months, there was a significant difference in the proportion of patients achieving the ACR20 response in the two groups receiving 10mg/kg when compared to placebo (table 11). A lower response rate was seen in the 3mg group and this was not significantly higher than the placebo rate. When considering skin responses, both 3mg and 10mg/kg doses significantly improved psoriasis target lesion scores (Mease et al. 2009a).

Outcome	Placebo	Abatacept		
		3mg/kg	10mg/kg	30/10mg/kg
ACR20 (%)				
All patients (%)	19	33	48	42
No prev TNF (%)	20	35	56	48
Prev TNF (%)	17	31	31	36
Target lesion 50 (%)	17	36	33	30
Target lesion 75 (%)	10	29	10	16
Improvement in HAQ-DI (%)	19	36	45	35

Table 11 – Results of the abatacept in PsA trial at day 169

During sub-analysis, it was noted that patients who had previously been exposed to anti-TNF therapy had poorer response rates. This is clearly demonstrated in table 11 where ACR20 responses appear lower for this group. Investigators also used this as a reason to explain the relatively poorer responses in the 30/10mg/kg group as this group had a higher rate of prior TNF exposure (51% vs 29-36%) (Mease et al. 2009a). Although this is perhaps not surprising, it is disappointing, as it was hoped that drugs with a different mode of action would work in TNF resistant patients.

At present this trial has only been presented in abstract form and the full paper is not available. It is disappointing that the results given in the table above (taken from the published abstract) only include ACR20 as an arthritis response measures and do not include any results for higher response rates (ACR50 and 70). It appears, like ustekinumab, that the response rates seem lower than expected when compared to studies of TNF blockers. Further data from this study and larger future trials are necessary to characterise the response rate in more detail.

Apremilast

Apremilast is a new phosphodiesterase-4 (PD4) inhibitor which is orally active. The inhibition of PD4 causes suppression of multiple inflammatory cytokines including TNF. Studies in psoriasis showed moderate activity, similar in response rate to ciclosporin (Gottlieb et al. 2008). Phase II trials in PsA have now been completed. Although the response rates are significantly lower than those seen in a trial of anti-TNF therapy, it does show efficacy in arthritis (see table 12). There were significant differences in the proportions of people achieving ACR20 and ACR50 response rates when compared with placebo (Schett et al. 2009).

	Treatment Groups		
	Placebo	Apremilast 20mg BD	Apremilast 40mg OD
ACR20 (%)	11.8	43.5	35.8
ACR50 (%)	2.9	17.4	13.4
ACR70 (%)	1.5	5.8	7.5

Table 12 – 12 week results from the apremilast in PsA trial

2.4.2 Early treatment

For around 15 years, the concept of early treatment for RA has been considered and has become the established management plan for those newly diagnosed with RA. Multiple studies have shown that aggressive early treatment can improve outcome in the medium to long term. A meta-analysis, including six follow-up studies and six cohort studies, showed that early treatment with DMARDs resulted in a significant 33% reduction in long term radiographic damage when compared with a later initiation of treatment (Finckh et al. 2006). This has informed the concept of the "therapeutic window of opportunity" where treatment is more effective if given early in the course of disease. Following on from the data using traditional DMARDs, TNF blocking therapies have also been used in early interventional studies. These studies have shown a remarkable benefit with high rates of remission (Emery et al. 2008).

This concept has not previously been well investigated in PsA. The only equivalent paper concerning PsA, is a small unblinded study which was published by Scarpa et al in 2008. They enrolled a small cohort of 35 patients with a recent onset (<12 weeks) psoriatic oligoarthritis. Patients were randomised to either daily NSAIDs for three months followed by methotrexate treatment, or to a combination of NSAIDs and methotrexate from baseline. At three months, both groups showed a significant improvement compared to baseline, but the combination therapy group had a significantly greater improvement in their tender and swollen joint counts ($p<0.05$). Other parameters including CRP and ESR did not differentiate the two treatment groups. At six months, there was no significant difference between the groups in terms of joint counts, blood results or physician/patient global disease activity VAS. The authors concluded that methotrexate was only providing partial disease control, and recommended treatment with combination TNF blocking therapy and methotrexate (Scarpa et al. 2008b). However the dose of methotrexate given is not specified and the study was only of six months duration. Long term outcome in this small cohort is unknown.

An observational cohort study comparing RA and PsA found a surprisingly high frequency of remission using a modification of the ACR remission criteria for RA. These patients were treated with methotrexate or a methotrexate/CyA combination in the case of resistant disease. From 2003, infliximab and etanercept were also used in the case of non-response to methotrexate or multiple DMARDs. They found that 57/236 patients (24%) with PsA achieved remission (defined as low VAS scores, no active joints, CRP<0.5mg/dl, no dactylitis/enthesitis/inflammatory spinal pain). Although the frequency of remission was higher in those treated with

TNF blocking therapy (79.5% vs 20.4%, $p<0.001$), the duration of remission did not differ depending on treatment (Cantini et al. 2008).

To date, only one study, the RESPOND (REmicade Study in PsA patients Of methotrexate-Naïve Disease) trial, has investigated the use of early TNF blocking therapy in PsA. A cohort of 110 DMARD-naïve patients with polyarticular PsA (>5 active joints) of less than two years duration, were randomised to receive either methotrexate or a combination of methotrexate and infliximab. There was a significant improvement in all outcomes in favour of infliximab with an ACR20 response of 86% and an ACR70 response of 50% (see table 13). This study has also provided evidence for the benefit of methotrexate in early PsA with an ACR20 of 66.7% (Nasonov et al. 2009).

	Infliximab+ methotrexate	Methotrexate alone
Baseline		
TJC (mean)	21	20
SJC (mean)	5	4
CRP (mg/L)	29	25
DAS	5.16	5.07
PASI	8.27	11.62
Follow up		
ACR20 / 50 / 70 (%)	86 / 72 / 50	66.7 / 39.6 / 18.8
Good / Mod EULAR (%)	82.4 / 15.7	33.3 / 39.6
DAS28 response (reduction of 1.2) (%)	68.6	29.2
PASI 50 / 75 / 90 (%)	100 / 97 / 70.6	80 / 54 / 28.6

Table 13 – Results of the RESPOND trial

2.4.3 Tight control

In addition to early treatment with disease-modifying therapies, the concept of "tight control" has also revolutionised care in RA. Multiple studies have confirmed that sustained inflammation causes joint damage, and the aim of disease-modifying therapy in RA is to control inflammation and prevent such ongoing damage. The concept of tight control was introduced to RA by the TICORA study. This study randomised 111 patients with active RA to either standard care or intensive management. Intensive management involved monthly assessments and a protocol led treatment algorithm where therapy was escalated if the patient had a DAS score of >2.4 (moderate disease activity). Despite only using conventional DMARDs in established disease, the study was able to demonstrate a significant benefit in terms of reduction in clinical disease activity and radiographic progression for those treated in the intensive management arm. However, even in the intensive management group, significant progression in joint damage was seen over the 18 month study period (increase in total Sharp score 4.5) (Grigor et al. 2004).

Since this demonstration of "tight control", large numbers of studies in RA have adopted the use of DAS within a treatment protocol. The BeSt study, which compared four different treatment strategies in early RA also used a DAS44 of <2.4 as a target for treatment. Treatment adjustments were made every three months if this low level of disease activity was not achieved (Goekoop-Ruiterman et al. 2005).

Observational data in PsA has indicated that there is a similar link between inflammation and damage. Cohort studies have shown that number of active joints at baseline and follow up visits predicts long term joint damage in terms of both clinically assessed and radiographic joint damage (Gladman et al. 1987; Gladman and Farewell 1999; Bond et al. 2007). As in other inflammatory arthritides, remission is the ultimate goal of therapy in PsA and a definition proposed by Kavanaugh et al suggested that remission in PsA should be characterised by "a complete absence of disease activity, with no signs or symptoms of active disease" (Kavanaugh and Fransen 2006). However, this paper also recognised that remission was not only difficult to achieve and maintain, but that, in some patients, mild disease activity in one domain may be acceptable. Given this, they concluded that "near remission" or "low disease activity" could be an appropriate goal for individual patient's treatment (Kavanaugh and Fransen 2006).

The concept of "tight control" has never previously been investigated in PsA. The obvious limitation in designing such a study is that there is no measure of an acceptable disease state available for PsA that could be utilised instead of the DAS low disease activity state. Whilst DAS responses have been partially validated in polyarticular PsA (Fransen et al. 2006), the cut points for disease activity have never been investigated. Until such a measure exists, there is no objective target for treatment in such a study.

3 Validation of the CASPAR criteria in early disease

3.1 Introduction

The CASPAR criteria were developed as new classification criteria for PsA using a large cohort of patients with PsA and controls with other inflammatory arthritides. They include characteristic features of PsA and have been shown to have a high sensitivity and specificity in a population with established disease (Taylor et al. 2006).

The main limitation of the CASPAR criteria is that they have not been validated in early disease. Research done by the Toronto group found that the CASPAR criteria had a high sensitivity for identifying early disease within their PsA clinic population (Chandran et al. 2007b). However, this study only included patients referred to a specialist tertiary referral clinic; therefore there is a significant risk of overestimating the sensitivity of the criteria. Studies in Sweden and Italy have also investigated the sensitivity of the criteria in early PsA (D'Angelo et al. 2008; Lindqvist et al. 2008; D'Angelo et al. 2009), but as yet no studies have been completed with a control population to address the sensitivity and specificity of the CASPAR criteria in early disease. At present, they cannot currently be recommended for use in studies of early PsA for this reason. This study aimed to emulate the methodology of the original CASPAR study and to recruit both early PsA cases and controls with other inflammatory arthritides to allow calculation of the sensitivity and specificity of the criteria in this group.

The other key issue raised with the CASPAR criteria is the entry criteria that state that the patients must have “Inflammatory articular disease (joint, spine, or entheseal)”. Particularly in early PsA, the pattern of disease may be evolving and may be different from that of established disease. For that reason, an assessment of arthritis, enthesitis and axial involvement was included to investigate the pattern of disease in treatment-naive early arthritis patients.

3.2 Methods

3.2.1 Patient and control selection

Patients and controls were recruited from Early Arthritis Clinics and from new referrals to rheumatology clinics in four hospitals based in the Yorkshire region. Clinic attendees with a new diagnosis of PsA were enrolled in the study. For each case enrolled, the consecutive patient with new onset inflammatory arthritis was enrolled also. All cases and controls were required to have disease duration of less than 2 years (from onset of symptoms) and to be DMARD naive.

3.2.2 Data collection

Data were recorded on standardised proformas including demographics, date of onset of arthritis, duration of early morning stiffness, activity of arthritis, enthesitis and axial disease, and application of the CASPAR criteria. Activity of arthritis and enthesitis was assessed using clinical examination. All patients underwent a 66/68 swollen/tender joint count and assessment of entheses including those entheseal sites required for the LEI (Healy and Helliwell 2008), the MASES (Heuft-Dorenbosch et al. 2003) and sites used in the IMPACT and IMPACT2 clinical trials (bilateral Achilles tendon and plantar fascia) (Antoni et al. 2005a; Antoni et al. 2005b). Results of any relevant investigations were also recorded including presence or absence of periosteal new bone formation on radiographs and evidence of axial involvement identified by plain radiography or MRI.

3.2.3 Statistical methods

3.2.3.1 Power calculation

Figures for sensitivity and specificity for the CASPAR criteria in established disease are 0.91 and 0.99 respectively. Prior to the development of the CASPAR criteria, the Moll and Wright criteria have traditionally been used in both early and late disease and the figures for these criteria are 0.99 and 0.92 respectively. Assuming that in early case definition the emphasis is on specificity the null hypothesis is that the specificity for the CASPAR criteria will be equivalent to that for the Moll and Wright ($H_A = H_O$). The alternative hypothesis is that the specificity of CASPAR differs from that of Moll and Wright ($H_A > H_O$). From Obuchowski (Obuchowski 1998) the number of patients required to test the alternative (two tailed) hypothesis, with an alpha value of 0.05 and a beta of 0.20 is 111. Therefore 111 cases and 111 consecutive controls are required.

3.2.3.2 Results Analysis

Sensitivity and specificity of the CASPAR and Moll and Wright criteria were compared using McNemar's tests for paired variables. Receiver operator characteristic (ROC) curves were used to estimate the area under the curve (AUC) for both criteria and the optimal cut-point for the CASPAR criteria for the diagnosis of early PsA. Univariate and multivariate forward step-wise binary logistic regression was used to identify which features included in the CASPAR criteria were independently associated with PsA.

When considering patterns of arthritis, oligoarthritis was defined as less than 5 active joints and polyarthritis as 5 or more joints. Small joints were defined as temperomandibular joints, sternoclavicular joints, acromioclavicular joints, carpo-meta-carpal joints, MCP joints, PIP and DIP joints, MTP joints and IP joints of the toes (total 58 joints). Large joints were defined as the glenohumeral joints, elbows, hips, knees and ankle joints (total 10 joints). The symmetry number was calculated as the number of joints as symmetric pairs/total number of joints involved. Each joint pair (n=34) was assessed for symmetry individually. Symmetry was defined as a symmetry number of ≥0.5. Significance testing was performed using McNemar's tests for categorical variables and Mann-Whitney U tests for continuous variables.

3.3 Results

In total, 111 cases of early PsA and 111 controls with other forms of inflammatory arthritis were recruited to the study. The baseline features of these patients are shown in table 14.

The sensitivity of the CASPAR criteria (score ≥3) in classifying early PsA was 87.4% compared to 80.2% for the Moll and Wright criteria (p=0.008). The specificity for both criteria was 99.1%, with only 1 control patient fulfilling both criteria for PsA.

Using ROC analysis, the AUC for the CASPAR criteria was 0.991 compared to 0.896 for the Moll & Wright criteria. When considering different cut-points for the CASPAR criteria, the best cut-point for classification remained a score of ≥3 as in the original CASPAR analysis (table 15 and figure 3). Considering a score of ≥2 gave a higher sensitivity but resulted in a drop in specificity that would not be ideal for classification criteria.

	PsA Cases	Controls
Median age, years (IQ range)	44 (34-55)	52 (38-66)
Median disease duration, months (IQ range)	8 (5-14)	5 (3-9.25)
Consultant Diagnosis (n)		
Psoriatic arthritis	111	0
Rheumatoid arthritis	0	82
Undifferentiated arthritis	0	13
Spondyloarthritis	0	9
Inflammatory OA	0	4
Crystal arthritis	0	3
Percentage with		
Arthritis	100	99
Enthesitis	67	52
Axial Symptoms	5	1
Median early morning stiffness, minutes (IQ range)	60 (20-120)	60 (30-120)
% fulfilling Moll and Wright criteria for PsA	80	1
% fulfilling CASPAR criteria for PsA	87	1

Table 14 - baseline features of cases and controls recruited to the CASPAR study

Criteria	Score	Sensitivity	Specificity
Moll & Wright	Positive	80.2	99.1
CASPAR	≥1	100	42.3
	≥2	99.1	94.6
	≥3	87.4	99.1
	≥4	42.3	100
	≥5	15.3	100

Table 15 - ROC analysis of Moll & Wright and CASPAR criteria

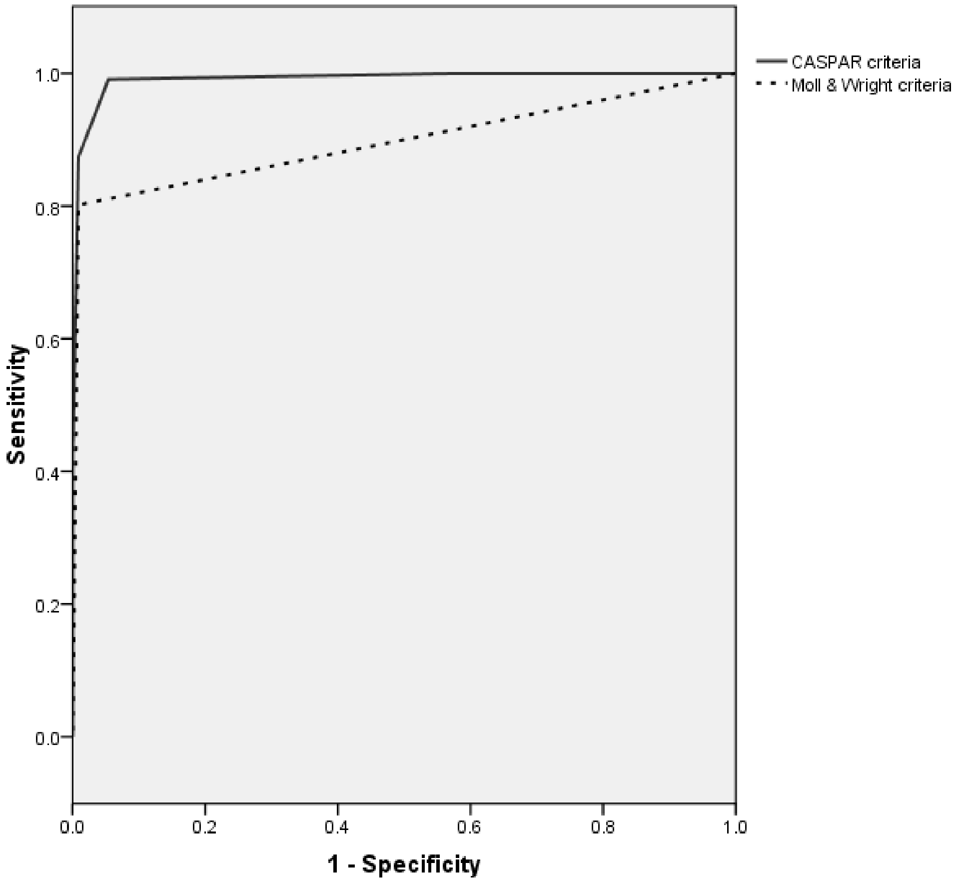

Figure 3 - ROC curve for CASPAR and Moll & Wright criteria predicting PsA diagnosis

When considering the individual components of the CASPAR criteria, 96.4% of cases had current, previous or a family history of psoriasis with 84% having current psoriasis. Dactylitis and nail psoriasis were highly discriminatory as only one control patient had dactylitis and another one had nail psoriasis. Univariate binary logistic regression analysis identified that all of the features of the CASPAR criteria, with the exception of radiographic new bone formation were significant in differentiating between PsA and controls. Multivariate forward step-wise logistic regression identified that current psoriasis, negative RF, nail psoriasis, family history of psoriasis and dactylitis were all associated with PsA. Table 16 shows in more detail what proportion of the patients fulfilled each individual aspect of the CASPAR criteria.

When considering the diagnosis of inflammatory articular disease (joint, spine or entheseal) required for the first aspect of the CASPAR criteria, there were some minor differences between the cases and controls. Nearly all patients had arthritis. Presence of enthesitis was significantly more frequent in the PsA patients compared to controls (67% vs 52%, p=0.029). There was a trend towards higher enthesitis counts in PsA cases compared to control patients but this was not significant (see table 17). Spondylitis appeared more frequent in the PsA patients but the difference was not significant due to small numbers (5% vs 1%, p=0.055).

	PsA Cases (%)	Controls (%)
Any psoriasis	96	12
Current psoriasis	84	4
Previous psoriasis	6	1
Family history of psoriasis	18	8
Nail psoriasis	38	1
Negative RF	96	47
Current or previous dactylitis	28	1
Xray evidence of new bone formation	2	0

Table 16 - Proportion of cases and control fulfilling each aspect of the CASPAR criteria

	Cases (n=111)	Controls (n=111)	RA controls (n=82)
Proportion with arthritis (%)	100	99	100
Oligoarthritis	30	24	15
Polyarthritis	70	76	85
Median TJC (IQ range)	7 (13)	8 (15)	12 (16)
Median SJC (IQ range)	5 (7)	5 (9)	7 (11)
Median active joint count (IQ range)	9 (13)	10 (15)	12.5 (16.25)
Proportion with enthesitis (%)	67	52	52
Median enthesitis count (IQ range)	2 (4)	1 (3)	1 (4)
Proportion with spondylitis (%)	5	1	0

Table 17 – disease patterns in cases, controls and RA controls

Further analysis examined the pattern of arthritis seen in PsA and other inflammatory arthritides (Table 18). The average tender and swollen joint counts and the proportions of people with oligoarticular and polyarticular disease did not differ significantly between cases and controls. When comparing PsA cases to only controls with RA (n=82), PsA cases had significantly lower joint counts ($p<0.008$).

The higher number of joints involved in RA when compared to PsA was principally due to an increased number of small joints involved. In PsA cases, there were a similar proportion of patients with predominantly large and predominantly small joint disease. However in RA controls, over 60% had predominantly small joint disease. There was no significant difference seen in large vs small joint arthritis when comparing PsA cases to all controls, or when comparing PsA patients with RA controls. Specifically in small joint arthritis, DIP joint involvement was significantly more common in PsA cases than controls (32% vs 16%, $p=0.007$).

A symmetry number of ≥ 0.5 defines symmetrical disease. The symmetry number was significantly higher in controls than PsA cases ($p=0.003$) and this difference was even more pronounced when comparing RA controls with PsA ($p<0.0001$). The remaining control patients had a lower median symmetry number but this was not significant to PsA cases (0.27 vs 0.5, $p=0.58$). Analysing this in another way, when comparing the proportion of patients with symmetrical disease, the controls, particularly those with RA, had a higher proportion of symmetrical disease when compared to PsA. Comparing PsA to all controls, there was no significant difference in the proportion with symmetrical disease ($p=0.11$), however when comparing PsA to RA controls, there was a significant difference ($p=0.001$).

	Cases (n=111)	Controls (n=111)	RA controls (n=82)
Predominantly small joint arthritis, N (%)	59 (54)	59 (54)	50 (62)
Predominantly large joint arthritis, N (%)	51 (46)	50 (45)	31 (38)
Median no of small joints involved N (% of total)	7 (12)	9 (16)	11.5 (20)
Median no of large joints involved N (% of total)	1 (10)	1 (10)	1.5 (15)
DIP involvement, N (%)	35 (32)	18 (16)	15 (18)
Median Symmetry Number (IQ range)	0.5 (0.78)	0.67 (0.54)	0.73 (0.39)
Symmetrical disease, N (%)	58 (52)	72 (65)	62 (76)

Table 18 – Patterns of arthritis in cases, controls and RA controls

3.4 Discussion

These data confirm that the CASPAR criteria have greater sensitivity compared to the Moll and Wright criteria in the identification of early PsA. The most important difference between the two criteria is that the CASPAR criteria allow a diagnosis of PsA to be made in patients without skin psoriasis. These criteria utilise additional features such as dactylitis, nail psoriasis and positive family history to increases the sensitivity of the CASPAR criteria. This is particularly relevant in early disease when not all features of PsA may have manifest. In particular, 20% of people presenting with PsA do not have skin psoriasis, therefore excluding them from a diagnosis using the Moll and Wright criteria. All patients who fulfil the Moll and Wright criteria with a negative RF will also fulfil CASPAR so there is significant overlap between the two criteria.

In comparison with established disease, sensitivity remains slightly lower. A short duration of disease means that many patients will not yet have experienced all of the typical features of PsA that they may develop during the course of their disease. In particular, there is a much lower incidence of typical radiographic changes that can be identified in early patients. The vast majority of patients with new onset of inflammatory arthritis have normal radiographic appearances at presentation. This problem has been identified in previous early PsA cohorts where little new bone formation could be identified (D'Angelo et al. 2009).

When considering the pattern of inflammatory articular disease, there was a higher proportion of patients with active enthesitis in PsA cases compared to controls. There were also more patients in the PsA group who had axial disease, although this difference was not significant due to small numbers affected in both groups. Patterns of arthritis showed that PsA patients have a lower total number of joints involved compared to RA controls and this difference was principally explained by a higher number of small joints involved in RA patients, confirming the identification of RA as a predominantly small joint polyarthropathy. Symmetrical joint disease was less common in PsA patients compared RA controls, and there was a significant difference in symmetry number between the patient groups.

3.5 Limitations

The most significant limitation of this study relates to the selection of the cases. Cases were recruited only if they had a consultant diagnosis of PsA and few patients presenting with undifferentiated arthritis were included in this study. This may be less important when considering the use of the CASPAR criteria as classification criteria, as originally intended. The results of this study support their use as inclusion criteria for future research studies with recent onset PsA. However these data will result in an overestimate of the sensitivity of the criteria if considering their use as a diagnostic tool in a general early arthritis clinic population.

In this circumstance, the CASPAR criteria remain superior to the Moll and Wright criteria because they allow other characteristic features of the disease to identify PsA in patients without psoriasis. However they still do not account for patients who initially present as undifferentiated arthritis and later evolve into a typical psoriatic phenotype. Patients who are unaware of their family history of psoriasis or who may have had dactylitis, but not had this confirmed by a specialist may be left undiagnosed using these criteria.

The other limitation is the identification of ideal controls. Again, controls are more likely to have a certain diagnosis, such as RA, and undifferentiated arthritis patients were not seen in significant numbers. There is also a difficulty in identifying controls with axial SpA who were eligible for this study, as patients were required to have a disease duration of less than two years. A significant number of cases with axial disease present to rheumatology with over two years symptom duration, thus making them ineligible.

Future research ideally should apply these criteria routinely to all new rheumatology referrals within an early arthritis or similar clinic. They should be recorded at presentation and then long term follow up must be completed to ensure that patients are accurately classified as PsA or controls. This is particularly crucial in the undifferentiated arthritis cohort where additional diagnostic tools are required to predict what type of arthritis may develop.

3.6 Conclusion

This work supports the use of the CASPAR criteria as classification criteria for future research in early PsA. Although the sensitivity is slightly lower than that in established disease, the specificity is reassuring. Their use as diagnostic criteria in cases where diagnosis is unclear cannot be recommended based on this study, but future work evaluating their use in an unselected early arthritis clinic population would address this issue.

Different clinical phenotypes cannot be relied upon in isolation to identify early PsA, but different patterns are seen in PsA patients compared to other inflammatory arthritides. Enthesitis and DIP joint involvement are more frequent in early PsA compared to other forms of inflammatory arthritis, however a significant proportion of controls (including a significant proportion of patients with RA) also have enthesitis. Spondylitis is likely to be more frequent in PsA than in RA, however it cannot be relied upon to differentiate from other forms of inflammatory arthritis. Patterns of arthritis confirm the typical view that RA is a symmetrical small joint predominant polyarthropathy, whereas patients with PsA generally present with fewer joints involved, particularly small joints, and, as a consequence, with less symmetrical disease (Helliwell et al. 2000).

4 Imaging in Early Psoriatic Arthritis – the extent of sub-clinical disease

4.1 Introduction

Since the seminal works of Moll and Wright (Moll and Wright 1973), it has been customary to divide patients with PsA into those with polyarticular and oligoarticular disease. Research has shown that the number of active joints at presentation influences the long term outcome of these patients (Gladman et al. 1987), and therefore this subdivision may have prognostic value. Traditionally, assessment of joint involvement has been done clinically using tender and swollen joint counts. However, research in mixed oligoarthritis cohorts has shown that a significant proportion of patients have subclinical joint involvement, identifiable on US, that would result in their re-classification from oligoarthritis to polyarthritis (Wakefield et al. 2004).

US has been validated in PsA as a method for assessing joint inflammation. Two studies have compared US with other imaging modalities in PsA. The first imaged 13 patients with established PsA using US, MRI, radiography and scintigraphy in addition to clinical assessments (Weiner et al. 2008). This showed a sensitivity of 40% and specificity of 91% for joint erosions when compared to conventional radiography. When assessing joint inflammation, MRI was used as the gold standard. US showed a sensitivity of 48% and a specificity of 91% for the detection of joint inflammation. Unfortunately, this study used only GS or B-mode US and did not utilise PD.

A second study imaged 15 PsA patients in addition to 5 RA patients and 5 healthy controls for comparison. This study used both GS and PD US giving an optimal assessment of this technique. US and MRI showed good agreement in the assessment of bony changes (absolute agreement 85-100%) and synovitis (absolute agreement 73-100%) but with variable kappa statistics. When looking at sensitivity and specificity in this study, MRI was used as the gold standard for both bone changes and inflammatory changes. US showed good sensitivity and specificity for synovitis (sensitivity 40-70%, specificity 87-88%) as well as high specificity for bone erosions (88-99%). However there was lower sensitivity of US for erosions (0-57%) (Wiell et al. 2007).

Little research is available in PsA comparing clinical and imaging findings. Of the 80 patients imaged in the previous paper investigating sub-clinical arthritis in oligoarthritis, only 6 had a clinical diagnosis of PsA (Wakefield et al. 2004). One of the validation studies discussed above compared imaging and clinical examination but only in 13 cases. They found that 17% of joints showed US abnormalities despite being clinically normal (Weiner et al. 2008). However this study did not use PD which may have affected the specificity of the US findings. Further data in larger cohorts is required to improve our understanding of the relationship between clinical examination and US in early PsA.

No longitudinal studies exist in PsA or oligoarthritis to establish the significance of this sub-clinical synovitis. However studies following patients with RA who were considered to be in remission (i.e. with low numbers of active joints) have shown that sub-clinical US evidence of PD inflammation correlates significantly with progressive radiographic damage after 12 months of follow up (Brown et al. 2006).

In addition to evidence of sub-clinical arthritis, there are many papers identifying the presence of significant levels of sub-clinical enthesitis in patients with established PsA and other SpA which is detectable by US (D'Agostino et al. 2003). Some theories of pathogenesis in PsA have postulated that inflammation starts at the enthesis in early SpA and PsA patients before spreading to the joint (McGonagle et al. 1999). This suggests that there is an entheseal initiation of disease, meaning that scanning patients with early disease could be crucial in identifying early sub-clinical inflammation that is yet to spread to the joints to create further synovitis. Unfortunately the majority of previous studies with PsA and SpA patients have recruited patients with established disease.

One study has looked at enthesitis using US and bone scintigraphy imaging of patients with early PsA (Scarpa et al. 2008a). It confirmed the existence of both sub-clinical arthritis and enthesitis on bone scintigraphy and then used US in these areas to confirm their findings. All patients had ultrasonography on the joints and entheses that showed increased tracer uptake on scintigraphy (both those that were clinically involved and those that were not clinically involved) and on two control joints with normal clinical examination and normal tracer uptake. It reported that US showed some abnormal changes in all articular and entheseal sites identified on scintigraphy. Only 2 of the 94 control joints that were examined with US showed any degree of joint involvement. In 71% of the clinically involved joints there was evidence of PD but in the “sub-clinically” involved joints, they did not find any evidence of PD in the areas of tracer uptake. Thus there is some doubt cast over whether this truly represents “sub-clinical inflammation” where both GS and PD US signal would be expected, or whether some of these changes could be either mechanical or within normal physiological limits. Other studies comparing scintigraphy and US showed a similar lack of agreement on the presence of synovitis where tracer uptake can be found at a site with normal US assessment and where joints with no tracer uptake had evidence of synovitis on US (Weiner et al. 2008).

4.2 Methods

Patients with new onset PsA, according to the CASPAR criteria (Taylor et al. 2006), were recruited. They were all required to be DMARD naïve and have a disease duration of less than 2 years. All patients had active disease (defined as ≥1 active joint, active entheseal site or BASDAI >4 for axial disease). All patients had a clinical assessment including a 66/68 swollen/tender joint count and assessment of entheses including those entheseal sites required for the LEI (Healy and Helliwell 2008), the MASES (Heuft-Dorenbosch et al. 2003) and sites used in the IMPACT and IMPACT2 clinical trials (bilateral Achilles tendon and plantar fascia) (Antoni et al. 2005a; Antoni et al. 2005b). In addition to this, dactylitis was assessed using a simple dactylitic digit count and the LDI (Helliwell et al. 2005).

4.2.1 Ultrasound

US was performed using a Philips HDI 5000 machine with a 12-5 or 13-7 MHz probe as appropriate. For PD scanning a medium wall filter was applied. All scans were performed by a rheumatologist experienced in musculoskeletal US (Dr J E Freeston). Gel was applied to the skin to provide an acoustic interface.

All patients underwent GS and PD US of the most symptomatic hand and wrist (11 joints per patient) and additional target joints that the patients identified as symptomatic. The digits of the 4 fingers on this hand were also scanned for FT (defined as presence of GS and/or PD). GS and PD were scored separately on a 0-3 semi-quantitative scale for each joint imaged. A GS score of ≥2 and/or a PD score >0 were used to identify US active joints.

All patients underwent GS and PD US of bilateral lateral epicondyles of the elbow, Achilles tendons and plantar fascia. GS and PD were scored separately on a 0-3 semi-quantitative scale for each enthesis imaged. A GS score of ≥2 and/or a PD score >0 were used to identify active US enthesitis.

4.2.2 Statistical analysis

Joints, entheses and digits were all considered individually to compare clinical and imaging assessment of arthritis, enthesitis and dactylitis. A prevalence and bias adjusted Kappa (PABAK) was used to compare agreement for clinical and US assessment of active disease. This statistic adjusts the raw kappa value for differences in prevalence and bias. This is particularly relevant when the distributions of positive and negative results are not equally split in the population.

4.3 Results

40 patients (18 male, 22 female) with new onset, DMARD naive PsA were recruited. Their average age was 47 years (range 19-71 years) and they had a median disease duration of 10 months (IQ range 5-15 months). All of the patients were negative for RF and anti-CCP tests. On clinical examination, they were found to have a mean of 10.7 tender joints and 6.2 swollen joints. Nineteen patients were classified as having oligoarthritis (<5 active joints on clinical examination) and 21 were classified as having polyarticular disease.

When considering joint inflammation at the patient level, only one of the 19 oligoarthritic patients had 5 or more involved joints on US and was therefore re-classified from oligoarticular to polyarticular.

When considering each joint individually, a total of 431 joints were assessed by both clinical and US examination. Of these joints, 68.9% had imaging findings consistent with their clinical examination (table 19). A substantial agreement (Kappa =0.36, PABAK =0.38) was identified between clinical assessment of activity (tender and/or swollen) and imaging assessment of activity. The agreement over active joints was 60.1% whereas the agreement over inactive joints was 74.5%. Clinical examination rarely over-estimated activity, particularly the SJC where 95/100 swollen joints show imaging activity. However, subclinical disease was present with 93 clinically inactive joints scanned showing significant imaging findings.

Dactylitis was less common with only 10 patients having dactylitis in the fingers or toes. Those who had dactylitis had an average of two digits involved. A total of 160 digits (fingers only) were examined for clinical dactylitis and FT on US. Of these, 88% had consistent findings (two digits were clinically dactylitic with FT on US). FT was found in an additional 20 digits (13%) that were not clinically considered to be dactylitic.

	US active	US inactive	Total
CE active	101 (23%)	41 (10%)	142
CE inactive	93 (22%)	196 (45%)	289
Total	194	237	431

Table 19 - Comparison of clinical and US assessment of disease activity by individual joint (CE=clinical examination, US=ultrasound).

Clinically, enthesitis was common with 31/40 patients having clinical evidence of tender enthesitis using any of the clinical tools discussed above, and an average of three sites involved per patient. Considering the bilateral lateral epicondyles of the elbow, Achilles tendons and plantar fascia which were examined by both clinical examination and US, 34/202 entheses were found to be tender, but none were clinically swollen. Using combined GS and PD, 14/202 had active enthesitis on US. Of all entheses examined, 85% had imaging findings consistent with clinical examination. A substantial correlation (PABAK = 0.70) was identified between clinical assessment of activity (tender enthesis) and imaging assessment of activity (see table 20).

In this early cohort, there was little evidence of sub-clinical enthesitis with only 2% (5/202) of non-tender entheses showing significant US changes. All of the 5 non-tender, US active entheses were in the lower limb, and there was no sub-clinical disease seen at the lateral epicondyles. However, clinical examination over-estimated activity in 12% of entheses. Of the 25 tender but US inactive entheses, 7 were adjacent to clinically tender joints. Bony erosion was only present in 8 of 202 entheses.

Type of assessment	US active	US inactive	Total
Tender	9 (4%)	25 (12%)	34
Non-tender	5 (2%)	163 (81%)	168
Total	14	188	202

Table 20 – Comparison of clinical and US assessment of disease activity by individual entheses

4.4 Discussion

When comparing US and clinical examination of arthritis at the patient level in this cohort, there was only one patient identified who was clinically diagnosed as having oligoarthritis which was reclassified as polyarthritis following US assessment. The other nineteen patients with oligoarthritis did not have evidence of significant sub-clinical arthritis that would result in their reclassification. This is in contrast to previous research in oligoarthritis cohorts (Wakefield et al. 2004). This may be due to the fact that previous research has looked at undifferentiated oligoarthritis rather than concentrating on one particular subtype. These previous cohorts of undifferentiated oligoarthritis may have evolved to other forms of arthritis, including even RA which was undiagnosed at the time. There is also the issue of clinical skill effect. All of these patients underwent clinical examination as part of a research procedure by two examiners experienced in PsA. In this setting, it is possible that more involvement is identified clinically when enough time is available for assessment and examiners are experienced in performing full joint counts.

Considering arthritis at the joint level, there was reasonable correlation between US and clinical examination particularly when compared to previous research in other inflammatory arthritides. However, subclinical arthritis was identified using PD US, particularly in patients with multiple joints involved clinically. This is in keeping with previous research showing a higher sensitivity of US to detect clinical synovitis.

When considering enthesitis, there was surprisingly little evidence of enthesitis in this early PsA cohort. Considering stated hypotheses that PsA originates in the enthesis and then spreads to the joint, it is surprising that only 9 of 202 entheses assessed had evidence of US enthesitis. This is certainly a very different picture to that seen in established disease where significant US abnormalities are identified in PsA and SpA cohorts (D'Agostino et al. 2003). This may reflect the difference between early and established disease patterns and it may also be explained partially by an increase in entheseal abnormalities with increasing age. All of the non-tender entheses with US changes were in the lower limb where mechanical factors are likely to be a larger issue. No subclinical enthesitis was identified at the elbow. The data seem to suggest an overestimate of enthesitis using clinical examination with a number of tender entheses showing no US abnormality. This may represent disease not identified by US (such as bone oedema) or the tenderness identified may be related to other pathologies such as fibromyalgia.

4.5 Limitations

This study represents a step forward in assessing a more homogeneous cohort of patients, all with PsA and all with less than 2 years disease duration. This allows us to look in detail at the presentation of these patients. However due to time limitations, US examination was not complete for all joints and entheses. It therefore raises the possibility that some subclinical disease could have been missed. Ideally all patients should have had US assessment of all of their joints and entheses, but this would be extremely time-consuming for both ultrasonographer and patient.

All patients were required to have active disease and be DMARD naive. A selection bias therefore exists in this cohort where patients with borderline or very little disease activity were not included. The characteristics of this cohort also define how this data can be extrapolated. All of these patients were off treatment with active disease. Therefore such data cannot be extrapolated to patients on treatment. Ideally, a similar study needs to be repeated, to scan patients on treatment, particularly those whose disease control is thought to be adequate to identify if subclinical disease is an important issue in such a cohort. If significant subclinical disease is identified, then longitudinal data will be required to assess the long term implications of such findings.

4.6 Conclusion

In early PsA there is a significant correlation between clinical examination and US of joints and entheses. Around one-fifth of joints have subclinical synovitis which can be detected on US using PD and this is more common in those with clinically-identified polyarticular joint involvement. Enthesitis was not identified in the majority of patients; indeed clinical examination seemed to overestimate the involvement of these structures. Further research is required to address whether this sub-clinical synovitis persists in patients once they are started on therapy and whether this has any prognostic implications.

5 **Defining Minimal Disease Activity in PsA – a proposed objective target**

5.1 Introduction

The conceptual definition of MDA was agreed at the OMERACT 6 conference as “that state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations” (Wells et al. 2005). MDA encompasses both remission and “low disease activity” as acceptable targets for therapy.

Any criteria for disease activity in PsA must assess many aspects of this complex disease and a core set of measures for future PsA research was agreed at OMERACT 8 in 2006. The six core measures agreed were peripheral joint activity, skin activity, patient’s assessment of pain, patient’s assessment of global disease activity, physical function and HRQOL (Gladman et al. 2007d). Other important domains included spinal disease, dactylitis, enthesitis, fatigue, nail disease, radiography, physician global assessment and acute-phase reactants (Gladman et al. 2007d). Using these core and important measures, this study was designed to develop criteria for MDA in PsA, using expert opinion on real-life cases.

5.2 Methods

5.2.1 Domains to be included

Firstly, a decision was taken on which aspects of the PsA disease spectrum needed to be included to create the MDA definition. Ideally, any criteria need to contain the minimum of measurements (to allow feasibility) but must incorporate measures of all of the important aspects of the disease. The starting point was the OMERACT agreed core set of domains for PsA (as above). Analysis of PsA cases with a low disease activity (defined as physician global disease activity VAS of <3) showed large variation in HRQOL (measured by the Psoriatic arthritis Quality Of Life scale or PsQOL). HRQOL was excluded because of concerns that it may be unrelated to disease activity and unduly influenced by external factors.

As recommended by OMERACT, peripheral joint activity was measured using the 68 tender/66 swollen joint count. Skin activity was initially planned to be represented by a PASI score as this is the most commonly used outcome measure for psoriasis. However, concern was raised by key dermatologists within GRAPPA that the PASI was not representative in patients with low psoriasis disease activity, in particular with a PASI of <10. Therefore both PASI and BSA were included. The aim of this was to allow physicians to use either PASI or BSA depending on their personal preference, and to provide a maximum cut-off level for each. Pain and patient’s global assessment were measured using 100mm VAS scales, and the HAQ-DI was used as a measure of physical function.

Next, the five domains of PsA, peripheral joint disease, skin, enthesitis, dactylitis and axial disease, were considered to see how they would be represented by these core measures. Peripheral joint and skin activity were included, but there was no specific measure of dactylitis, enthesitis or spinal disease. The concern was that activity in any of these domains would not be recognised by the MDA criteria, allowing a person to be incorrectly classified as being in MDA. Minimising the likelihood of false positives is particularly important in this exercise to ensure that patients with active disease are not undertreated. Dactylitis is identified as part of a peripheral joint count, where dactylitic digits will result in a quantifiable tender and/or swollen joint count. Therefore further measurement was not felt necessary.

Enthesitis was felt to be an important measure that may not be accurately identified using any of the other core measures. Therefore a decision was made to include an enthesitis count. Multiple enthesitis outcome measures have been proposed for clinical research, some “borrowed” from AS and other SpA research, but there is no clear optimal measure for use in PsA. Therefore, the design of the MDA criteria did not specify a certain enthesitis outcome measure but was designed to be used with any of the commonly used enthesitis scores in PsA. As such, a raw enthesitis count was included with a maximum value of 13 representing the maximum score of these commonly used measures (IMPACT – 4, LEI – 6, MASES – 13). This allows the criteria to be used with any of the enthesitis outcome measures.

Spinal disease is particularly under-researched in PsA and no validated disease activity measures are available. The BASDAI has been evaluated in PsA and was not shown to correlate with doctor’s perception of disease activity or with treatment decisions (Taylor and Harrison 2004). Interestingly, it was found to correlate highly with the patient’s global disease activity VAS in both axial and peripheral joint disease, which is a core set measure in PsA and was already planned to be included in the profiles. Given the lack of outcome measures available, no specific measurement of axial disease activity was included. It was felt that active axial disease would be identified by the patient’s assessment of pain, global disease activity and physical function.

5.2.2 Materials

A questionnaire was compiled consisting of 40 PsA patient profiles, using measures agreed above (TJC: 0-68, SJC: 0-66, enthesitis count: 0-13, PASI: 0-72, BSA: 0-100, patient VAS pain: 0-100, patient VAS global disease activity: 0-100 and HAQ-DI: 0-3). The profiles were created using data from real patients with PsA selected from a prospective longitudinal database. The profiles included a full range of disease activity but with additional patients with low disease activity (based on physician's assessment). The questionnaire included the OMERACT definition of MDA and the instructions stated "this patient comes to see you in clinic. He/she has been on a stable dose of disease modifying anti-rheumatic drug (DMARD) therapy for over 6 months." They were then asked "Do you consider this patient to be in a 'minimal disease activity' state?". This was then circulated to rheumatologists and dermatologists with an interest in PsA, identified through the GRAPPA membership.

5.2.3 Statistical methods

Summary statistics were calculated for different levels of consensus (>90%, >80% and >70%). Providing there were no major differences between these values, the >70% agreement would be used to maximise the number of cases for further analysis. Assuming this is the case, if ≥70% of respondents classified the profile as MDA, then it was taken to correspond to a patient in MDA, the other profiles were not. Summary statistics for each outcome measure, using the profiles agreed to be in MDA, were calculated including mean, rounded mean, upper 95% confidence interval (CI), rounded upper 95% CI and maximum. These were investigated as potential cutpoints to define a maximum value for each of the outcome measures. Then the number of outcome measure results that must not exceed this cutpoint for the patient to be considered as in a MDA state was investigated. There were 7 measures creating 7 variations on the number of cutpoints that must be met. This created 35 possible definitions for MDA when each of the five possible cutpoints were combined with the 7 variations in the number of cutpoints to be met. For each definition, sensitivity and specificity was calculated using receiver operating curves. From these, the best definition was selected.

5.3 Results

A total of 60 respondents (82% rheumatology, 18% dermatology background) completed the questionnaire. Nearly all were physicians, but one was a rheumatology specialist nurse with an interest in PsA. There was substantial consensus between the experts who completed the questionnaire on the profiles that represented MDA. There was a ≥90%, ≥80% and ≥70% agreement that 7, 10 and 13 profiles, respectively, were in MDA. Summary statistics are shown for each of these levels of agreement and show little variation (table 21).

In view of this, the 70% consensus was used to maximise the number of cases. Therefore 13 cases were taken as being in MDA, and the other 27 cases were considered not to be in MDA. Using these 13 cases, 5 cutpoints were calculated for each core measure (table 22). Application of these cutpoints with 7 variations depending on the number of cutpoints achieved yielded 35 definitions which were tested using receiver operating curves. ROC curves showed high sensitivity and specificity and an AUC ≥0.895 for all definitions (figure 4).

The maximum value, rounded mean and rounded upper 95% CI were felt to be more practical for use in a criteria as they were integers and were therefore considered preferentially. The definition based on achieving 7/7 of the maximum tolerated values had the best combination of sensitivity and specificity (100% for both) and the highest area under the curve (AUC =1). However these maximums included outlying values (in particular, patient global disease activity VAS 87 and enthesitis 6) that were felt to be unrepresentative of minimal disease activity. The best criteria using the rounded mean cutpoint (AUC 0.946) was with 5/7 criteria met (sensitivity 92%, specificity 89%, AUC 0.946). Two possible criteria using the rounded 95% CI (AUC 0.974) were identified with 5/7 criteria met (sensitivity 100%, specificity 82%) and 6/7 criteria met (sensitivity 85%, specificity 96%).

	TJC	SJC	PASI	BSA	Pain VAS	Global VAS	HAQ-DI	Enthesitis
>70% agreement (n=13)								
Mean (SD)	0.46 (0.88)	0.31 (0.48)	0.55 (0.70)	2.08 (2.93)	14.3 (8.53)	23.5 (23.0)	0.36 (0.31)	0.46 (1.66)
95% CI	-0.07, 0.99	0.02, 0.60	0.13, 0.98	0.31, 3.85	9.11, 19.4	9.57, 37.4	0.17, 0.54	-0.54, 1.47
Min, max	0, 3	0, 1	0, 1.7	0, 8	0, 28	0, 87	0, 1.13	0, 6
>80% agreement (n=10)								
Mean (SD)	0.10 (0.32)	0.10 (0.32)	0.46 (0.69)	1.60 (2.76)	14.9 (9.60)	25.7 (25.8)	0.40 (0.34)	0 (0)
95% CI	-0.13, 0.33	-0.13, 0.33	-0.03, 0.95	-0.37, 3.57	8.04, 21.8	7.27, 44.1	0.16, 0.64	n/a
Min, max	0, 1	0, 1	0, 1.7	0, 8	0, 28	0, 87	0, 1.13	0, 0
>90% agreement (n=7)								
Mean (SD)	0 (0)	0 (0)	0.41 (0.61)	2.00 (3.21)	11.1 (8.41)	14.6 (13.0)	0.29 (0.26)	0 (0)
95% CI	n/a	n/a	-0.15, 0.98	-0.97, 4.97	3.29 (18.9)	2.55 (26.6)	0.05 (0.52)	n/a
Min, max	0, 0	0, 0	0, 1.3	0, 8	0, 20	0, 39	0, 0.75	0, 0

Table 21 - Average value for each outcome measure for profiles designated as MDA by different levels of agreement by respondents

	TJC	SJC	PASI	BSA	VAS pain	VAS global	HAQ-DI	Enthesitis
mean	0.462	0.308	0.554	2.08	14.3	23.5	0.356	0.462
rounded mean	1	1	1	3	15	25	0.5	1
95% CI	0.992	0.598	0.975	3.85	19.4	37.4	0.541	1.47
rounded 95% CI	1	1	1	4	20	40	0.75	2
maximum	3	1	1.7	8	28	87	1.13	6

Table 22 - Possible cut points of each outcome measure for the different potential definitions of MDA

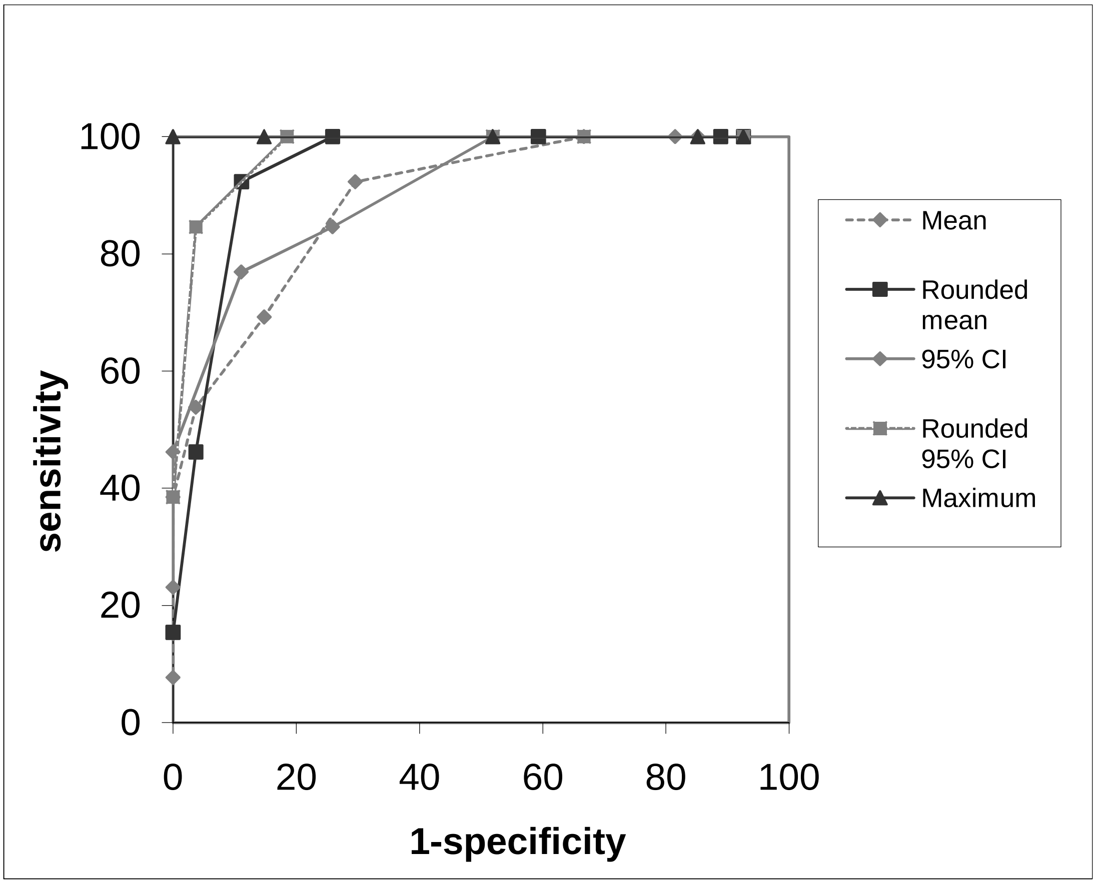

Figure 4 - ROC curve for candidate definitions of minimal disease activity

When considering these three candidate definitions, thought was given to the ideal characteristics of the criteria. When balancing sensitivity and specificity, it was felt that specificity was of more importance. This is because it would be preferable to miss a few patients who were truly in MDA, than to misclassify patients with significant disease activity into an MDA group where they may potentially be undertreated. Therefore the definition based on meeting 5/7 of the cutpoints based on the upper 95% CI was discarded as it had a lower specificity.

The final decision was between using the rounded mean cutpoint with 5/7 criteria met (sensitivity 92%, specificity 89%) or the rounded 95% CI with 6/7 criteria met (sensitivity 85%, specificity 96%). Again, there was concern that one of the rounded 95% CI cutpoints may be too high to truly represent MDA (global disease activity VAS 40) and so the final definition selected used the rounded mean values.

Therefore, a core set definition places patients with PsA in MDA when they meet 5 of 7 of the following criteria

- TJC ≤1
- SJC ≤1
- PASI ≤1 or BSA ≤3
- patient pain VAS ≤15
- patient global activity VAS ≤20
- HAQ-DI ≤0.5
- tender entheseal points ≤1

5.4 Discussion

The aim of this study was to produce clinical criteria for MDA in PsA, and it provides the first measure of state in PsA as a composite outcome. Such measures of state defining remission, low and high disease activity have been available in RA for some time and have been shown to be important for use in research trials and in daily clinical practice.

Research in RA supports the link between inflammation and subsequent joint damage. It has been established in both clinical and imaging studies that inflammation in the joints, in the form of synovitis, results in subsequent bony damage (Conaghan et al. 2003; Forslind et al. 2004). The concept of “tight control” was originally introduced by the TICORA study. This demonstrated that tight control of disease utilising pre-defined, objective activity levels to guide therapeutic changes resulted in significantly better clinical and radiographic outcomes compared to routine care with no formal therapeutic protocol (Grigor et al. 2004). Following on from this research, many studies in RA have adopted the use of an objective measure of response to guide therapeutic decisions (Goekoop-Ruiterman et al. 2005).

Observational data in PsA has also suggested a link between inflammation and damage as it has been shown that clinical and radiological joint damage is related to the number of actively inflamed joints as a time-varying indicator (Gladman et al. 1995; Gladman and Farewell 1999),. Therapeutic trials of highly effective biological therapies such as TNF blockers in PsA have shown a reduction in disease activity and a corresponding reduction in radiological progression (Mease et al. 2004; Mease et al. 2005b). However the lack of a criteria or cut-off for remission or low disease activity in PsA has meant that the concept of 'tight control' of disease activity using objective measures has never been evaluated.

5.5 Limitations

This study is based on a questionnaire using profiles of patients sent to experts in PsA including both rheumatologists and dermatologists. This raises some limitations in the research. In RA, research has shown that there is a high correlation between judgments made on "paper patients" and those based on real patients seen in clinical practice (Kirwan et al. 1983). However it is not known in PsA whether judgments about these profiles or "paper patients" are truly reflective of clinical assessments. Our profiles also contained more information than that given in the validation study in RA (Kirwan et al. 1983) to counteract the problem of a more complex and heterogeneous disease. This variability of disease patterns with different aspects of the disease involved may make it harder to make judgments about "paper patients".

A link to the questionnaire was sent to all members of GRAPPA with a request for their participation. A follow up email was also sent two weeks later when the response rate had started to decrease. This recruited 60 respondents and the response rate is similar to that of previous GRAPPA membership surveys. The online tool used to complete the questionnaires is familiar to many GRAPPA members and allowed respondents to link to the questionnaire on repeated occasions if they did not have time to complete it in one sitting. It also ensured that respondents could not answer the questionnaire more than once. A lower proportion of dermatologists completed the questionnaire, probably partially because dermatologists constitute a minority of the experts who were contacted. However analysis has not shown a significant difference in their responses. Interestingly the possible cutpoints for skin disease are identical in both groups' assessments.

The number of profiles included is limited in these questionnaire based exercises by the number of profiles that physicians can be expected to rate reliably. All profiles contained 7 variables resulting in thousands of possible combinations in different profiles. Using random sampling of possible profiles (according to Hahn and Shapiro) across a range of disease activity reduced the minimum number of profiles to 32 and a compromise at 40 was reached. The results of this study are based on a particular sample of 40 patients and these results need validating on larger and distinct samples.

Importantly, this analysis of expert opinion represents current views and may change in the future. The OMERACT definition of MDA is "that state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations". This relationship to current treatment possibilities means that acceptable targets of treatment are likely to have changed rapidly in the last few decades as new therapies have become available. Studies in RA have shown a lowering target for remission and low disease activity based on expert opinion over time, and it is suggested that this is related to the increasing potential to achieve these states with newer therapies (Aletaha et al. 2005). Similarly, in future, the acceptable levels of disease activity may drop further as the quest for remission becomes increasingly important.

5.6 Conclusion

In summary, this study provides the first definition of a "state" of disease activity in PsA and defines a target for treatment. It is based on current expert opinion and uses a composite of key outcome measures in PsA to encompass all of the domains of the disease. Given the new therapeutic options in PsA, patients with PsA are likely to benefit if these disease activity states are targeted, rather than simply looking for a clinical response.

6 **Validation of the Minimal Disease Activity Criteria**

6.1 Introduction

Before a new outcome measure can be recommended for routine use, it must prove to be valid in assessment. The OMERACT filter domains of truth, discrimination and feasibility provide a framework to assess new tools for use in research trials and clinical practice. These three domains can be summarised as follows. Truth aims to assess whether the measure is relevant and truthful and can measure what is intended without bias. Discrimination assesses the ability of the measure to discriminate between states at one time or different times as well as assessing reliability and sensitivity to change. Feasibility assesses whether the measure is easy to use, quick and inexpensive (Boers et al. 1998).

The truth domain includes face, content, criterion (or concurrent) and construct validity. Face validity provides evidence that the criteria are sensible to practitioners who will use them. Content validity asks if the criteria include the most relevant characteristics of the condition and if each variable contributes something distinct and important to facilitate classification of the patient. Criterion validity asks if the criteria produce the same or similar results as does a gold standard criterion. If no gold standard is available, concurrent validity can be assessed to ask if the criteria agree with other criteria designed to measures the same or similar constructs. Overall do the criteria adequately measure the underlying construct? This is based on an accumulation of knowledge about the criteria and their relationship to other tests.

Discrimination asks if the criteria are able to distinguish between states of interest and can be further sub-divided into classification, prognosis, responsiveness and reliability. Classification represents the division of patients according to the criteria into two or more groups, in this case MDA or not. Prognosis questions whether the states defined by the criteria have clinical relevance. This is clearly key to their usefulness in research and clinical practice. Responsiveness is the ability of subjects to change disease states over time. The proposed criteria must allow patients to shift from one disease state to another. Reliability measures how concordant different assessors are when classifying patients with the same clinical picture into the same disease state category.

Feasibility asks three questions: can it be done quickly, easily and cheaply? This is a key component of the filter as unfeasible outcome measures will never be routinely adopted into practice.

The new MDA criteria developed for PsA are a composite measure. Patients must fulfil 5 or more of the 7 following criteria: TJC ≤1; SJC ≤1; PASI ≤1 or BSA ≤3; patient pain VAS ≤15; patient global disease activity VAS ≤20; HAQ-DI ≤0.5; tender entheseal points ≤1 (Coates et al. 2010b) to be classified as in MDA. The work in this chapter aims to provide preliminary validation work for the criteria using the OMERACT filter framework.

6.2 Methods

6.2.1 Observational Cohort Data

The observational cohort study was conducted at the University of Toronto PsA clinic. Patients were evaluated using a standard protocol every 6-12 months. Clinical assessments include a 68 tender/66 swollen joint count, the SPARCC enthesitis instrument and dactylitis using the LDI (Gladman et al. 2007a; Healy and Helliwell 2007). Skin assessment includes both the BSA and the PASI (Fredriksson and Pettersson 1978). A clinically damaged joint count is recorded in addition to tender and swollen joint counts at each visit. The number of damaged joints includes those that have a reduced range of motion >20% of the range that cannot be explained by joint effusion, joints showing deformity, subluxation, loosening or ankylosis or that have undergone surgery. The reliability of this measure in PsA has been demonstrated both in the Toronto clinic and across Canada (Gladman et al. 1990; Gladman et al. 2004). A physician global assessment is completed and patients complete self reported questionnaires including the HAQ-DI and patient global assessments routinely. Blood results including ESR are recorded at each visit. ESR levels are recorded as a continuous variable and also as normal or raised (>15 for male patients, >20 for female patients).

As the MDA criteria require data on joint counts, enthesitis counts, skin activity, pain, patient's assessment of global disease activity and HAQ-DI, the analysis was restricted to those visits occurring after 2003 when all information was available. Patients were classified as achieving MDA if they achieved the criteria at consecutive visits for a minimum of 12 months. These patients were compared to controls who had persistently active disease or achieved the criteria for less than 12 months. The change in the clinically damaged joint count was measured from the first visit in which patients achieved MDA to the last visit or from the prior visit closest to the median time of achieving MDA for the controls. Progression of clinical damage was said to have occurred if any joint changed from being 'non-damaged' to 'damaged'.

6.2.1.1 Statistical Analysis

Patients achieving MDA and the control group (non-MDA) were compared using descriptive statistics. Factors affecting the likelihood of patients achieving MDA were investigated using logistic regression models. Three outcomes were defined based on the change in damaged joint count. Regression models were fitted for the raw change in damaged joint count, the change standardized by the patient-years at risk, and a binary response indicating whether one or more joints became damaged. Linear regression was used for the first two outcomes and logistic regression for the latter. The independent variables investigated were MDA status, age at onset of PsA, and ESR, duration of PsA, and an indicator of having at least one damaged joint as measured at the first visit following January 1, 2003. In addition, we examined the role of anti-TNF agents both before and after the time of MDA for those achieving MDA or the median time of MDA for controls. Univariate and multivariate regression models were fitted, with backwards elimination carried out to identify variables that were independently predictive of joint damage.

6.2.2 Randomised Controlled Trial Data

The trial data available for this analysis included most patients in the previously published phase II and III randomised placebo-controlled trials of infliximab in PsA (IMPACT 1 and 2). In both studies, patients with active PsA were treated with infliximab 5mg/kg or placebo, followed by open label treatment. The data from a randomly selected 80% of patients from both studies were available for analysis.

The IMPACT1 study recruited 104 patients with established PsA who had active arthritis (≥5 tender and swollen joints and raised inflammatory markers or significant early morning stiffness) and had failed at least one DMARD. Patients received infliximab or placebo infusions at weeks 0, 2, 6, and 14 before switching to open label infliximab therapy up to week 46.

The IMPACT2 study recruited 200 patients with very similar inclusion criteria except that these patients had to have failed either ≥1 DMARD or ≥1 NSAID, meaning that some of the patients were DMARD naïve. Patients in the IMPACT2 study received infliximab or placebo infusions at weeks 0, 2, 6, 14, and 22, but were eligible for "early escape" to open label infliximab at week 16 if they had <10% improvement in both tender and swollen joint counts.

A comparison was made of the proportion of patients achieving MDA in treatment and placebo groups at the primary endpoint (IMPACT 1- week 16, IMPACT 2 – week 24) using intention-to-treat analysis. Long term outcome was also analysed by assessing the proportion of all patients achieving MDA at the end of one year in both studies.

Radiological progression was assessed using mS-vdH scores for the hands and feet. Radiographs were performed at baseline and weeks 52 and 104 (IMPACT1) or weeks 24 and 54 (IMPACT2). For this report, baseline, one and two year radiographs were analysed where available.

6.2.2.1 Statistical analysis

All analysis was on an intention-to-treat basis, including the analysis of those patients who entered the "early escape" arm of the IMPACT2 study. Radiological progression was defined as an increase in the mS-vdH score of ≥ 0. Significance testing was performed using Chi-squared tests for categorical variables and Mann-Whitney U tests for continuous variables. All analysis was performed using SPSS 12.

6.2.3 Application of the OMERACT filter

Face and content validity were assessed when the criteria were designed. Criterion validity is difficult to assess as this is the first such measure of minimal disease activity in PsA, and therefore there is no formal outcome measure that can be used as a gold standard. The gold standard in this case is physician opinion. The criteria were created using the gold standard as a comparison but need further evaluation against physician opinions in other cohorts. Using longitudinal observational or trial datasets provides an opportunity to test concurrent validity. In both of these datasets, the criteria were tested for concordance with other prognostic measures and with other response measures. ACR responses have been shown to be useful in PsA clinical trials (Fransen et al. 2006) and correlation of achieving MDA with achieving high ACR responses can be used to assess concurrent validity. Construct validity represents a broad view of the total validity of the criteria. It can be summarised by investigating convergent and divergent validity in relationship to other criteria developed to measure similar or different constructs. In PsA, this remains difficult as no other validated measures of disease state have been developed to date. A literature review was performed to identify criteria used in previous publications for various disease activity states such as remission, and convergent validity with these other definitions was assessed.

During the development of the criteria, their ability to classify patients correctly was assessed using the sensitivity and specificity of the criteria compared to the physician's opinion. Further confirmation was performed using the observational dataset investigating the characteristics of those patients who were classified as being in MDA.

Whether the criteria have prognostic ability (related to joint damage progression) was tested using the observational and trial dataset. In the observational cohort there is an element of concern that this is testing only discrimination between different groups of patients, and not changes within patients related to time or therapy. Patients with less severe PsA are more likely to achieve MDA and have less joint damage but this may not be related to treatment, just their natural disease course. To investigate the discrimination within patients, the clinical trial dataset was used. In this case, all patients have high levels of disease activity at entry and usually have severe disease according to traditional prognostic indicators, such as polyarticular disease and high inflammatory markers. The responsiveness was also analysed using data from the observational database and the trial datasets. Analysis of observational data investigated whether patients move in and out of MDA as their disease and treatment varies. RCT data investigated whether a significantly higher proportion of patients with active disease who start a therapeutic trial in the active drug arm can achieve MDA when compared to those on placebo.

The reliability of this criteria set relies upon the reliability of all of its component outcome measures. A literature review was performed to assess the reliability of the outcome measures included in the criteria. The assessment of feasibility is made during development of the criteria and with ongoing use. Feasible outcome measures should be quick, easy and cheap.

6.3 Results

6.3.1 Truth

6.3.1.1 Face validity

Face validity provides evidence that the criteria are sensible to practitioners who will use them. The MDA criteria were developed following extensive discussion with members of the GRAPPA executive and steering committee, a panel of international experts in the field of PsA (Helliwell 2007). This discussion informed the choice of which domains should be included in the consensus exercise to ensure that all aspects of the disease were assessed. The creation of the criteria was then performed using expert consensus on a selection of “paper cases” representing real-life patients with PsA.

6.3.1.2 Content validity

Content validity is a measure of whether the criteria include the most relevant characteristics of the condition and if each variable contributes something distinct and important to facilitate classification of the patient.

The criteria were developed using commonly used outcome measures in a composite definition. The outcome measures to be included and excluded from the criteria were based on international experts' opinion as discussed at the OMERACT PsA group (Gladman et al. 2007d) and by careful review of other important domains. Discussion was facilitated through the GRAPPA group of international experts and the outcome measures used cover all of the relevant core domains plus one other important domain (enthesitis). This aimed to cover all aspects of psoriatic disease (peripheral joints, skin, enthesitis, dactylitis, pain, function and a global measure). They also represent the minimum number of measures that could do this. The only aspect of disease not specifically measured is spinal disease, as no validated disease activity measures are available. The BASDAI has been evaluated in PsA and was not shown to correlate with doctor's perception of disease activity or with treatment decisions (Taylor and Harrison 2004). Interestingly, it was found to correlate highly with the patient's global disease activity VAS, which is included in the profiles. The group felt that active axial disease would be identified by the patient's assessment of pain, global disease activity and physical function.

6.3.1.3 Criterion validity

As this is the first such measure of minimal disease activity in PsA, there is no formal outcome measure that can be used as a gold standard. Concurrent validity is therefore tested as an alternative to criterion validity.

Those patients who achieved MDA were significantly more likely to achieve all of the ACR outcome measures (ACR20, ACR50 and ACR70 - $p<0.001$ – see figure 5 and 6).

In addition to the relationship with composite measures, there was an association seen between achievement of MDA and the levels of systemic inflammatory response. There was a significant difference between the levels of CRP in patients who achieved the MDA criteria and those who did not (median (IQ range) CRP 0.4mg/L (0.4, 0.6) vs 0.5mg/L (0.4, 1.3) respectively, $p=0.019$). There was also an association seen with the physicians' assessment of disease where there was a significant difference in the physicians' global assessment of disease in patients who achieved the MDA criteria and those who did not (median (IQ range) VAS 0.5 (0.1, 1.0) vs 2.4 (0.8, 5.4) respectively, $p<0.001$).

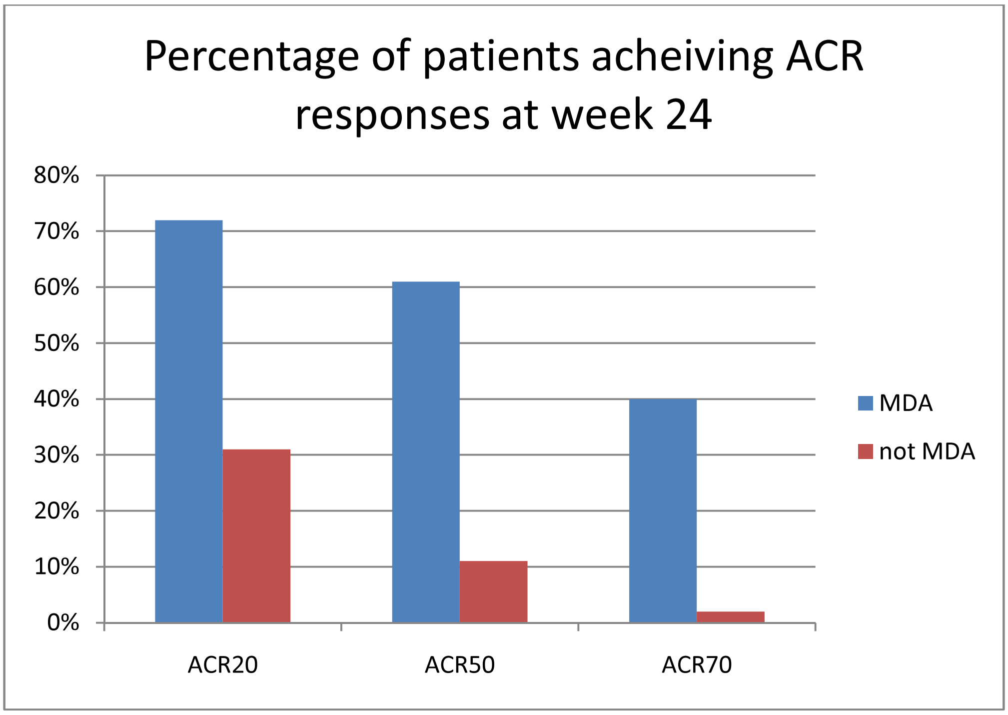

Figure 5 - Percentage of MDA & non-MDA patients achieving ACR responses at wk 24

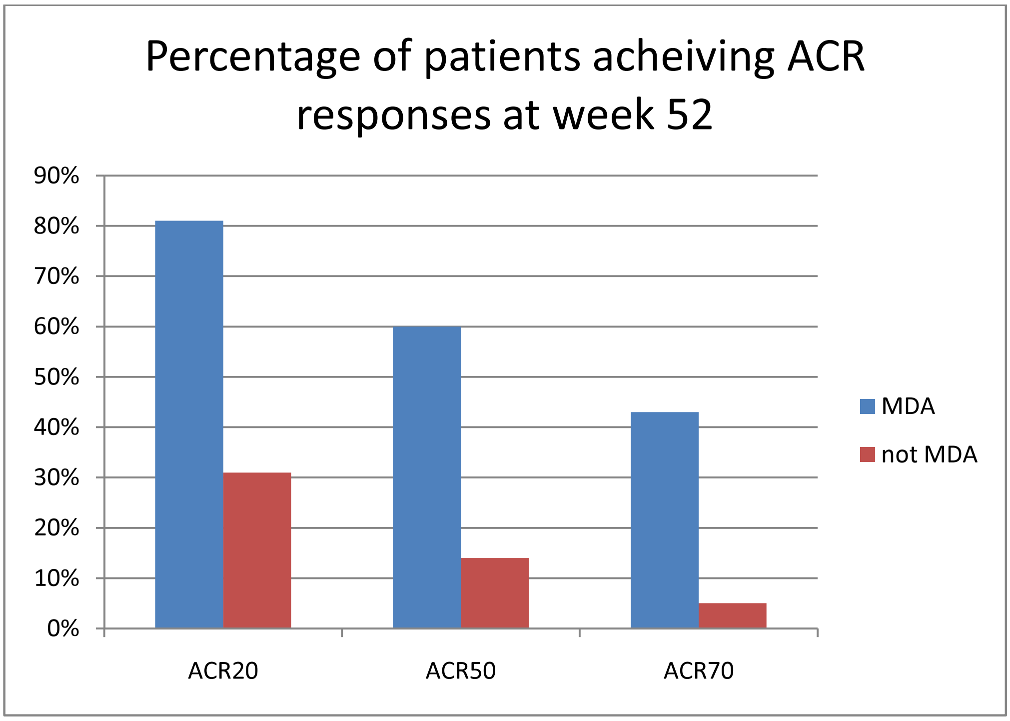

Figure 6 - Percentage of MDA & non-MDA patients achieving ACR responses at wk 52

6.3.1.4 Construct validity

Three previous studies investigating the frequency of remission in PsA were identified in the literature review. There are no publications investigating minimal or low disease activity. Two of the published studies assessed remission in the peripheral joints and did not take into account any of the other aspects of the disease (Gladman et al. 2001; Lindqvist et al. 2008). In a previous Toronto study, it was shown that 18% of patients achieved remission in their peripheral joint activity (no actively inflamed joints) for at least 12 months but 52% of these patients relapsed during follow up (Gladman et al. 2001). In the Swedish early PsA cohort, 17% were found to be in remission at 2 years (no tender or swollen joints and normal inflammatory markers) (Lindqvist et al. 2008). A further study of remission in early disease used more stringent criteria requiring no enthesitis or dactylitis disease activity, in addition to peripheral joint disease, but did not include skin disease (Cantini et al. 2008). This showed a higher frequency of remission, 24%, which may partially represent the changing availability of treatments over the last decade.

These rates of remission compare to a rate of 34% of patients achieving MDA in the Toronto observational study. This higher rate can be accounted for as the MDA criteria should encompass both remission and low disease activity. The remission criteria used for peripheral disease activity and enthesitis are lower than the domain cut-point used in the MDA criteria, in keeping with the fact that the remission criteria should be more stringent. Patients classified as remission would achieve the cut points for the joint and entheses domains in the MDA criteria. However it is impossible to say if they would achieve the full MDA criteria as there was no inclusion of PROMs.

6.3.2 Discrimination

6.3.2.1 Classification

Although the sensitivity and specificity of the criteria whilst in development were high, there is always a risk of misclassification of patients, particularly those who are “borderline” on the criteria. The most crucial part of classification of these criteria is their specificity, to ensure that patients with active disease are not falsely classified as MDA which may result in a suboptimal treatment. Analysis of data from the observational cohort has examined the characteristics of those patients who met the MDA criteria. This showed that of the 208 patients who achieved MDA at one or more visit, 110 patients (37%) met five of the seven criteria, 114 (38%) met six criteria and 76 (25%) fulfilled all seven criteria. Of those who did not fulfil all seven criteria, the most common active domain was skin psoriasis (n=44) followed by patient global VAS (n=17). None of the patients had a SJC of >1. Of the patients maintaining MDA, only 15 patients (12.9%) had escalation of their drug therapy made during their time in MDA.

6.3.2.2 Prognosis

Firstly, the prognostic ability of the criteria was analysed in the observational cohort. Patients in sustained MDA were compared to 200 controls who did not achieve the MDA criteria for >12 months. The average follow up time to assess progression of disease was matched at 34 months for both groups. The mean change in damaged joint counts over the study period was 0.93 (range 0 to 12) in the MDA group and 2.25 (range 0 to 17) in the controls ($p<0.001$). Of the MDA patients, 69% showed no progression of joint damage, compared to 51% in the control group. Reduced multivariate regression models looking at predictors for changes in damaged joint counts identified that those patients who achieved the MDA state had a lower rate of progression of clinical damage ($p=0.03$).

Prognosis was addressed in the trial data using radiographic evidence of progressive joint damage. In the IMPACT1 study, 96% of those patients who achieved MDA showed no progression of radiological disease at week 52 (increase in mS-vdH score of ≥ 0), compared to 67% of those who did not achieve MDA ($p=0.012$). At week 104 numbers were greatly reduced and 12/37 (30%) were in MDA. All patients who achieved MDA at week 104 showed no progression of radiological disease, compared to 58% of those who did not achieve MDA ($p=0.03$).

In the IMPACT2 study, 78% of those patients who achieved MDA showed no progression of radiological disease at week 52, compared to 57% of those who did not achieve MDA ($p=0.009$). There was a trend towards a reduced progression in total mS-vdH score and the erosion score at week 52 in patients who achieved MDA at this time ($p=0.052$, $p=0.053$ respectively) but no significant difference in progression of JSN. There was no significant difference seen at week 24 related to MDA.

Cumulative probability plots of changes in mS-vdH score through week 54 are shown (figure 7). The curve for patients consistently in MDA (at week 24 and 52) lies to the right of the control curve indicating less radiographic progression and a smaller amount of radiographic progression per patient in MDA patients.

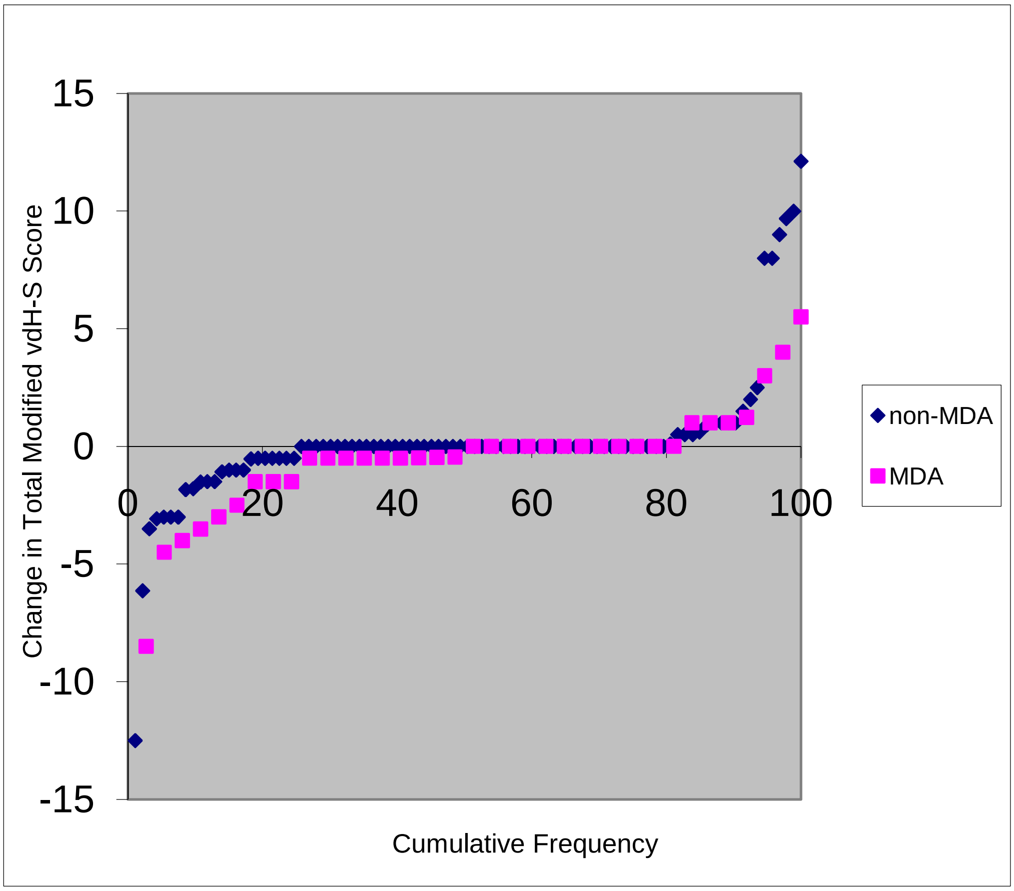

Figure 7 - Probability plot for change in total mS-vdH score for those in MDA and those not.

6.3.2.3 Responsiveness

Firstly, the number of patients achieving the MDA criteria in the observational cohort was studied. Of the 344 patients, 208 (61%) achieved MDA at one or more visit, and 116 (34%) achieved MDA on consecutive visits for a minimum duration of 12 months. The median duration of MDA was 28 months (range 12 to 48). The characteristics of the patients who met and sustained the MDA criteria are shown in Table 1. After the minimum 12 month period required for inclusion, twelve patients (10%) experienced a flare of their disease and ceased to fulfil the MDA criteria after an average of 34 months in MDA. The remainder were still in MDA at their most recent follow-up.

When considering the trial data, the responsiveness of the criteria was confirmed by comparing the proportion of patients achieving MDA in the placebo and treatment groups. In the IMPACT1 study data were available for 63 patients. Of those receiving infliximab, 48% (15/31) achieved MDA at week 16 compared to 3% (1/32) on placebo ($p<0.0001$). At week 52, when all patients were treated with infliximab, 42% were in MDA. In the IMPACT2 study data were available on 157 patients. At the primary endpoint (week 24), 52% (40/77) of the patients randomised to receiving infliximab achieved MDA compared to 21% (17/80) randomised to placebo ($p<0.001$). At week 52, when all patients were on infliximab, 40% were in MDA.

6.3.2.4 Reliability

The literature review identified previous evidence of reliability for each of the outcome measures included in the criteria. This had been assessed in previous studies including INSPIRE and IMPART (International Multicentre Psoriasis and Psoriatic Arthritis Reliability Trial) which analysed the reliability of TJC, SJC, PASI, BSA and a variety of enthesitis measures (Gladman et al. 2007a; Chandran et al. 2009). The HAQ-DI is self-administered by the patient and has been shown to be reliable in PsA without modification (Leung et al. 2008). The patient reported outcomes such as the VAS scales are again self-administered by the patients and they have been shown to be reliable in PsA (Cauli et al. 2007). Further reliability data are therefore not required.

6.3.3 Feasibility

All of these outcome measures included within the criteria are considered routine to researchers in this field. Three of the seven outcome measures are completed by the patient and can be done in the waiting room prior to their appointment. As part of the assessment, the assessor must complete a joint count, PASI or BSA and enthesitis count all of which can be completed within 5-10 minutes in the clinic setting. Where doubt exists about the best outcome measure to apply, the criteria have been left open so that researchers can use the outcome measure that they are familiar with (eg PASI vs BSA and different enthesitis scores). None of the outcome measures included require any special equipment to perform, so the only significant cost to the assessor is of time. As stated above, the time needed to complete these measures is minimal.

6.4 Discussion

Until recently, there were no composite disease activity measures available to measure a "state" of disease in PsA. The proposed criteria for minimal disease activity in PsA encompass different aspects of this heterogeneous disease, and could provide a new outcome measure for future clinical trials in PsA (Coates et al. 2010b). Preliminary validation work, highlighted here, provides support for their further investigation and use.

The data in this study show that sustained MDA occurs in approximately one-third of the PsA population. The higher prevalence is not surprising as the criteria are less strict than those used for remission in previous studies. Low levels of disease activity are allowed in all domains and only five of the seven cut points must be met. As seen in the previous remission studies, flare of disease occurred after a significant duration of time in MDA in around 10% of the patients demonstrating the variable activity of disease both on and off therapy. The vast majority of patients in MDA stayed on stable therapy, but 15 did have an escalation of their treatment. This may represent specific treatment for a certain high domain (e.g. active skin psoriasis only) or an increasing focus by the PsA clinic on the target of remission.

Although there is a marked reduction in progression of joint damage, there is still evidence of some progression despite patients consistently achieving MDA. It must be noted that these criteria are not remission criteria but minimal disease activity and therefore a small amount of disease activity may be present. The patients achieving the MDA criteria can have active disease in one or two domains whilst still fulfilling the criteria and even in the other domains, low disease activity is considered acceptable by the criteria (e.g. 1 tender joint). This may account for the lower rate of joint damage. We also know that clinical examination does not identify all inflamed joints and it is particularly insensitive to low levels of inflammation (subclinical disease) (Wakefield et al. 2004). Even in patients with RA who are in remission (as defined by DAS), joint damage progression has been shown to occur and is related to subclinical inflammation seen on imaging (Brown et al. 2006).

6.4.1 Truth

Face and content validity were carefully considered during the design and development phase of the MDA criteria. International consensus from members of GRAPPA provides support of this. Assessment of criterion validity in trial data has shown evidence of concurrent validity with other measures used to identify disease activity including composite disease activity measures such as ACR outcomes, laboratory tests such as CRP and physician assessments of disease activity. Ideally convergent and divergent validity should be assessed by comparing the new criteria to criteria measuring similar disease states (such as low disease activity/remission) and those measuring different disease states (such as active disease). The only criteria available for comparison are previous definitions of remission used in publications. Patients in remission should be encompassed within MDA, but the MDA criteria should also include patients who have some low disease activity. There is some evidence for convergent and divergent validity with remission criteria in PsA but direct comparisons with these cannot be used as they use distinct conceptual definitions. Therefore there is very limited evidence for construct validity at this time.

6.4.2 Discrimination

The ability of the criteria to classify patients as MDA seemed high in the initial development of the criteria when compared to physician opinion. However misclassification is always a risk. As stated previously, the risk to the patient of misclassification is particularly important when considering patients with active disease who are misclassified as MDA and potentially denied additional therapy. Observational cohort data has been reassuring in this regard as it has shown that none of the MDA patients had swollen joints and that very few had an escalation of therapy providing some reassurance that there was a low rate of misclassification in this cohort. Ideally further validation should be undertaken in a prospective cohort with borderline patients.

The impact of MDA on prognosis in terms of joint damage has been confirmed in both the observational (with regard to clinically damaged joint counts) and trial cohort data (with radiographic outcomes). It is clearly shown that patients can change states over time both in the observational cohort and in a randomised trial where drug and placebo groups are compared. There is a significant difference in the achievement of MDA between patients treated with anti-TNF therapy and placebo, suggesting that this could be used as a trial outcome measure for new therapies.

Reliability of the individual outcome measures included in the criteria has been confirmed in a literature review. In this situation, the reliability of the MDA criteria are validated by the reliability of their constituent parts.

6.4.3 Feasibility

All of these outcome measures included within the criteria are quick and easy to perform with no equipment required, and three of the seven outcome measures are completed by the patient. The criteria are being used in further ongoing studies and have proved easy to integrate into a standard clinic visit.

6.5 Limitations

Although provisional data are available to address each of the constituents of the OMERACT filter, further data are required before they can be classified as valid. Ongoing use in prospective studies should provide further evidence towards their suitability as an outcome measure. Specifically, further evidence is required of their classification ability, construct and criterion validity. There is no confirmed gold standard of MDA limiting the assessment of criterion validity. Ideally a further study should be performed in an independent population comparing the criteria against physician and patient opinion. The assessments of convergent and divergent validity are also limited at present as no other criteria for minimal disease activity or low disease activity at present. If other criteria are developed, further testing could be done.

There are some limitations introduced by the type of datasets used to assess validity. Some of these are overcome by the use of two different data cohorts. The advantage of using observational data from a cohort such as the PsA program in Toronto is that it provides relevant information on real-life patients all treated according to their clinical need rather than any set trial protocol. However exactly because of this, there are some limitations on the conclusions that can be drawn from the data.

There is a significant potential for confounding in data from observational cohorts. PsA is known to be a heterogeneous disorder and the progression of joint damage is highly variable between individuals. Patients presenting with active disease and joint damage are highly likely to be prescribed biological therapies given their active disease, but also have a more severe disease phenotype and a higher potential for damage progression. Although we have shown an improved prognosis in those patients achieving a state of MDA, we cannot be sure what proportion of this is due to the natural history of the disease and what impact successful treatment has on outcome. Also, in the observational study, a clinically damaged joint count was used, rather than assessment of joint damage on conventional radiography. This outcome measures has been validated against conventional radiography (Gladman et al. 1990; Gladman et al. 2004), but is probably less sensitive to early joint damage and to minor changes than radiography. Therefore the progression in both groups may be an underestimate of the progression of damage in PsA.

Analysis of interventional therapeutic trials can remove much of the potential for confounding and can provide stronger evidence for the prognostic ability of the MDA criteria. Data for prognosis in this study used radiological outcomes with a validated scoring system providing a more robust assessment of joint damage. However, the assessment of joint damage is only one aspect of prognosis. Further long term research is required to look at other measures of impact on patients' long term outcome, such as functional ability, quality of life and work status.

Finally, the development of the criteria based on expert opinion represents current views and these may change in the future. The OMERACT definition of MDA is "that state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations". This relationship to current treatment possibilities means that acceptable targets of treatment may drop further as additional therapeutic options are available.

6.6 Conclusion

Data from both observational and controlled clinical trial cohorts have provided initial evidence supporting the validity of the MDA criteria as an outcome measure. Although further work is required in some areas, initial assessments of the truth, discrimination and feasibility of the PsA MDA criteria are positive and the MDA criteria can be recommended for use in future research. Further use of these criteria in prospective studies will provide further validation evidence.

7 **Tight Control of Psoriatic Arthritis**

7.1 Introduction

Since the TICORA study highlighted the benefit of tight control in RA (Grigor et al. 2004), it has become standard of care in the majority of RA clinical trials and is gradually becoming adopted in clinical practice. The use of an objective target to guide treatment decisions has been shown to be associated with improved clinical and radiographic outcomes in RA.

Until recently, there were no objective targets designed specifically for PsA. With the development and validation of the MDA criteria (Coates et al. 2010a; Coates et al. 2010b; Coates and Helliwell 2010), a disease specific target for treatment has been established in PsA and it is possible to investigate the use of tight control in PsA. The aim of this study was to utilise the MDA criteria in a tight control protocol to treat newly diagnosed PsA.

7.2 Methods

The TICOPA study is a multicentre national trial currently running at 6 sites. It is designed as a randomised, controlled, parallel group, open label, clinical trial of 206 patients with recent onset PsA. Patients are randomised on a 1:1 basis to receive either standard care or tight control for a period of 48 weeks. The study was approved by national and local ethics committees and all patients gave written consent before inclusion.

7.2.1 Patients

Recruitment started in May 2008 and inclusion criteria are PsA of less than two years symptom duration with active arthritis or enthesitis. As the CASPAR criteria were unvalidated in short disease duration PsA at the time of study design, a consultant diagnosis of PsA was used as the inclusion criteria. Exclusion criteria included age less than 18 years, previous treatment for arthritis with DMARDs, recent or concomitant use of an experimental drug, wish to conceive during the study period or within 6 months of the end of the study or inadequate contraception. Patients are also required to have an adequate baseline full blood count (haemoglobin > 8.5 g/dL, white cell count > 3.5 x 10^9/L, neutrophils > 1.5 x 10^9/L, platelets > 100 x 10^9/L) and hepatobiliary function (aspartate aminotransferase or alanine aminotransferase (ALT) <3 times the upper limit of normal).

7.2.2 Treatment allocation and intervention

Patients are randomised 1:1 using dynamic allocation incorporating a random element, via a computer-generated programme, to ensure treatment groups are well-balanced for randomising centre and pattern of arthritis (oligoarticular vs polyarticular). The trial uses a dynamic allocation process to allocate the interventions and thus minimise imbalance between the two trial arms.

Patients assigned to the intensive group are seen every 4 weeks by the study physician at each centre. A strict treatment protocol (see figure 8) is followed for treatment. At each visit, from three months onwards, the MDA criteria (Coates et al. 2010b) are assessed. These criteria include assessment of 66/68 joint count, PASI, enthesitis count, patient global and pain VAS and HAQ-DI. Treatment with DMARDs is escalated to the maximum dose according to the protocol in figure 1 if patients do not achieve the MDA criteria. In the case of intolerance, that drug is discontinued and the next step on the protocol is initiated. Any patient who cannot tolerate the maximum dose specified in the protocol due to toxicity or intolerance, is permitted to continue on the highest tolerable dose and then progress to the next step in the protocol if required. IA and intra-muscular steroids are also permitted in the intensive group arm to control disease. Patients are offered local joint injections to active joints and/or intramuscular steroid by the physicians if considered appropriate.

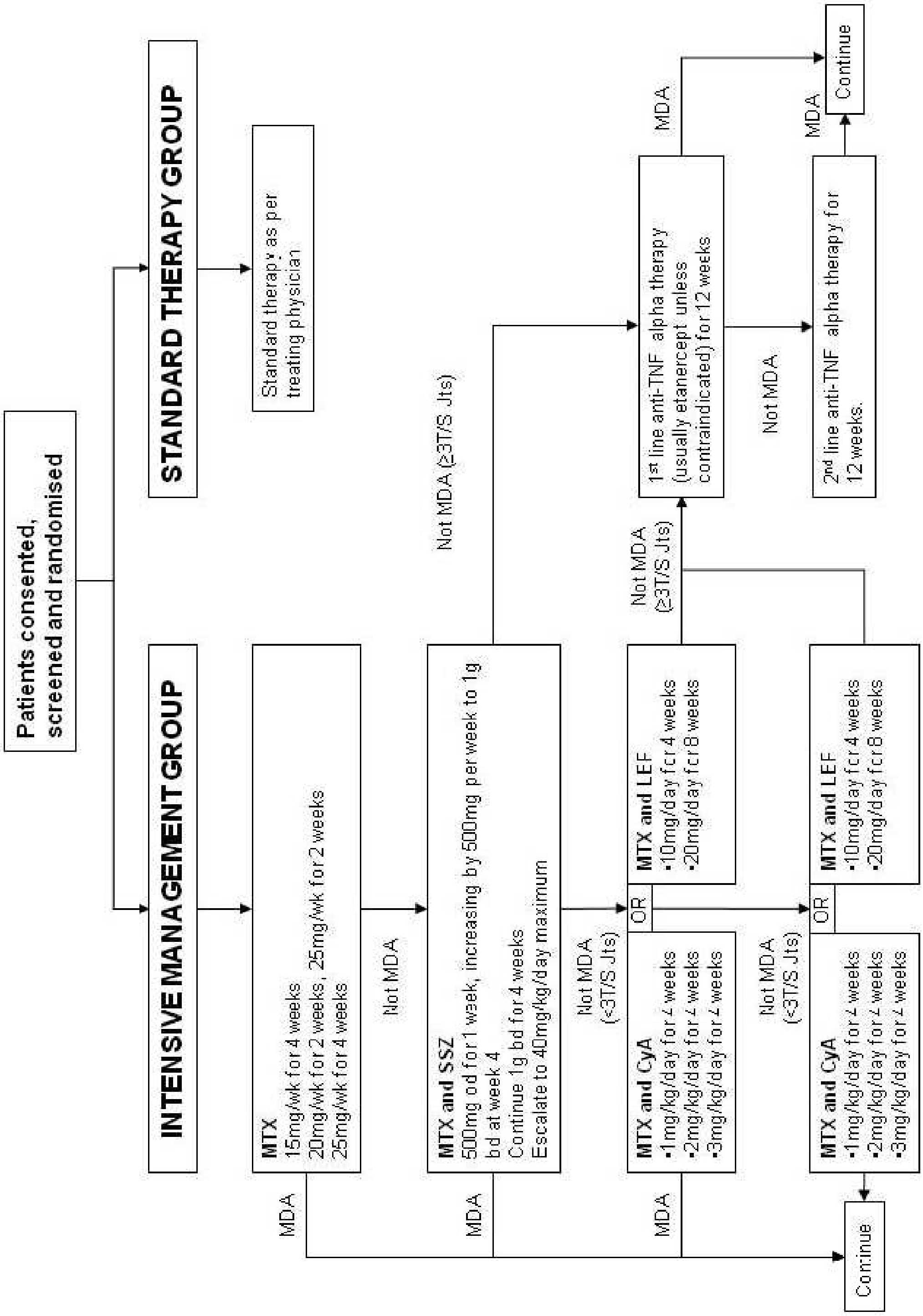

Figure 8 – Protocol for treatment in the TICOPA study

Patients randomised to the standard therapy group are treated in a general rheumatology outpatient clinic supervised by a consultant rheumatologist and including trainee rheumatologists working under supervision. These participants are reviewed as directed by the physician but generally every 12 weeks, with no formal measures of disease activity used in clinical decision making. There is no requirement or restriction on prescribing within this arm of the study.

7.2.3 Assessment of end-points

Every 12 weeks, clinical assessments are performed by a research nurse or metrologist blinded to the allocated treatment group. These include 66/68 joint count, PASI (Fredriksson and Pettersson 1978), nail psoriasis scoring using the mNAPSI (Cassell et al. 2007) and a comprehensive assessment of enthesitis including entheseal sites required for the LEI (Healy and Helliwell 2008), the MASES (Heuft-Dorenbosch et al. 2003) and sites used in the IMPACT and IMPACT2 clinical trials (bilateral Achilles tendon and plantar fascia) (Antoni et al. 2005a; Antoni et al. 2005b) and dactylitis assessment using the LDI (Helliwell et al. 2005).

At baseline and 48 weeks, plain radiographs of the hands and feet and an US scan of the most symptomatic or dominant hand were performed. Radiographs were scored using the mS-vdH scoring system for PsA (van der Heijde et al. 2005b). They were scored as paired images but assessors were blinded to patient identity and timepoint. US was performed using a Philips HDI 5000 machine with a 12-5 or 13-7 MHz probe as appropriate. For PD scanning a medium wall filter was applied. All scans were performed by a rheumatologist experienced in musculoskeletal US (Dr J E Freeston). Gel was applied to the skin to provide an acoustic interface. All patients underwent GS and PD US of the most symptomatic hand and wrist (wrist, MCP2-5 and PIP2-5 joints - 11 joints per patient). GS and PD were scored separately on a 0-3 semi-quantitative scale for each joint imaged. A GS score of ≥2 and/or a PD score >0 were used to identify US active joints

The primary endpoint of the study is achievement of ACR20 response at 48 weeks. This was chosen as research has shown that it is responsive in PsA and has a lower placebo response than is seen with the PsARC (Fransen et al. 2006). This analysis also identified the EULAR responses based on the DAS as being responsive in PsA, but there was concern about using an outcome measure based on a 28-joint count in oligoarticular disease. Secondary endpoints at week 48 include ACR50, ACR70, achievement of MDA criteria and radiographic joint damage according to change in mS-vdH score.

7.2.4 Statistical analysis

The primary outcome in this study is the proportion of patients who achieve an ACR 20 response at 48 weeks from baseline. Previous data for patients with PsA (Healy and Helliwell 2007) starting on DMARDs (predominantly methotrexate) has shown ACR 20 at 3 and 6 months to be 50% and 43% respectively. We have therefore assumed that the proportion of patients achieving ACR20 in the standard care arm will be approximately 50% at 48 weeks. An absolute difference in ACR20 rates of 20% has been deemed to be a clinically significant difference. Therefore, with 80% power and based on a chi-squared test without continuity at the 2-sided 5% significance level, 93 patients per arm (186 patients in total) are required to detect and increase on ACR 20 rates of 20%. To allow for a 10% drop-out rate, 206 patients will be recruited in total.

This large RCT is currently ongoing and therefore analysis for this thesis has been restricted to blinded data. To date 40 patients have been randomised into the study and have completed their 48 week follow up. Data regarding treatment is provided in summary form for the cohort, but detailed analysis comparing treatment and response has been limited to ensure that treatment groups remain unblinded.

Significance testing was performed using Chi-squared tests for categorical variables, Mann-Whitney U tests for independent continuous variables and Wilcoxon signed rank tests for paired continuous variables. Univariate forward step-wise binary logistic regression was used to identify which baseline features were associated with achievement of MDA at the 48 week timepoint. All analysis was performed using SPSS 16.

7.3 Results

To date, in the main RCT, 96 patients have been recruited. A flowchart detailing their recruitment and follow up is shown in figure 9. The remainder of this chapter includes the analysis of the first 40 patients to be randomised and to complete follow-up.

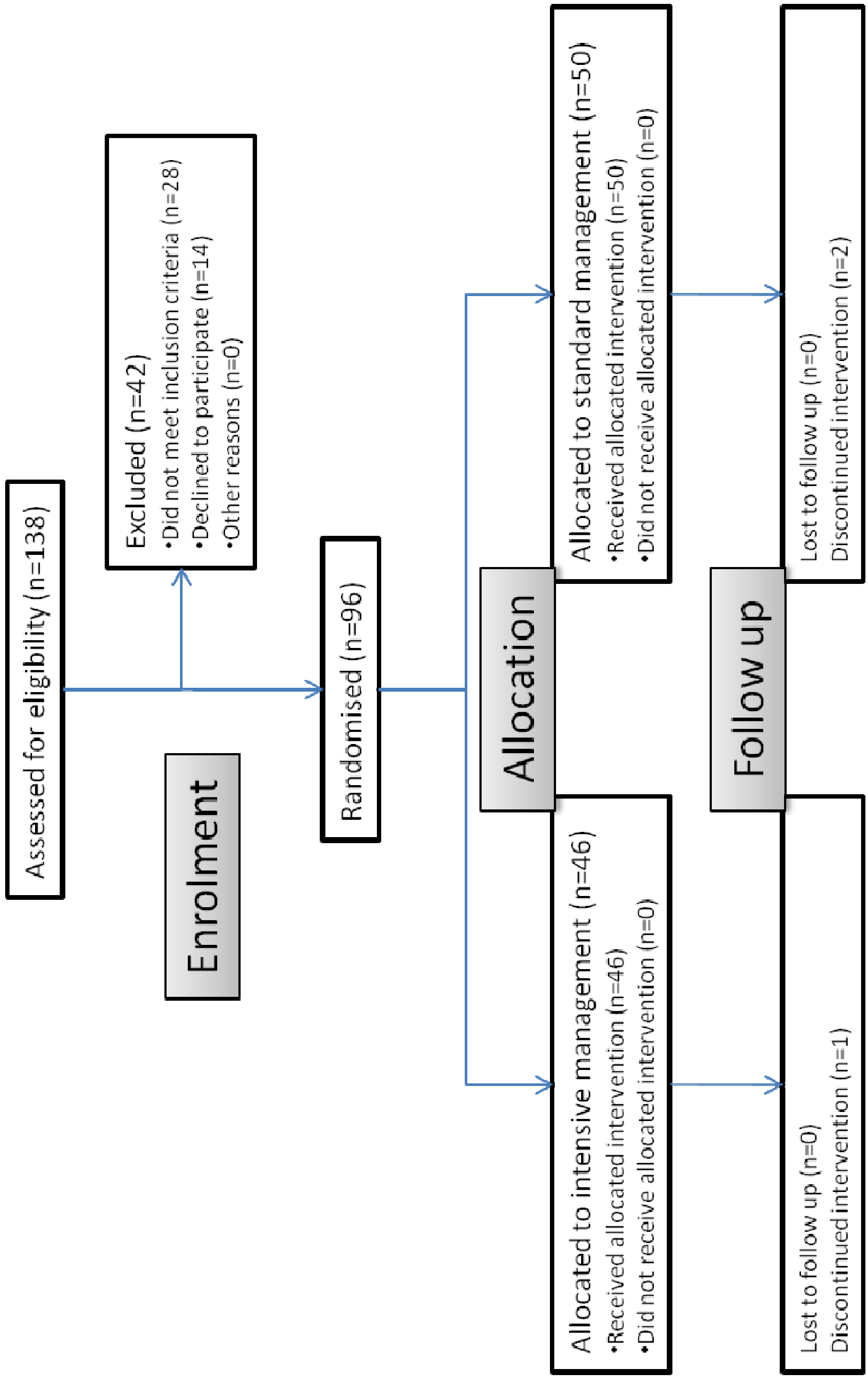

Figure 9 – Enrolment flow diagram for TICOPA study

7.3.1 Baseline Demographics

Of the 40 patients completing TICOPA to date, all had a consultant diagnosis of PsA, but only 34 met the CASPAR criteria. The remaining 6 patients all scored 2 points in the CASPAR criteria. These patients did not have current psoriasis, but all had 2 indicators of PsA from the other features included in the CASPAR criteria. Baseline characteristics of the cohort are shown in table 23.

Considering imaging at baseline, plain radiographs of the hands and feet were available for 29 patients and US of the most affected or dominant hand was available for 38 patients. At baseline, the majority of patients had little or no evidence of radiographic damage (median mS-vdH score 1, IQ range 0-4.5). JSN was seen in around half of the cohort (n=15) and the median score for those with JSN was 4 (IQ range 1 to 5). Erosions were identified in only 5 patients (17%) with a median score of 4 (IQ range 1 to 6.5). US at baseline identified relatively low levels of disease in the hand and wrist with predominant GS synovitis and low levels of PD. The median total GS score was 11.5 (IQ range 8 to 18.25) with a median PD score of 0 (IQ range 0 to 3.25). When the number of US active joints (GS score of ≥2 and/or a PD score >0) was considered, only 16 patients had active disease in the one hand that was scanned at baseline, and these patients had a median active US joint count of 2.

Number of joints involved	N
Oligoarthritis	20
Polyarthritis	20
Subtypes of disease	**N**
DIP disease predominant	2
Axial disease	2
Mutilans	0
Active dactylitis	7
Skin disease	**N**
Current psoriasis	32
Plaque	21
Scalp	18
Flexural	5
Erythrodermic	1
Pustular	2
Previous psoriasis	4
Family history of psoriasis	10
Nail disease	**N**
Nail psoriasis	22
Onycholysis	16
Pitting	12
Nail plate crumbling	6
Leukonychia	4
Antibodies	**N**
RF negative	40
Anti-CCP negative	40

Table 23 – baseline characteristics of the TICOPA cohort

7.3.2 Treatment during study period

During the 48 week study period, the majority of patients received one or more DMARDs and the frequency chart of drug prescriptions is given in table 24. Details about the doses of DMARDs are provided in table 25. For all of the drugs except methotrexate, doses given were standard and there was just a short titration period at the start of treatment in the case of sulfasalazine, leflunomide and cyclosporin. Maximum doses of sulfasalazine prescribed varied from 2-3g per day. In the case of methotrexate, doses were more variable given the slower titration and different target doses chosen by different physicians.

Of the eight patients who received treatment with a biologic drug, there were five patients who received one anti-TNF drug each and three patients who received two different anti-TNF drugs due to primary inefficacy or adverse events.

Treatment Prescribed	Number of patients - N (%)
No DMARD treatment	5 (12.5%)
1 synthetic DMARD only	20 (50%)
Multiple synthetic DMARDs	15 (37.5%)
Biologics	8 (20%)

Table 24 – frequency of patients receiving synthetic and biologic DMARDs

Drug	Number of patients – N (%)	Average dose
Methotrexate	34 (85%)	20.7mg per week
Sulfasalazine	15 (38%)	2.1g daily
Leflunomide	1 (3%)	18.3mg daily
Cyclosporin	2 (5%)	
Etanercept	6 (15%)	50mg weekly
Adalimumab	4 (10%)	40mg every other week
Infliximab	1 (3%)	5mg/kg every 8 weeks

Table 25 – frequency and average doses for DMARDs prescribed

7.3.3 Response measures

7.3.3.1 Minimal Disease Activity

The proportion of patients achieving the MDA state increased steadily over the 48 week study period (table 26) to a maximum of 53%. Univariate logistic regression analysis identified that a low patient's global disease activity VAS at baseline (OR=0.96; 95% CI = 0.93, 0.99; p=0.020) and the absence of enthesitis at baseline (OR=10.46; 95% CI = 1.16, 94.48; p=0.037) were associated with a increased chance of achieving MDA at 48 weeks. Other factors investigated were not significant including joint counts, pattern of arthritis (oligoarthritis or polyarthritis), presence of dactylitis, baseline physicians global disease activity VAS, quality of life (PsQOL), function (HAQ-DI) or baseline CRP levels.

7.3.3.2 Outcome measures for individual domains of PsA

All patients had arthritis at study entry and so all were assessed for the composite ACR and EULAR joint response measures. Table 27 shows the proportion of patients achieving both the ACR response measures and the EULAR response criteria based on the DAS28 score. The response rates improved over the course of the 48 week study period.

Both the ACR and EULAR outcomes have been validated in polyarticular PsA, but less is known about their responsiveness in oligoarticular disease. The 20 patients with oligoarticular disease at baseline were compared to those presenting with polyarticular disease, to identify any differential response in these outcome measures at 48 weeks (table 28). For all of the responder indices (ACR and EULAR outcomes), a slightly higher proportion of patients with polyarticular disease achieved the outcomes, with a difference that was more pronounced for ACR70 in comparison to ACR20. In contrast, the MDA criteria were more commonly achieved by patients with oligoarthritis at baseline.

	Week 12	Week 24	Week 36	Week 48
Number (%) acheiving MDA	10 (25)	12 (30)	15 (38)	21 (53)

Table 26 – proportions of patients achieving MDA at key timepoints

	Number (%) achieving outcome				
Timepoint	ACR20	ACR50	ACR70	Mod EULAR response	Good EULAR response
Week 12	22(55)	8 (20)	1 (3)	9 (23)	3 (8)
Week 24	17 (43)	12 (30)	6 (15)	12 (30)	10 (25)
Week 36	18 (45)	11 (28)	7 (18)	12 (30)	10 (25)
Week 48	23 (58)	18 (45)	15 (38)	16 (40)	16 (40)

Table 27 – Composite arthritis outcomes at key timepoints

	Number (%) achieving outcome at 48 weeks				
Subtype	ACR20	ACR50	ACR70	Mod/Good EULAR response	MDA
Oligoarthritis	11 (55)	8 (40)	6 (30)	6 (30)	12 (63)
Polyarthritis	12 (60)	10 (50)	9 (45)	10 (50)	9 (45)

Table 28 – composite arthritis outcomes and MDA by joint disease subtype

In addition to clinical outcome measures for articular disease, data are available for imaging with plain radiographs and US. Radiographic data identified that the majority of patients had no change in mS-vdH score during the 48 week period. There was no significant difference found between baseline and week 48 scores for erosions, JSN or total score ($p>0.83$). At week 48, the median mS-vdH score was 2 (IQ range 0-4) with an erosion score of 0 and JSN of 2. Only 3 patients changed their status from non-erosive to erosive disease during the time period and their erosion scores remained low (median 1, range 1-2).

US data at baseline and 48 weeks were available for 38 of the 40 patients. US showed a significant reduction in imaging activity both in terms of GS synovitis and PD score ($p<0.002$). When the number of US active joints (GS score of $\geq$2 and/or a PD score >0) was considered, only 16 patients had active disease in the hand at baseline. Again there was a significant reduction in US activity seen in these patients with a reduction in the median joint count from 2 to 0.5 ($p=0.008$).

Whilst peripheral joint outcome measures detailed above were calculated using all patients, the outcomes for the other domains of PsA (skin, nails, enthesitis and dactylitis) have been restricted to those with involvement of that particular domain at baseline. Skin psoriasis was documented in 32 patients at baseline and PASI scores at baseline were low (median 2.3) with only 14 patients with PASI $\geq$ 3 and only one patient who had a baseline PASI score of greater than 10. PASI responses for both of these groups (all patients with psoriasis and those with baseline PASI $\geq$ 3) are given in table 29.

	Timepoint	Number (%) achieving outcome		
		PASI50	PASI75	PASI90
All patients with psoriasis at baseline (n=32)	Week 12	12 (38)	6 (19)	3 (9)
	Week 24	15 (47)	9 (28)	5 (16)
	Week 36	15 (47)	11 (34)	9 (28)
	Week 48	17 (53)	13 (41)	7 (22)
All patients with baseline PASI $\geq$ 3	Week 12	5 (36)	1 (7)	0 (0)
	Week 24	8 (57)	6 (43)	3 (21)
	Week 36	7 (50)	5 (36)	3 (21)
	Week 48	8 (57)	6 (43)	3 (21)

Table 29 – PASI responses at key timepoints

Enthesitis, dactylitis and nail disease were less prevalent in the cohort affecting 31, 12 and 20 patients respectively. Enthesitis score shown in figure 10 relates to a total sum of all enthesitis sites examined (n=19). Individual results are also shown for the MASES, LEI and IMPACT enthesitis indices. The LEI and MASES scores all showed a reduction in enthesitis activity over the 48 week study period, but the IMPACT index did not identify significant amounts of enthesitis.

Results for count of dactylitic digits and LDI score are shown in figure 11. A significant improvement in dactylitis outcomes was noted within the first 12 weeks ($p=0.002$ for dactylitic digit count and LDI score) with median scores of 0 after this timepoint. The decrease in mNAPSI scores for nail psoriasis was rapid and sustained to the 6 month timepoint when a slowing of improvement was noted (figure 11).

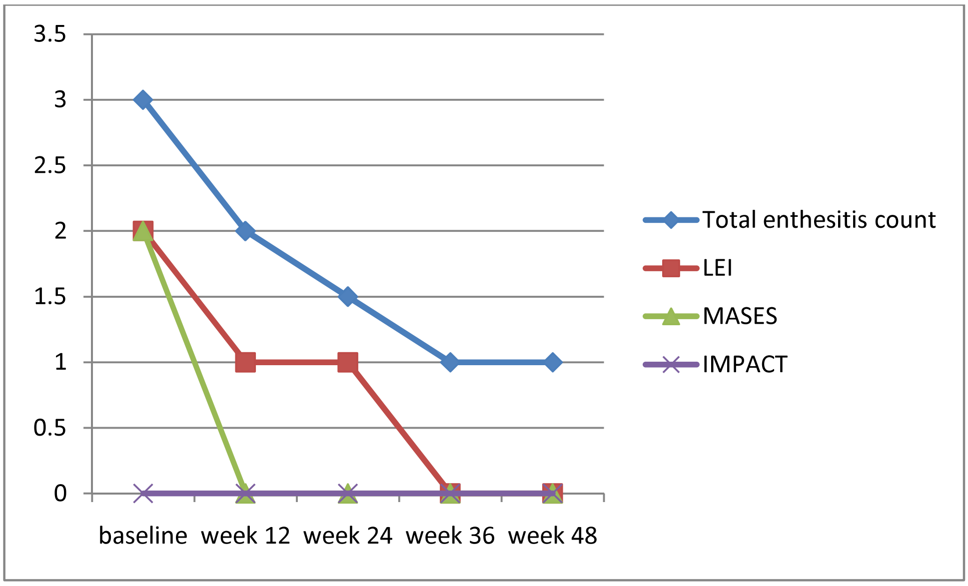

Figure 10 – Change in median scores for enthesitis outcomes for those with involvement at baseline

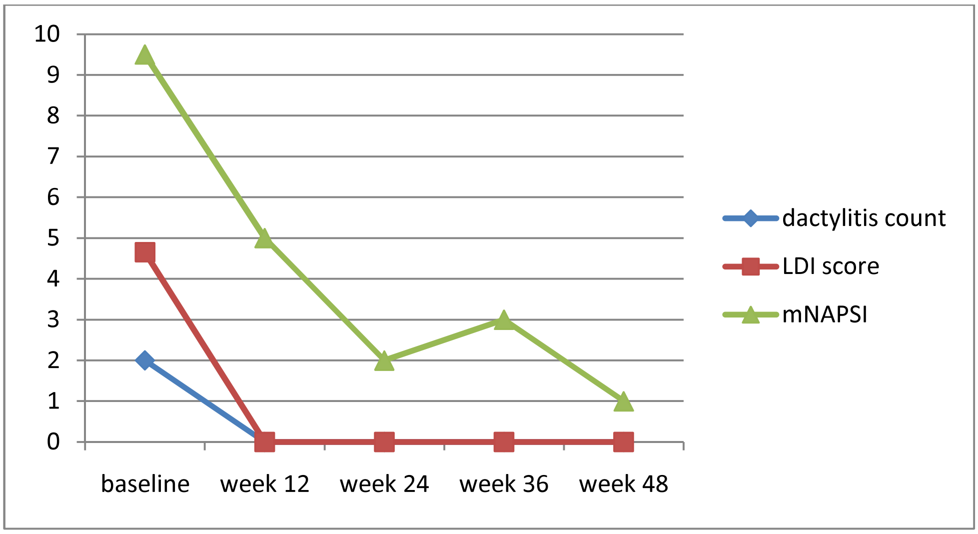

Figure 11 - Change in median score over time for dactylitis and nail outcomes for those with involvement in that domain at baseline

7.3.4 Patient reported outcomes

All patients completed PROMs at 12 weekly intervals. Over the study period, there was a reduction in VAS scores for pain, global disease activity, fatigue and global health, all indicating an improvement in health status (figure 12). Quality of life, as measured by the PsQOL, and functional ability, measured by the HAQ-DI, also showed an improvement over the study period (table 30).

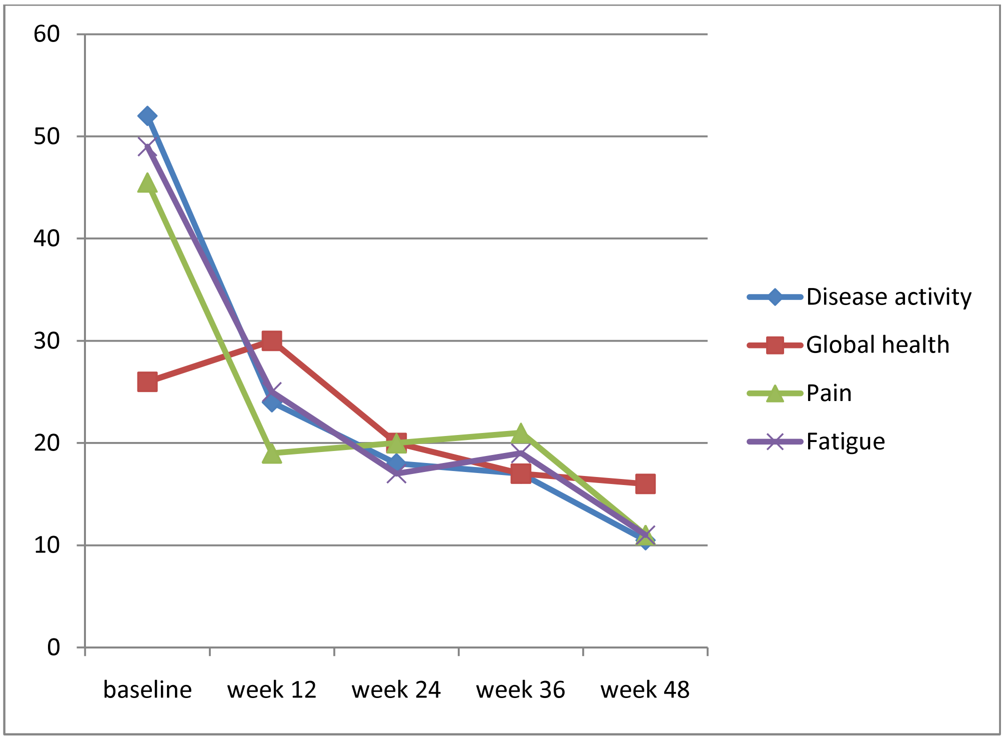

Figure 12 - changes in median VAS scores at key timepoints

	Baseline	Week 12	Week 24	Week 36	Week 48
Median PsQOL	6	4	2	3	2
Median HAQ-DI	0.75	0.44	0.13	0.38	0.13

Table 30 – Quality of life and functional questionnaire scores at key timepoints

7.3.5 Relationship between MDA and other outcome measures

There was a strong association seen between achieving the MDA disease state and the ACR outcome response rate from week 24 onwards ($p<0.004$ for all except ACR20 at week 24, see figure 13). This was most marked at week 48. However, even at week 48, there was not total agreement between ACR outcome measures and the MDA state. When considering the ACR70 response rate, there was one patient who achieved this response but was still not in MDA. Conversely there were seven patients in MDA who did not achieve a 70% reduction in the ACR outcome (table 31). The majority of patients (6 of 7) who achieved MDA but did not achieve an ACR70 response were patients with oligoarthritis. Some patients had shown an improvement in joint counts but not a 70% reduction (eg from three tender joints to one tender joint), and some fulfilled the MDA criteria despite activity in the TJC which prevented them from achieving the ACR outcome.

When comparing blood levels of inflammatory markers in patients with different MDA outcomes, the association was less clear. There was no significant difference between CRP, plasma viscosity (PV) and ESR results for those in MDA and those who were not at any of the key timepoints. However, there were a number of patients in the cohort who did not demonstrate raised inflammatory markers, even at baseline. Analyses were repeated, limiting the patients to those with inflammatory markers greater than the normal reference range (CRP≥10, ESR≥20, PV≥1.72) at baseline. CRP levels were significantly lower at week 48 for those patients in MDA ($p=0.03$), although a significant difference was not found at other timepoints. ESR levels were significantly different at week 24 ($p<0.03$) but not at other timepoints. There were no significant relationships between PV and MDA found at any of the key timepoints.

US data was also used to compare to different MDA outcomes. At week 48 there was a trend towards lower US scores for those in MDA (median GS score 9.5 vs 11, $p=0.48$, median PD score 0 vs 1.5, $p=0.10$) but the difference did not reach significance. Similarly, there was a trend towards a lower number of US active joints at week 48 in those with MDA compared to those who were not (median no 0 vs 1, $p=0.23$) but this was not significant, probably due to the low numbers in this subanalysis (n=15).

		MDA	Non-MDA
ACR20	Yes	19	4
	No	2	14
ACR50	Yes	16	2
	No	5	16
ACR70	Yes	14	1
	No	7	17

Table 31 – Comparison of patients achieving MDA and ACR outcome measures

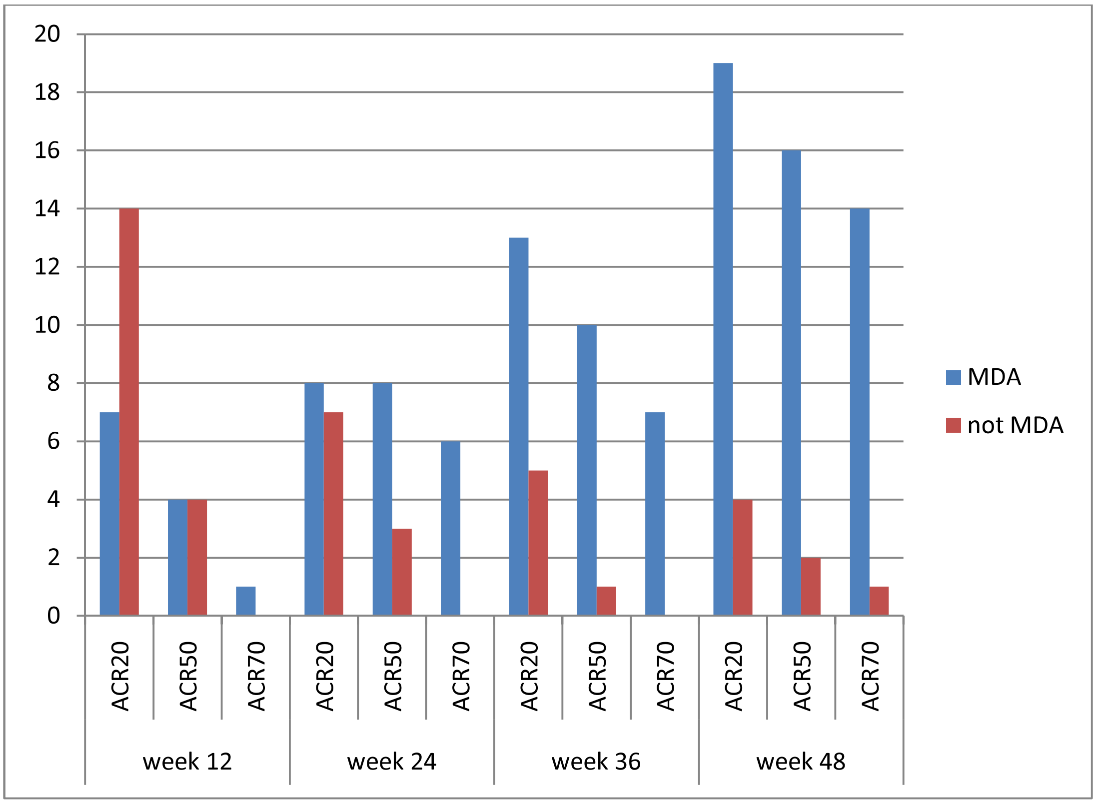

Figure 13 – comparison of ACR responses in those achieving MDA and those not

7.4 Discussion

The TICOPA study is a large RCT designed to investigate the benefits of early and tight control in PsA. There are few studies examining such an early PsA cohort particularly of the planned recruitment size (n=206). The patients all had a disease duration of less than 2 years and the majority fulfilled the CASPAR criteria. Those who did not, had other typical features of PsA and all were found to be seronegative for both RF and anti-CCP antibodies. The vast majority had normal or near-normal radiographs at baseline compatible with early disease.

As the study is currently ongoing, and recruitment is planned to continue until April 2011, unblinded data are not available for analysis. However, of interest, is the fact that this study is the first to prospectively use the newly developed MDA criteria and the blinded data can be used to further evaluate the validity of these criteria.

In this small cohort (n=40), over 50% of the patients combined from the intensive and standard arm achieved MDA over the 48 week study period. Interestingly this exceeds the number seen in the previous validation studies (both observational cohort data (Coates et al. 2010a) and results of the anti-TNF drug trial (Coates and Helliwell 2010)). There are two likely reasons that may contribute to this increased proportion in MDA. Firstly, the patients in TICOPA had early disease and were DMARD naïve prior to starting treatment in the study. They therefore represent a different population from those seen in the established disease cohort in Toronto and the patients recruited to the IMPACT and IMPACT2 studies who had established polyarticular disease and many of whom had previously failed synthetic DMARDs. The other key difference is the use of MDA as a target for treatment for those patients treated in the intensive arm of the TICOPA study. Half of the patients in this cohort had their treatment escalated until they achieved MDA, so the rate of MDA at the end of the study is expected to be higher.

When considering all of the individual aspects of PsA, there were good responses seen in all of these areas. Composite joint scores showed an impressive improvement in arthritis over the study period. In particular, the proportion of patients achieving good responses (such as the ACR70 and EULAR good response) were higher than expected when compared to other published data (Nasonov et al. 2009). There was no significant change identified in measures of radiographic damage over the study period. There are two likely reasons for this. Firstly, in a cohort of PsA patients, even those with established disease, the rate of radiographic progression is not particularly rapid with an average increase of around 1 in the mS-vdH score in one year (Ravindran et al. 2010). Secondly, in contrast to the population of patients recruited to many drug trials previously reported in PsA, this study recruited all patients with any active disease and did not select for polyarticular disease or raised inflammatory markers. Therefore the likelihood of radiographic progression over 48 weeks is lower than that seen in previous studies.

Unlike radiographs, US has the ability to measure active inflammation and was able to identify a change in imaging assessment of disease activity in the study period. To maintain feasibility within the study, only one hand was scanned using US at both baseline and follow up. Due to the heterogeneity of PsA phenotype, only 16 patients had involvement seen in the hand at baseline, but despite the low numbers a significant change in US disease activity was seen over the 48 weeks.

There were good proportions achieving PASI responses despite low levels of skin psoriasis involvement at baseline. Interestingly similar PASI response rates were seen in those with baseline PASI>3 and in the total cohort with skin disease. Although PASI is recognised to be less responsive at the lower end of the scale, it can clearly identify responses in a proportion of patients.

When considering the responses in other domains, a rapid and significant improvement in both dactylitis and nail psoriasis was seen within the first 12 weeks of the study period. During this time, patients had only received synthetic DMARDs, with no prescriptions given for anti-TNF therapy at this stage. The vast majority of patients were treated only with methotrexate which has not been recognised as a treatment for dactylitis or nail disease previously (Cassell and Kavanaugh 2006; Helliwell 2006). The improvement in enthesitis was slower, showing some improvement within the first 12 weeks, but ongoing improvement up to the 48 week visit. Although these data relate to open label treatment in a small number of patients, they suggest efficacy of DMARDs, particularly methotrexate, in many domains of PsA.

PROMs showed a steady improvement over the course of the study period with the largest change seen in the first 12 weeks. There was a significant improvement in patients' VAS scales for global disease activity, pain and global health in addition to questionnaires assessing quality of life and function.

In further investigation of the MDA criteria as an outcome measure, response rates of other outcome measures were compared for those in MDA and those not achieving the target. There is a clear link between MDA and composite joint outcomes such as the ACR outcomes confirming previous validation work. Not surprisingly, the correlation appears strongest for the higher level of responses such as ACR70 where the majority of patients achieving such a significant improvement, also achieve MDA. However there were some discrepancies seen with one patient achieving the ACR70 response but not in MDA and seven patients in MDA who did not achieve a 70% reduction in the ACR outcome.

When considering the different outcome measures in detail, this is not particularly surprising. Firstly, the MDA criteria encompass other aspects of disease such as enthesitis and skin disease that are not taken into account in the composite arthritis outcomes. This may account for some of the discrepancies. Secondly, the ACR outcome measures are response measures in comparison to MDA which is a measure of a certain disease state. Patients with particularly active disease can show an improvement of 70% in their arthritis outcome measures, but still have residual active disease that prevents them from being classified as in MDA. Conversely patients with oligoarticular disease at baseline may be able to achieve MDA but do not have such a reduction of 70% in their joint counts. This differential response between oligoarticular and polyarticular disease subtypes is highlighted by comparing the proportions achieving each of the outcomes. For all of the response measures, a higher proportion of polyarticular patients met these outcomes compared to those with oligoarticular disease. In contrast, the MDA criteria, which measure an absolute level of joint involvement, were more likely to be met by those with oligoarticular disease. This has important implications for choice of outcome measures in psoriatic disease. Arthritis responder indices are likely to be less sensitive to change in patients with oligoarticular disease at baseline.

Relationships between MDA and other measures of disease activity including systemic markers of inflammation and US evidence of synovitis showed some trends but few significant differences. In this small cohort, these analyses are limited due to the small numbers of patients included. Many patients with PsA do not have a significant acute phase response despite active disease. US scans at baseline and follow up were only available for the joints of one hand. The heterogeneity of PsA means that many patients have little or no disease in the small joints of the hand and therefore in a small group, significant associations are unlikely to be demonstrated. Baseline predictors of MDA were briefly addressed using univariate analysis but due to the small numbers in the cohort, multivariate analysis could not be attempted. There was some evidence that patient global disease activity VAS and presence of enthesitis at baseline were predictors of MDA, but this is difficult to interpret as both of these measures are included in the assessment of MDA. Given the small numbers and the link between predictive baseline factors and the outcome measures included in the MDA criteria, it seems that no clear conclusions can be drawn regarding this. Data from the full TICOPA study with 206 patients will allow a future multivariate analysis of multiple factors and this may provide information on predictors of MDA.

7.5 Limitations

The principle limitations of this analysis are the small numbers and the restriction to blinded data to preserve the blinding of the main study. The small numbers analysed mean that predictors of MDA could not be accurately investigated. Only univariate regression could be performed and with small numbers, subtle influences will not have been identified. As discussed above, the associations identified are not truly independent of the assessment of the MDA criteria so they should be interpreted with caution. Detailed analysis of medications used are not available as this would lead to an “unblinding” of the data, so only summaries of treatment data are available to be presented.

However this is the first study using MDA prospectively and offers some insight into outcomes in early PsA treated with synthetic and biologic DMARDs as required. The large range of outcome measures collected covering all domains of psoriatic disease allow assessment of response in all areas of the disease.

7.6 Conclusion

This interim analysis of the larger TICOPA RCT provides insight into the outcomes seen in multiple domains of early PsA. A high proportion of patients achieve the MDA state within the 48 week study period and good responses are seen in all domains of disease and in PROMs. Further validation of the MDA criteria is provided by their concurrent validity with the ACR outcome measures as seen in previous validation work. Due to the small size of the sample, it is not possible, at this stage, to properly investigated predictors of response. However in future this should be possible with the full TICOPA dataset.

8 Conclusions and Future Directions

This thesis is concerned with developing clinical tools and methodology to improve the outcome of PsA. This final chapter will present an overview of the results of the thesis, looking at all of the studies performed and analysing the findings in the context of current literature. The potential research questions arising from the work in this thesis will then be considered.

PsA is now recognised as a potentially damaging and destructive disease and the aim of this research was to provide tools to improve disease management and optimise outcome. The first priority is to identify patients early in the course of their disease so that assessment and therapy can be initiated. However it was identified that there was a lack of validated classification criteria to aid identification of patients with early PsA for both clinical interventions and future research. The recently developed CASPAR criteria have both high sensitivity and specificity in established disease (Taylor et al. 2006), but it is stated in the paper that less than 5% of the original study population had a disease duration of less than 12 months. A few small studies have suggested that the CASPAR criteria may be useful in early disease but no properly powered studies have addressed their validity in early PsA.

Once identified, the next challenge was to optimise management for patients with early PsA. In RA, management has focused on early intervention in the course of disease with "tight control" of inflammatory disease to improve prognosis. However, this concept of "tight control" has not been investigated in PsA. In the RA studies, validated outcome measures such as DAS, clinical disease activity index (CDAI) and simplified disease activity index (SDAI) give definitions of low disease activity or remission that can be used as a target for therapy. One of the major issues preventing research in this area, perhaps reflecting a lack of research in PsA, was the lack of validated criteria to define an "acceptable" disease state. The concept of minimal disease activity had been defined by OMERACT but validated criteria had only been developed for RA using this framework.

This thesis therefore concentrated on these two major challenges to the optimal management of early PsA, and aimed to provide feasible clinical solutions to the early identification of PsA and management using optimal treatment targets.

Chapter Three The validity of the CASPAR criteria in early PsA

In Chapter Three, the CASPAR criteria were found to be sensitive and specific in identifying early PsA. Although their sensitivity is slightly lower than that found in established disease, they performed better than the previous gold standard classification criteria developed by Moll & Wright. Detailed assessment of the patients and controls included in this study highlighted some of the clinical phenotypical differences between early PsA and other form of early inflammatory arthritis. However, there were no individual features that could be relied upon to differentiate diagnosis between PsA and other forms of inflammatory arthritis.

Chapter Four Imaging in early PsA – the extent of sub-clinical disease

Modern imaging is more sensitive than clinical examination for detecting a variety of important joint pathologies. A detailed assessment of a sub-group of patients with early PsA investigated the US evidence for arthritis and enthesitis. There were low levels of sub-clinical arthritis and particularly low levels of US-identified enthesitis. Similarly, the correlation between clinical and US assessment was high suggesting that, in most cases of early PsA, clinical examination provides a reasonable assessment of disease activity for both synovitis and enthesitis.

Chapter Five Defining MDA in PsA

MDA criteria were developed for use in PsA using a web-based questionnaire of international experts. The criteria include clinical measures of arthritis, enthesitis, skin disease and PROMs to ensure that all aspects of psoriatic disease are encompassed.

Chapter Six Validation of the MDA criteria for PsA

Following on from the development of the MDA criteria in the previous chapter, validation work was completed following the methodology of the OMERACT filter. This analysis provided evidence within the domains of truth, discrimination and feasibility proving the performance metrics of the PsA MDA criteria. A large observational cohort and two large datasets from interventional randomised controlled trials were utilised in order to assess their validity in routine clinical practice and as a potential outcome measure for future interventional trials.

Chapter Seven Tight Control of PsA – preliminary analysis of a large RCT

The TICOPA study is the first prospective study to utilise the MDA criteria as a target for treatment in an intensive treatment regime. The study is ongoing and therefore data are limited within this thesis chapter. The preliminary analysis identified significant clinical improvements seen with treatment of early PsA in all domains of the disease. It also confirmed the concurrent validity of the MDA criteria with significant agreement seen between these and other composite outcome measures used in PsA that were designed to measure similar constructs.

In summary, the work in this thesis provides a sensitive and specific tool for early identification of PsA patients and a validated target for treatment that can be utilised in clinical practice, while also presenting preliminary data from a study of a tight-control treatment regimen.

Discussion and limitations of current work

Research addressing the use of the CASPAR criteria in early disease in Chapter Three provides evidence for their use as classification criteria in early disease. Early diagnosis of PsA is recognised to be difficult due to the heterogeneity in clinical phenotype, the potential for patients to present "sine psoriasis" and the lack of confirmatory blood tests. Prior studies developing and validating the CASPAR criteria have concentrated on established disease. The few studies addressing their use in short duration disease have only included a small number of patients and the majority have lacked controls, meaning that only sensitivity and not specificity can be calculated. The sensitivity for the CASPAR criteria was found to be slightly lower in early disease than that in established PsA. Previous authors have predicted this finding as there is little chance of patients fulfilling the radiological element of the CASPAR criteria at an early stage in disease (D'Angelo et al. 2009). However, the criteria do have better sensitivity than the Moll and Wright criteria as they allow a diagnosis of PsA without a requirement to have both arthritis and current evidence of psoriasis. The use of other typical features of PsA to make a diagnosis using the CASPAR criteria means that these criteria are more inclusive when classifying PsA.

The main limitation of the work in Chapter Three is that it does not address the need for diagnostic criteria in an unselected early arthritis population. The ideal characteristics for such criteria are defined according to their planned use. Classification is a separate issue to clinical diagnosis, although following the publication of classification criteria, clinicians frequently misuse them for diagnosis. Classification criteria, used in research, should have a greater emphasis on specificity to ensure a homogeneous population for therapeutic trials and laboratory and genetic studies. Diagnostic criteria should be designed with a higher sensitivity to 'screen' for a particular disease. In diagnosis the impact of misclassification for an individual may have a great impact on their future care and is therefore significant. However in classification, the criteria are applied to a group recruited for research where misclassification of one individual will have less impact.

There are therefore two issues which prevent the work in Chapter Three from addressing this need for diagnostic criteria. Firstly, the CASPAR criteria were developed as classification criteria rather than diagnostic criteria and have also been tested as such in this cohort. The high specificity found in this study means that the criteria are ideal for the classification of patients for future clinical trials. However, their lower sensitivity means that their use as diagnostic criteria is limited.

Secondly the selection of patients used to test the criteria creates limitations. Patients were assigned to either the case or control cohort if the consultant felt they had a diagnosis of PsA or an alternative inflammatory arthritis. Therefore there will have been some patients excluded from the recruitment where the diagnosis was more uncertain. This results in a higher sensitivity and specificity when testing the criteria in this cohort, compared to their true validity in a mixed undifferentiated arthritis population.

The development, subsequent validation and prospective routine use of the MDA criteria has provided a tool for future research and clinical assessment of PsA patients. There is evidence provided in Chapter Four that clinical assessment shows good correlation with US for both arthritis and enthesitis activity suggesting that clinical assessment is reliable in PsA. The concept of MDA was developed by OMERACT, firstly in the field of RA (Wells et al. 2005), and has now been utilised in other forms of arthritis (Magni-Manzoni et al. 2008). The conceptual definition was agreed by a large international group of experts within the OMERACT framework. The development of the MDA criteria for PsA was done with the assistance and expertise of the GRAPPA steering committee and wider membership. The criteria are based on “paper cases” of real clinical patients and were created using expert consensus of a worldwide sample of rheumatology and dermatology experts in psoriasis and PsA.

In Chapter Six the validity of the MDA criteria was tested in both observational cohorts and interventional trial datasets. Using both of these settings allows evaluation of multiple aspects of the OMERACT filter and provides evidence of their utility both as an outcome measure for future research and as a tool for clinical practice. Importantly, their prognostic ability was identified in both cohorts providing encouraging evidence that treating to an objective target can impact on long term outcome. Some aspects of the OMERACT filter have not been assessed or could benefit from further work. The assessment of criterion validity is not possible as there is no recognised gold standard. In these situations, concurrent validity is assessed as an alternative. However this is also difficult as it requires comparing the MDA criteria against other criteria measuring similar constructs. The level of agreement between certain response criteria (such as the ACR measures) and other measures of disease activity has been assessed in the IMPACT data in Chapter Six as well as in the preliminary analysis of the TICOPA data in Chapter Seven. However, at present, there are few composite disease activity measures that encompass all aspects of psoriatic disease and these are still in development.

8.1 Recent research developments relevant to thesis work

8.1.1 Novel diagnostic tools

During the course of this PhD, additional studies have confirmed a high sensitivity and specificity of the CASPAR criteria in established PsA in a variety of populations (Congi and Roussou 2010; Leung et al. 2010). However, no further studies evaluating the use of classification or diagnostic criteria, such as the CASPAR criteria, have been published in early disease. No other potential diagnostic or classification criteria have been suggested. Work in the current literature aiming to identify PsA early has concentrated on the use of screening tools, particularly aimed at dermatology clinics.

There are four PsA screening tools available; the Psoriatic Arthritis Questionnaire (PAQ) (Alenius et al. 2002), the Psoriatic Arthritis Screening and Evaluation tool (PASE) (Husni et al. 2007), the Toronto Psoriatic Arthritis Screening tool (ToPAS) (Gladman et al. 2009) and the Psoriasis Epidemiology Screening Tool (PEST) (Ibrahim et al. 2009a). All are paper-based questionnaires with 5-15 questions designed for completion by the patient prior to their dermatology appointment. All have been tested in dermatology clinics and found to be sensitive and specific as screening tools for arthritis. Some of the questionnaires have also been used in other settings such as UK general practice populations and US family medicine clinics. These screening tools can then be used as a brief intervention by dermatologists or primary care physicians to identify which patients should be referred to a rheumatologist. A head-to-head study comparing three of these questionnaires (PASE, ToPAS and PEST) in dermatology clinics is currently underway in the UK with the aim of identifying which tool performs the best (Helliwell 2010). Patients in the study will then be assessed by a physician for the presence of PsA and will also have the CASPAR criteria applied as classification criteria. This will allow further validation of the CASPAR criteria compared to physician diagnosis in an independent national cohort of newly diagnosed PsA.

8.1.2 Novel composite outcome measures in PsA

The MDA criteria developed as part of this PhD have also been assessed in the current literature by other groups. In particular, analyses of adalimumab clinical trials have looked at the proportion of patients achieving MDA in the ADEPT study (Mease et al. 2009b). The authors reported a significant difference in the proportion of patients achieving MDA after treatment with adalimumab when compared to placebo ($p<0.001$) in keeping with the results of the analysis of the IMPACT and IMPACT2 studies shown in Chapter Six. Interestingly, the authors of the ADEPT study have also proposed a modification to use an alternative psoriasis measure.

The original MDA criteria were developed for use with either BSA or PASI score. The researchers from the ADEPT study have suggested the use of the physicians global assessment (PGA) of psoriasis score of “clear” or “nearly clear” as a cut point for MDA in the skin domain and have analysed this again in the ADEPT data (Mease et al. 2010). This may be particularly useful in patients with little skin psoriasis where PASI in particular can be misleading. It also makes the tool more feasible for routine clinical use as the PGA is quick to complete.

Over the duration of this thesis, there has been significant work in the development of composite disease activity measures for psoriatic arthritis. The CPDAI uses a grid system to assess disease activity in each of the five domains of PsA (arthritis, skin disease, enthesitis, dactylitis, axial disease) and this can be summed to a disease activity score (Mumtaz et al. 2010). The DAPSA (originally the DAREA) is a composite measure of peripheral arthritis activity validated in PsA following its original development in reactive arthritis (Nell-Duxneuner et al. 2010). Both of these are summarised in section 2.3.1.6. Ongoing work under the umbrella of the OMERACT PsA and GRAPPA groups is providing more evidence comparing these existing measures of disease activity. There is data to support the use of the CPDAI and DAPSA within the GRACE dataset and from retrospective analyses of clinical trials. Both perform well but the DAPSA is recognised as a peripheral arthritis measure only; there is no attempt to quantify disease activity in the other domains of PsA. There is also work developing a novel composite index using data from the GRACE initiative (Coates et al. 2010c).

The advantages of the CPDAI, DAPSA and future GRACE composite measures in comparison to that of MDA, is that they allow assessment of a full range of disease activity rather than one particular state. In the future, potential cut offs could be defined for these measures to define remission, low disease activity and high disease activity. However, at present, there are no other proposed definitions of disease states and therefore nothing that could be used as a target for treatment.

8.1.3 Novel treatment regimens in PsA

Investigation of treatment algorithms for PsA is still in its infancy. To date, there have been few studies comparing different treatment algorithms, with the majority of studies concentrating on proving the efficacy of individual drugs against placebo. A small open label study attempted to address the issue of immediate vs delayed prescription of DMARDs. This showed a significant difference at 12 weeks after the differing treatment regimens but did not show any prolonged benefit once the delayed group had commenced on methotrexate (Scarpa et al. 2008b). One study, the RESPOND study, has compared methotrexate vs infliximab for early PsA

(Nasonov et al. 2009) but this study was open label and is likely to be affected by bias introduced by this study design.

There is growing interest in the investigation of optimal treatment for patients with PsA, and the TICOPA study should provide significant insight regarding treatment outcomes with tight control of disease activity. The study is recruiting at six UK sites. It is estimated that recruitment will be complete by July 2011 with results in available in 2012. The comprehensive outcome measures included in the blinded assessments may also shed some light onto the efficacy of synthetic DMARDs in PsA, particularly in less researched domains such as enthesitis and dactylitis.

8.2 Potential research questions arising from this thesis

8.2.1 Diagnosis and classification

Some of the future research questions arising from the work in this thesis have been highlighted in the preceding chapters. There is now evidence that the CASPAR criteria are valid as classification criteria for use in future early PsA research. However, the selection of cases and controls may mean that their sensitivity may have been overestimated. Ideally the criteria should be tested on all consecutive patients attending an early arthritis clinic with prospective follow up to ensure accurate diagnosis and to identify potential evolution of disease.

The CASPAR criteria were designed for use as classification criteria rather than as diagnostic criteria. However, given the lack of diagnostic criteria or algorithms for PsA, there is a risk that they will be used to aid diagnosis. The recent development of screening questionnaires, discussed earlier, will aid appropriate referrals to rheumatology, but validated diagnostic criteria for use in rheumatology clinics could then support an accurate diagnosis of PsA. Although different performance characteristics are required for classification and diagnostic functions, it is likely that similar ‘typical’ features of PsA would be used for diagnostic criteria. The ROC curve analysis of the CASPAR criteria in Chapter Three identified that a lower CASPAR score of 2 or more was associated with a high sensitivity (99%) and slightly lower specificity (95%) than the originally proposed score of 3. As stated above, these are likely to be overestimates due to the selection of cases and controls and the possible exclusion of grey cases. However a future prospective study with longitudinal follow up of early arthritis patients would be able to investigate the use of the CASPAR criteria with a lower required score as diagnostic criteria for early PsA

8.2.2 Assessment of disease activity in PsA

In the future, work on composite measures within the GRACE dataset will allow a powerful comparison of many different disease activity measures including the CPDAI, DAPSA and the eventual GRAPPA-developed composite disease activity measure. As the aim of the GRACE study is to address the validation of proposed composite disease activity measures and develop new measures, there may also be opportunities to compare the MDA criteria with future proposed measures. At present, there are no other definitions of disease state related to these proposed composite indices. However, any proposed definitions could be compared against the MDA criteria to provide evidence of their criterion and concurrent validity against a previously validated measure.

At present there is little longitudinal data regarding the use of US and MRI as outcome measures in PsA. Multiple imaging outcomes will be available in the TICOPA study to compare these different imaging modalities in early PsA. Definitions and semi-quantitative scoring systems developed in RA will be utilised for scoring US as an outcome measure in the study. As seen in Chapter Seven, only 16 of the 38 patients had active disease identified by US of one hand (wrist, MCP and PIP joints), potentially limiting the sensitivity of this measure. It will be interesting to investigate the sensitivity to change of this measure at the group level in a heterogeneous disease where involvement in the small joints of the hand is less universal than in RA.

In recent years, the OMERACT MRI in inflammatory arthritis group has developed and provided initial validation data for the PsAMRIS (McQueen et al. 2009; Ostergaard et al. 2009). Again this is based on RA scoring methods but has been modified to include typical MRI features of PsA. The TICOPA study will provide a large cohort to investigate the use of this scoring system using both high field (3 tesla) and low field MRI (0.2 tesla) scans. The PsAMRIS system scores disease activity in one hand (MCP, PIP and DIP joints) and therefore similar limitations in its sensitivity may exist in PsA given the low proportion of patients with hand involvement seen in Chapter Seven.

8.2.3 Defining disease activity states

Although development and preliminary validation of the MDA criteria has been completed within this PhD, further studies would provide further validation with additional supporting data. There is a plan for further validation of the MDA criteria within the GRACE dataset. To provide additional data on the classification aspect of the OMERACT filter, the MDA criteria will be compared to both physicians' and patients' opinion of disease activity. When the criteria were developed, they were based on physician's opinions of disease activity state, but no subsequent testing against physician's opinion has been conducted in an independent cohort. Correlation with patient's opinion of disease activity has not been investigated previously. This is crucial as the conceptual definition of MDA states that it should be an acceptable disease state for both patient and physician.

As part of the questionnaire sent to GRAPPA members to develop the MDA criteria, the respondents were also asked their opinion of whether or not the patients presented were in remission. The concept of remission is distinct from that of MDA which aims to combine remission and low disease activity. Other research groups have suggested remission criteria (Gladman et al. 2001; Cantini et al. 2008; Lindqvist et al. 2008), but all of these still require validation. Experts in PsA have suggested previously that remission should be defined as an absence of disease activity in any of the domains of PsA including arthritis, enthesitis, dactylitis, axial disease, skin and nail disease (Kavanaugh and Fransen 2006). The data on remission as part of the questionnaires have not yet been analysed. However, the data are available to perform a similar exercise as in Chapter Five to define clinical criteria for remission.

The current concern preventing progress with this project is related to the conceptual definition of remission and whether clinical criteria can accurately reflect this. Remission has been a commonly used concept for years in RA, related to certain DAS, CDAI or SDAI scores. However, studies in RA have shown that these clinical definitions have significant limitations, given that residual disease activity, identified with imaging, can be present (Brown et al. 2006). For this reason, clinical disease activity measures developed more recently, such as the ASDAS in AS, have specifically avoided the term remission when defining disease states. Although the burden of subclinical disease in recent onset PsA appears far lower than that in RA from the work in Chapter Four, there is evidence for some subclinical disease in active treatment-naive PsA. The prevalence of subclinical disease in patients with PsA in remission, and its prognostic significance, is still unknown and this may present similar limitations in clinical assessment. Applying a similar approach with imaging in patients who have achieved MDA at the end of the TICOPA study will allow the extent of subclinical arthritis and enthesitis to be assessed in such a cohort. Assuming that subclinical disease is identified, any criteria for PsA remission based on clinical assessments of disease activity should be clearly labelled as clinical remission criteria to recognise this limitation.

Developing criteria that more accurately represent the concept of disease remission is likely to require imaging techniques that can accurately assess inflammation. At present, ultrasound imaging is likely to be the best modality as it allows a relatively quick assessment of synovitis and enthesitis at multiple anatomical sites using GS and PD. However it does have its limitations. As the sound waves are unable to penetrate the bone cortex, bone marrow oedema (BMO) cannot be assessed, meaning that BMO would not be identified using this technique.

The other limitations in the development of ultrasound remission criteria relate to feasibility. Ultrasound is also both machine-dependent and operator-dependent meaning that significant training is required and standardisation across different clinical locations would be difficult. Current new developments in ultrasound techniques, particularly the advent of automated quantification of volumes and 3D scanning, may allow easier standardisation of techniques. Time is also a concern as scanning multiple joints to assess disease activity would result in a total time for US assessment that may limit its practical use. US research groups have developed a reduced 12 and 7 joint ultrasound counts for RA (Naredo et al. 2008; Backhaus et al. 2009) that show excellent correlation with both clinical disease activity measures and with a full US assessment of 60 joints. This provides a feasible method for longitudinal assessment of disease activity with US in RA. It still requires further testing in patients in clinical remission to ensure that these reduced joint counts identify all subclinical disease. Similar methodology could be applied in PsA to attempt to define a feasible US joint assessment. However, the heterogeneity of joint and entheseal involvement in PsA is likely to mean that more sites need to be assessed to ensure an accurate reflection of disease activity. This will be particularly true in attempting to define remission to ensure that all disease activity is excluded

MRI allows 3D assessment of inflammatory disease and has the advantage of visualising changes within bone such as BMO. This is therefore an attractive imaging option for the assessment of remission when all aspects of disease should be considered. However, at present MRI scans concentrate on one anatomical area to allow adequate resolution of images. It is also relatively time consuming, taking between 30 and 45 minutes to scan one particular anatomical area. In parallel with US, research in MRI has investigated which joint areas must be scanned in RA to identify disease activity and progression. Longitudinal studies frequently image one hand (wrist, MCP and PIP joints) to assess disease activity and progression in RA (Olech et al. 2008). As for US in the discussion above, similar research in PsA may identify key sites for assessment. However, the heterogeneity of joint and entheseal involvement in PsA means that it is likely that a number of anatomical areas would have to be scanned to ensure that there was no disease activity, limiting the feasibility of MRI in assessing remission. New techniques have the greatest potential to alter this, particularly with the advent of full body MRI scanning. This technique is still in development with little validation at present, but potentially means that a full body MRI scan to be performed in 45-60 minutes allowing assessment of multiple joint and entheseal sites.

8.2.4 Future directions for therapeutic studies

The TICOPA study is ongoing and follow-up is expected to be completed in 2012. The analysis of this study will address the issue of tight control and the potential benefits of protocol-led treatment in PsA as its primary outcome with multiple clinical and imaging outcome measures. In addition, the study should provide valuable data to assess the use of non-biologic DMARDs in PsA. There are very few placebo-controlled studies of these medications and therefore the open-label data from TICOPA will provide important clues to the effectiveness of these drugs in the different domains of psoriatic disease. Given the comprehensive nature of the outcome measures collected, future outcome measures currently in development, such as the future GRAPPA composite measure, will be tested within this dataset.

Further research will be needed beyond TICOPA on optimal treatment regimes for PsA using DMARDs and anti-TNF therapies that are currently available. Other algorithms for treatment will need investigating to establish the future direction of clinical care in PsA. Following on from the example in RA, it may be that earlier treatment with combination therapy or more potent drugs may be beneficial in comparison to the step-up approach in treatment utilised in TICOPA. The TICOPA treatment protocol was deliberately designed to follow current National Institute for Clinical Excellence (NICE) guidance (National Institute for Clinical Excellence 2010) for the use of biologics in PsA with the failure of two synthetic DMARDs prior to their use. This ensures that patients in TICOPA who respond well to these drugs can continue on them in the long term. However the early use of biologics has been shown to be beneficial in PsA compared to methotrexate in an open label study (Nasonov et al. 2009) and further research into this is warranted.

In the future, as newer therapies become available their role will also require further investigation. Drugs such as abatacept, apremilast and ustekinumab have all been tested in PsA in phase II clinical trials and further studies are underway. Other drugs, including tociluzimab (anti-IL6) and drugs targeting IL17, are also being trialled but no results are available at present. Biologic drugs directed against targets other than TNF have not shown results comparative to anti-TNF therapies to date, so it seems likely that anti-TNF drugs will remain the first line choice for biologic therapies in PsA. Often the response rate is particularly low in those patients who have previously failed treatment with TNF. This is particularly disappointing as options are limited for this resistant group of patients. Switching to an alternative anti-TNF therapy is the only option currently available and this is likely to remain the treatment of choice until another drug proves efficacy in this subgroup of patients.

The next question raised is whether a rigid treatment algorithm is optimal in a heterogeneous disease such as PsA. The aim of the TICOPA study is to assess the benefit of objective disease assessment linked to a prescriptive treatment protocol. Although objective assessment has logical conceptual benefits, particularly in a disease which can involve many domains, a single prescriptive treatment protocol may not be optimal for all patients with different phenotypes of PsA. The TICOPA protocol has attempted to address this partially by leaving some choices in therapy to the discretion of the treating physician as long as treatment is changed and escalated for those not achieving MDA. However the potential for differential treatment responses means that future studies may have to develop different treatment regimes for different subtypes of PsA. This idea of individualised medical care is has obvious benefits but means that much more research is required to find optimal regimes for different subtypes of disease.

The first potential way of addressing the idea of individualised care in PsA is to use prognostic features as a guide to a treatment algorithm. Research in observational cohorts has identified clinical features that can be used to stratify patients into different prognostic categories. It is recognised that patients with polyarthritis and high systemic levels of inflammation have a poorer prognosis with progressive joint damage and disability. Patients in this category are more likely to benefit from intensive therapy with multiple DMARDs or early use of biologics in a "step-down" approach. However, those with a more benign disease subtype could be treated with a gradual "step-up" approach trialling local therapy with corticosteroids and escalating to DMARDs as required.

The second possible approach would be to investigate optimal treatment regimens separately for different clinical subtypes of PsA. This has some overlap with the use of prognostic features discussed above. In routine practice, it is likely that clinicians use this methodology already to guide their therapy. It is likely that most rheumatologists would use different therapies for asymmetrical oligoarthritis, symmetrical polyarthritis and psoriatic spondyloarthritis in routine clinical practice. However, this idea also raises further issues with definitions of disease subtype which would have to be addressed prior to further research being conducted. Although there have been many different subtypes of PsA proposed and described, there are no clear definitions to classify such populations. Another potential complication is that previous observational studies have also shown that patients can move between different subtypes over time, related either to treatment or differing natural progression of the disease. This may be particularly important in early disease when a patient's disease phenotype may still be evolving.

Beyond the use of clinical features and subtypes to guide therapy, newer techniques such as genetics and translational basic science research may open up far more sophisticated methods for identifying personalised therapies. Very little research has addressed the issue of identifying which patients will respond to different therapies in PsA. To date, little is known about predictors of response to synthetic DMARDs in PsA, although a model combining clinical features and pharmacogenetic markers has been shown to be useful in RA (Wessels et al. 2007). When investigating the response to anti-TNF therapy, genetics research has identified a polymorphism at position -308 in the promoter of the TNF gene which is associated with a differential response in both RA and SpA patients (Seitz et al. 2007). Specific antibodies for IL6, IL17, IL12/23 and other cytokines are available and undergoing testing in PsA. A number of these studies are collecting tissue samples within the clinical trial to investigate genetic and cytokine markers and their correlation with clinical response. With the advent of these newer cytokine-specific targeted therapies, there is great potential for biochemical markers and pharmacogenetics to provide a personalised choice of medication.

Assuming that the prognosis for patients can be improved by the investigation of personalised treatment regimens, the next question raised will be that of treatment continuation. In RA, the concept of remission induction has been established, where initial use of intensive therapy with biologics or combination DMARDs to achieve remission or low disease activity has then been followed by a successful reduction or withdrawal of treatment. Potentially this has benefits for the patients who require less dramatic long-term immune-suppression and other risks related to ongoing therapy. It also has obvious positive cost implications due to reductions in ongoing drug prescribing. In the UK, due to the relatively high costs, the use of biologic drugs is restricted in PsA to those patients who have failed two standard DMARD therapies. However, assuming a positive response, patients are then permitted to stay on lifelong therapy with anti-TNF treatment with a significant cost of around £10,000 per year. If remission induction could also be achieved in PsA, the earlier use of anti-TNF therapy for a limited time period (such as 12 months or after six months in a pre-defined low disease activity state) may be more cost-effective in the longer term. It has been shown that health costs in PsA are closely related to functional ability (as measured by the HAQ-DI) (Poole et al. 2010), so prevention of deteriorating function will significantly reduce the overall cost burden of PsA.

Dose reduction and withdrawal of therapy have not been investigated in PsA. In some patients, PsA is characterised by a relapsing and remitting course where uninterrupted long term therapy may not be required. Therefore, the natural history of PsA in some patients may point to a successful outcome. Many patients ask about withdrawing therapy if they have felt well for a period of time, but their questions regarding the outcome of this have not been answered. Understandably, patients want to know how likely it is that their disease will flare given treatment withdrawal or reduction. There are no studies looking at the likelihood of flare given treatment withdrawal in a significant cohort. The other crucial data currently outstanding would address whether there any baseline patient characteristics that can be used to predict disease flare. Information regarding this in a large cohort would allow a more specific prediction of risks for individual patients rather than for a large cohort of patients with different phenotypes of disease. Finally, the other issue that must be investigated is whether re-introduction of prior therapy can regain control of disease activity so that if PsA becomes active again, it can be successfully treated.

Summary

In conclusion, the future clinical research agenda in PsA needs to continue to address the issues of early diagnosis and optimal treatment algorithms. There is a need to develop diagnostic algorithms for use in clinical practice, in addition to the classification criteria now validated. Current work on composite disease activity measures must be completed with subsequent validation to create a definitive measure for use in future clinical trials. Finally, investigation of different treatment algorithms, with potential withdrawal of treatment in selected individuals, will allow optimal, evidence-based clinical care of patients with PsA in the future.

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