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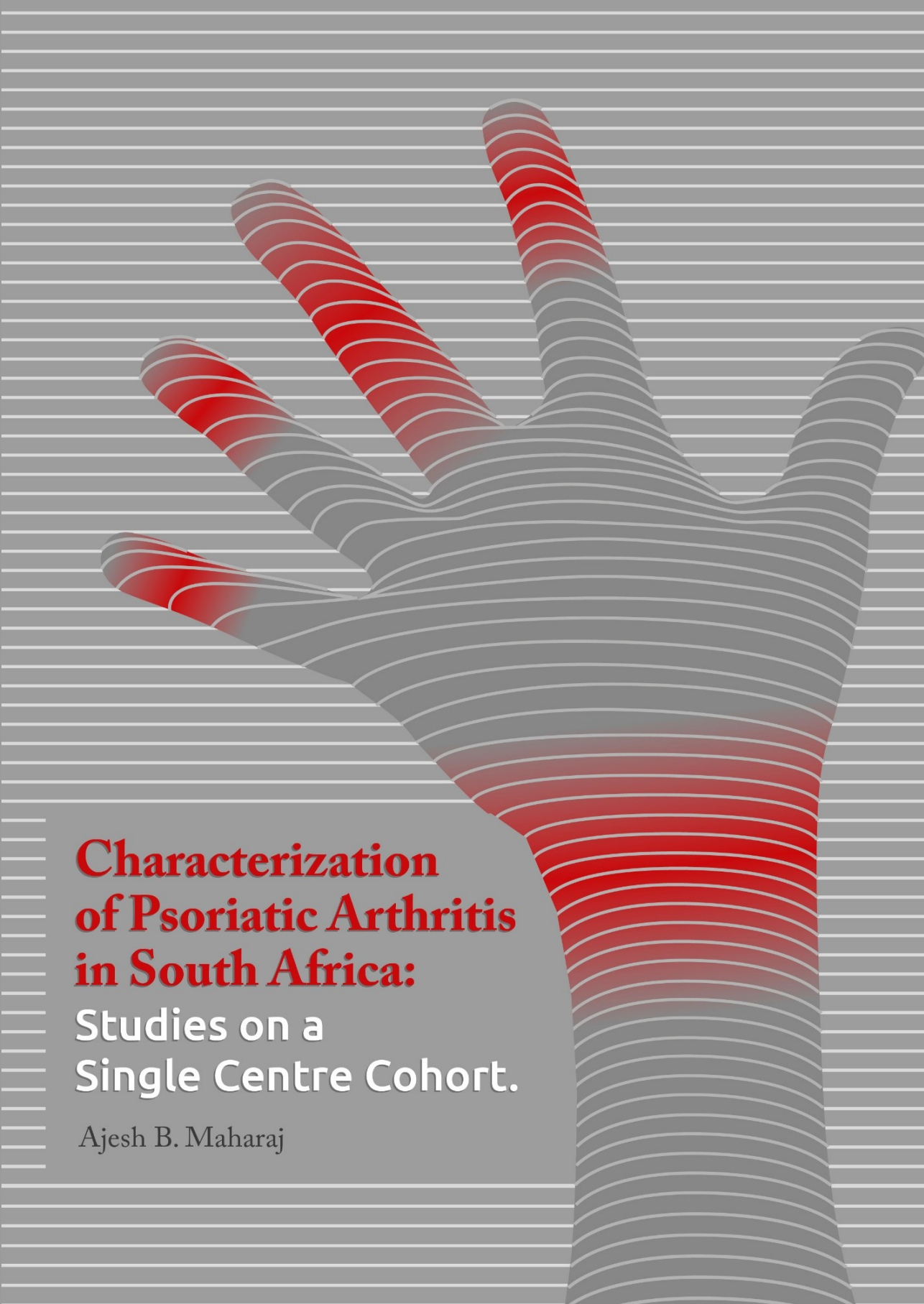

Characterization of Psoriatic Arthritis in South Africa:

Studies on a Single Centre Cohort.

Ajesh B. Maharaj

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Studies on a Single Centre Cohort

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ABBREVIATIONS

AS: Ankylosing Spondylitis
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
BASFI: Bath Ankylosing Spondylitis Functional Index
CASPAR: Classification Criteria for Psoriatic Arthritis
CVS: Cardiovascular system
DM: Diabetes mellitus
GWAS: Genome-wide association studies
HLA: human leucocyte antigen
IL: Interleukin
MHC: Major Histocompatibility complex
PsA: Psoriatic Arthritis
RA: Rheumatoid Arthritis
SpA: Spondyloarthritis
TNF: Tumour necrosis Factor
VAS: Visual analogue scale

PART 1: INTRODUCTION

Chapter 1

General introduction

Psoriasis & Psoriatic Arthritis

Psoriasis

Psoriasis is a heterogeneous chronic inflammatory skin disorder that affects approximately 2 to 3% of the population [1-3]. However, most of the published data are from Caucasian populations in the Western world. Although incidence and prevalence figures for South Africa are not available, its occurrence in African black people appears extremely uncommon. The onset of psoriasis is usually in the early teenage years through to 30 years of age, although individuals of any age may be affected [1-3].

Psoriasis can be triggered by environmental and physical factors in genetically susceptible individuals [4]. Physical trauma to the skin can result in psoriasis, the Koebner phenomenon. Administration of noxious or other proinflammatory stimuli and infection with Streptococcus or other bacteria can initiate the development of psoriasis [4]. Psoriasis usually develops as hyperkeratotic skin lesions, and several pathophysiological changes are noted within the plaques. Primary changes within the psoriatic plaque occur because of an interaction between epidermal keratinocytes, dendritic cells, and T lymphocytes [5]. The interaction between these cells results in the production of increasing amounts of pro- inflammatory cytokines including IL-23, IL-20, IL-1, IL-6, IL-17, IL-19, tumour necrosis factor (TNF) and interferon-gamma, resulting in increased production of β defensins and skin inflammation. Working in concert, these cytokines induce the characteristic keratinocyte proliferation and expansion [6]. While differentiation from a basal cell to a mature keratinocyte in healthy skin usually takes 4 to 6 weeks, in psoriatic plaques, this time is markedly reduced to a few days [4]. The result is a breakdown in the normal skin barrier [5]. Interestingly, several infectious agents have been isolated from psoriatic plaques [4]. The exact role of these agents in the development of psoriatic plaque is unclear.

Psoriatic arthritis

Psoriatic arthritis (PsA) is an inflammatory arthritis, member of the family of spondylarthritides (figure 1) [7-9]. It develops in up to 30% (6-42%) of the patients with psoriasis. It has been shown that in approximately 80% of patients, arthritis follows on psoriasis by about ten years [10]. However, the onset of psoriasis and psoriatic arthritis can be simultaneous [10], and in a small number of patients, arthritis may antedate

the cutaneous manifestations of PsA [10]. Triggers for the development of PsA in a patient with psoriasis are as yet undefined, although infective triggers have been suggested.

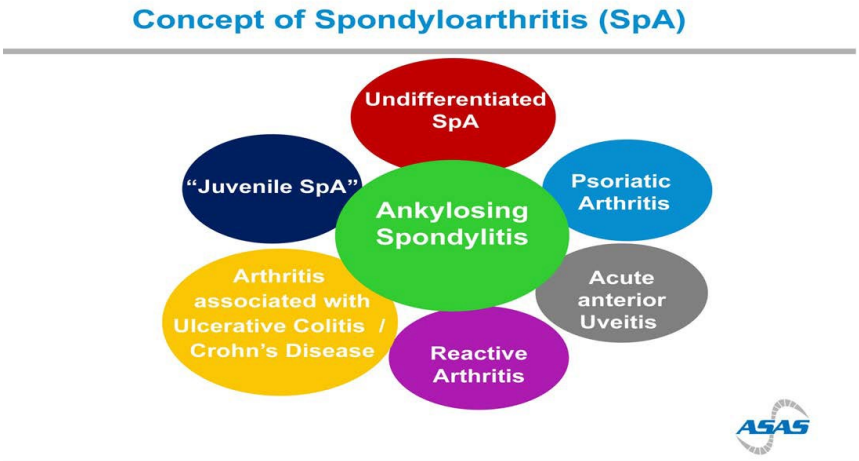

Figure 1. The spectrum of diseases within the spondyloarthritis group. Reproduced with permission from ASAS

Patients with PsA often present with joint pains, which are inflammatory in nature, limitation in the movement range of joints, fatigue and a decreased quality of life as compared to healthy individuals [8]. Another prominent feature may be the inflammation of the entheses, i.e., the insertion of ligaments or tendons into the bone. Mechanical factors seem to be able to induce enthesitis; a phenomenon sometimes referred to as an "internal Koebner phenomenon" [4].

Overall PsA is a heterogeneous disease. In 1973, Moll and Wright discriminated five clinical subtypes, including spondylitis, asymmetrical oligoarthritis, DIP involvement, a symmetrical polyarthritis, and arthritis mutilans [10]. They also noted that these patients were serologically negative for rheumatoid factors. The Moll and Wright criteria helped to differentiate patients with different forms of PsA and distinguish the disease from other rheumatic conditions. The latter may still result in clinical difficulties, since the symmetrical polyarthritis may be difficult to distinguish from seronegative rheumatoid arthritis, while the axial type of arthritis can mimic ankylosing spondylitis, even though PsA more often results in asymmetrical sacroiliitis and a discontinuous spinal involvement with skip lesions compared to ankylosing spondylitis.

The latter can be seen on plain radiographs or MRI scans. Radiological manifestations of PsA include erosions, new bone formation as well as periosteal reactions.

Following on the Moll and Wright criteria, the development of the CASPAR criteria (ClASsification criteria for Psoriatic Arthritis; see table 1) helped to standardise the reporting of PsA [11]. The CASPAR criteria were reported to have a specificity of 98.7% and sensitivity of 91.4% for PsA compared to a group of patients with other forms of inflammatory arthritis.

Table 1: CASPAR criteria: To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with 3 or more points from the following five categories:

Clinical Criteria	Points
Evidence of current psoriasis[1]	2
In the absence of current psoriasis: Personal history of psoriasis[2] or a family history of psoriasis[3]	1
Typical psoriatic nail dystrophy, e.g., onycholysis, pitting and/or hyperkeratosis on current physical examination.	1
Negative rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.	1
Dactylitis , defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist. (Current or on history as recorded by a rheumatologist)	1
Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.	1

[1] Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.

[2] A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.

[3] A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.

A systemic disease

It has now been shown that the inflammatory response extends beyond the skin, joints, and tendon, and that psoriasis and PsA are manifestations of a systemic disorder with a variety of manifestations in the gastrointestinal tract, inflammatory eye disease, cardiovascular disease, and a variety of metabolic abnormalities with the resulting metabolic syndrome (Figure 2) [12]. Indeed, 15 to 30% of patients with PsA and psoriasis have asymptomatic large bowel involvement with acute and chronic inflammation seen on colonoscopy [13,14]. The bowel pathology ranges from asymptomatic focal inflammatory lesions to frank inflammatory bowel disease with histologic features similar to those found in ulcerative colitis or Crohn's disease. It has been noted that bowel involvement is present more frequently in patients with axial involvement of PsA rather than the peripheral disease. The role of non-steroidal anti-inflammatory drugs (NSAID) enteropathy in these patients has not been defined.

Approximately 5 to 7% of patients with PsA develop inflammatory eye disease / uveitis, which is seen more commonly seen in patients with axial disease, males, as well as those who are HLA-B27 positive [15]. Compared to that seen in ankylosing spondylitis, the uveitis / iritis observed in PsA is more often bilateral and can also involve the posterior aspect of the eye and requires urgent therapy to prevent sequelae [16, 17].

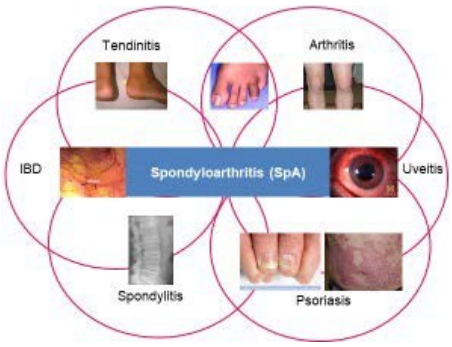

Figure 2. The spectrum of psoriatic arthritis with articular and extra-articular manifestations.

Epidemiology

As noted above psoriasis affects approximately 2 to 3% of the population [1-3]. However, most of the published data are from Caucasian populations in the Western world. Although incidence and prevalence figures for South Africa are not available, its occurrence in African black people seems to be extremely uncommon. The onset of psoriasis is usually in the early teenage years through to 30 years of age, although individuals of any age may be affected [1-3].

There is a wealth of epidemiological data that have documented the association of psoriasis and PsA [7]. A study from Sweden showed a much higher percentage of patients with psoriasis developed inflammatory arthritis as compared to healthy controls (5.4% versus 0.9%) [18]. Following the development of the classification criteria for psoriatic arthritis (Caspar criteria), more standardised reporting is envisaged [11]. In a majority of patients with PsA, the skin disease antedates the development of joint disease [8]. It is only in a minority of patients that joint disease occurs first with psoriasis later. These patients may have other features of PsA including dactylitis and enthesitis. The entity of PsA sine psoriasis has been well documented [19]. The degree of skin involvement does not necessarily parallel the severity of arthritis or predict the type joint involvement viz. peripheral or axial arthritis [20].

Just as there is an increased prevalence of inflammatory joint disease in patients with psoriasis, a population-based study of 661 patients with rheumatoid arthritis reported an increased prevalence of psoriasis as compared to controls (4.5% vs. 2.7%) [21]. This difference was noted to be statistically significant. In the Norfolk registry, it was observed that there was a higher prevalence of psoriasis in patients with seronegative rheumatoid arthritis as compared to seropositive rheumatoid arthritis (20.2% vs. 1.2%) [22]. In this registry, unfortunately, evidence for spondyloarthritis, dactylitis and enthesitis were not reported or examined for. This makes it difficult to judge whether misclassification regarding the underlying diagnosis rheumatoid arthritis plays a role.

Currently, there are no published data on the prevalence and incidence of psoriasis and PsA in South African patients. Therefore, population-based studies are desperately required to report the incidence and prevalence of psoriasis and inflammatory joint disease in our population.

Genetic and environmental factors.

Psoriasis and psoriatic arthritis: Similar disease mechanisms?

The co-occurrence of psoriasis and PsA suggests similarities in disease pathogenesis [23]. And indeed, in both diseases methotrexate and anti-TNF-alpha are effective drugs, suggesting that similar disease mechanisms are operative. However, clinical data suggest there are also clear differences: For example, patients with PsA respond to sulphasalazine and leflunomide, but psoriasis does not. Also, certain biologic agents, for instance, efalizumab, an agent that inhibits T-cell migration, is effective for cutaneous manifestations but does not have any effect on inflammatory arthritis [24].

These differences are supported by differences in recurrence risk in first-degree relatives between psoriasis and PsA [25-27]. The recurrence risk (λs: with a ratio of the risk to siblings and risk the general population) of PsA is more than 27 which is far greater than that for psoriasis alone (between 4 and 11) [28]. The heritability of PsA is greater than that of psoriasis alone. But also the prevalence of psoriasis is much higher among 1st degree relatives of probands with PsA as compared to the general population (19 x greater) [28], again supporting that common susceptibility factors are present.

Studies of gene polymorphisms have substantiated this observation. Psoriasis and PsA have both been linked to several major histocompatibility complex (MHC) class 1 alleles, e.g., *HLA-C*w6, HLA-B*13, B*17, B*27,* and *B*39* [29]**.** Although the association of HLA-C*w6 with cutaneous psoriasis has been well documented, earlier studies reported that its relationship with PsA is less clear [29]. Conversely stronger associations with PsA than with psoriasis were reported for *MICA-A9* [5, 29]. In recent years Genome Wide Association studies (GWAS) have been used to screen the genome for chromosomal locations associated with psoriasis and PsA using over 500,000 markers. These studies have shed more light on the genetic associations and showed that the strongest differential risk for PsA versus psoriasis is encoded by a glutamine located at position 45 in the antigen binding groove of the *HLA-B* gene [30,31] Other PsA-specific single nucleotide polymorphisms (SNPs) are located in the *IL23R* region [32], possibly *TNFAIP3* [31], while two other loci (SNPs on 1q21.3 and SNP rs4908742) did predispose to psoriasis, but hardly or not to PsA [31].

PSORS1 and other HLA antigens.

Psoriasis susceptibility 1 (*PSORS1*) was the first psoriasis susceptibility locus identified, and it was mapped to the MHC class I region [33]. The strong association with *HLA-C*06:02* is thought to account for approximately 1/3 to half of the genetic susceptibility of cutaneous psoriasis [28,33].

The frequency of *HLA-C*06:02* is also increased among patients with psoriatic arthritis as compared to control [5]. It is also associated with an earlier mean age of onset of psoriasis in a cohort of patients with PsA (p= 0.003).

Earlier studies on association of MHC-allele with PsA phenotypes were carried out within small cohorts of patients but may be worthy of note. Axial involvement in PsA was associated with *HLA-B*27* positivity, whereas *HLA-B*38* and *HLA-B*39* were associated predominantly with peripheral arthritis [5]. The presence of the shared epitope configuration in *HLA-DRB1* alleles in the HLA class 2 region in patients with PsA was associated with erosions on radiography [34]. *HLA-B*39, HLA-B*27* in the presence of *HLA-DR*7*, and *HLA- DQ*w3* were all associated with a greater risk for disease progression and poorer prognosis. *HLA-B*22* was reported to be protective against disease progression [5]. Patients with a combination of *HLA-C*w6* and *HLA-DRB1*07* were reported to have a more indolent course of arthritis than patients with these alleles individually. Whether these associations are due to linkage disequilibrium with one or more susceptibility genes within the HLA region, due to differential associations of clinical subtypes (e.g., psoriasis and PsA), due to inclusions of patients with other rheumatic diseases or represent primary associations that are themselves causative is unclear [5]. Studies on gene function, supplemented by data from large fine-mapping studies of the HLA class I region in phenotypically well-defined, homogeneous populations, and studies across different populations will be needed to separate out primary gene-phenotype associations from such effects.

Such an HLA fine-mapping study was recently reported by Okada et al. In this study they confirmed the strong association of *HLA-C*06:02* and *HLA-C*12:03* with both psoriasis and PsA [30]. However, a direct comparison between PsA and isolated skin psoriasis showed a significant effect only of *HLA-B*, notably the presence of glutamine in position 45 in the antigen binding groove of the HLA-B molecule. Of interest, this same glutamine residue is present in *HLA-B*27* and in *HLA-B*38* and *HLA-B*39* alleles previously associated with axial and peripheral PsA respectively. Stratifying on the *HLA-B* in this analysis did not show an additional effect of *HLA-C*.

The IL-23 / T_H 17 pathway

Increased susceptibility to both psoriasis and PsA is associated with genetic variation in the IL-12/IL-23 pathway [35,36]. The *TYK2* locus is associated with PsA at the genome wide significance level [31]; *TYK2* itself is a Janus kinase (JAK) with an important role in the intracellular signalling following cytokine receptor activation, including the IL-12 and IL-23 signalling. The IL-12 and IL-23 share a common p40 subunit. Polymorphisms in the IL-23 receptor (*IL23R)* are associated with risk for other autoimmune diseases such as inflammatory bowel disease and ankylosing spondylitis [37].

IL-23 released by myeloid dendritic cells is responsible for the conversion of naive CD4 T cells to a committed T_H17 cell through induction of the upregulated transcription factor ROR-γt (Figure 4).

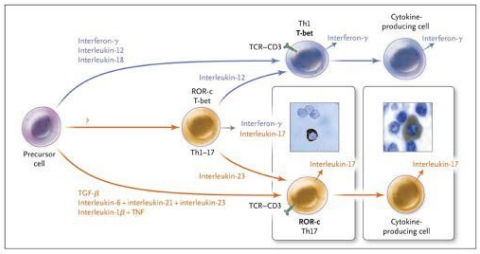

Figure 4. The T_H 17 pathway from precursors cell (CD_4 naive T cell) to committed T_H 17 cell. Reproduced with permission from Miossec P. et.at. N.E. Eng. Med 2009;36:888-898

T_H17 cells are functionally and developmentally distinct from T_H1 and T_H2 cells. There has been a paradigm shift regarding the immunobiology of psoriasis and psoriatic arthritis from being T_H1/T_H2 driven to be a predominantly T_H17 driven disease. T_H17 cells are responsible for the production of pro-inflammatory cytokines, mainly IL-17 and IL-22. Apart from the T_H17 cells, IL-17 is secreted by other cells including neutrophils, macrophages, mast cells, natural killer T cells, natural killer cells, innate lymphoid cells-3 (ILC 3), and γδ T- cells [38-43]. IL-17 A is a prototype of the IL-17 family which consists of 6 IL-17 cytokines, A-F [37,40]. IL-17 has important proinflammatory effects on other cells, illustrated in figure 5. One of the genes required for IL-17 mediated gene expression and -signaling is *TRAF3IP2*, also significantly associated with PsA [44,45].

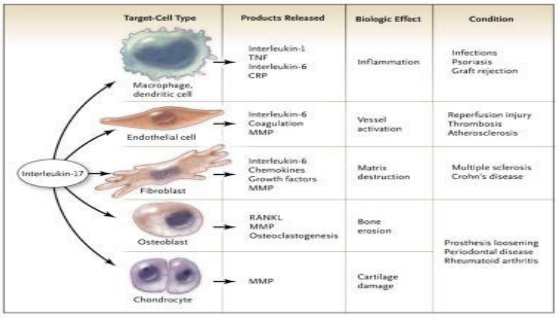

Figure 5. The effects of interleukin 17 on various cell types and their biologic effects. Reproduced with permission from Miossec P. et.at. N.E. Eng. Med 2009;36:888-8

The 5q31 Locus

The long arm of chromosome 5 at position 31 (5q31) contains genes encoding for interleukin 4, interleukin 13, as well as interleukin 5. These cytokines are upregulated in T_H2 cells [46]. Certain allelic variations in these genes confer susceptibility to several inflammatory diseases, including inflammatory bowel disease, especially Crohn's disease, bronchial asthma, and psoriasis [47]. Variants of psoriasis with extracutaneous manifestations may be associated with abnormal regulation upstream from interleukin 13 within the *SLC22A4* gene (also referred to as OCTN1) [47]. Another study showed that the same *SLC22A4* variant was associated with both Crohn's disease as well as PsA [48]. In animal models, IL-4 prevents the development of inflammatory arthritis induced by noxious agents by causing a switch from the T_H1 type to the T_H2 type response. IL-4 and IL-13 also cause downregulation of pathways related to TNF-α and interferon-gamma in keratinocytes through the activation of signal transducer and activator of transcription (STAT) 6 as well as suppressor of cytokine signalling (SOCS)-1 and SOCS-3 pathways [46]. Activation of these pathways causes interference with STAT1 and NF□□ signalling, resulting in reduced levels of β-defensins-4 and -103. IL-4 and IL-13 may also play a role in the induction and activation of T_{REG} cells from circulating naive CD4+ T cells. This process is independent of the presence of transforming growth factor-β or IL-10 but is dependent on antigen-specific stimulation and B7 co-stimulation.

Another genetic factor might also be a good candidate that (partially) explains the association of this region with PsA. It should be noted that in the 5q31 locus GWAS studies report the strongest association with PsA close to the *CSF2* gene [36]. CSF2, also known as GM-CSF, is secreted by macrophages, T cells, mast cells, NK cells, endothelial cells and fibroblasts [49]. This cytokine promotes production of granulocytes and monocytes, inhibits neutrophil migration and induces macrophages to produce reactive oxygen species. Thus, at the moment, in humans the exact role of the 5q31 locus in the initiation, development, and perpetuation of psoriasis and PsA is unclear.

The c-REL / TNIP1 / TNFAIP3 pathway

There is also an association between the alleles of *TNF alpha-induced protein 3 (TNFAIP3)* and psoriasis with an upstream variation of its partner the *TNFAIP3 interacting protein 1 (TNIP1)* [5, 35,44,50]**.** TNIP1 is associated with PsA at the genome wide significance level [35]. *TNFAIP3* encodes a zinc finger/ubiquitin enzyme, A 20 [50]. The proteins that these encode may play a role in restricting NF□B dependent signalling pathways in preventing the inflammatory process [35]. Polymorphisms in *TNFAIP3* are associated with other inflammatory joint diseases such as rheumatoid arthritis and systemic lupus erythematosus. *TNIP1* is upregulated in both psoriatic plaque lesions as well as unaffected skin in patients with psoriasis as compared with skin from healthy controls [51]. The reported association of PsA with c-Rel, as a member of the Rel/NF-κB family, influences both c-REL / TNIP1 / TNFAIP3 pathway and the IL-23 / T_H 17 pathway, since it regulates a.o. TNFAIP3, IL-12B and IL23 expression [52].

Other genetic associations requiring exploration

Several other genes have been associated with PsA at the genome wide significance level. *PTPN22* [53], which has also been reported to be associated with, e.g., rheumatoid arthritis, was selectively associated with PsA, not with psoriasis. Its association was still significant after correction for potential phenotypic misclassification of RA as PsA. PTPN22 inhibits T cell activation, potentially also in the CD8+ T cells that may be more important in PsA than in psoriasis [36].

An associated SNP maps to an intron of the *NOS2* gene, which encodes iNOS (inducible nitric oxide synthase) that is highly expressed in the synovial sublining in PsA [54,55]. An additional SNP maps close to FBXL19, a gene, overexpressed in psoriatic skin, which might indirectly induce expression of NF-κ-B [55]. A further significantly associated locus resides in the *RUNX-3* gene [56], with strongest SNP association in exon1 of the long isoform. This gene codes for a transcription factor that has been reported to promote the differentiation of T cells to CD8+ T cells in the thymus.

Cellular responses in psoriasis and psoriatic arthritis: a role for monocytes?

The importance of T lymphocytes in the initiation and early phases of psoriasis and PsA has been well documented. In a study published in the annals of rheumatic diseases by van Kuijk and co-workers that evaluated the use of adalimumab on PsA synovial tissue, they found that there was a reduction in T cells infiltration and MMP13 expression in the

synovium of the treatment group as compared to placebo [57]. IL-23 released by dendritic cells and keratinocytes in the psoriatic plaque can lead to activation of the T_H17 pathway, with naïve CD4 T cells being committed to becoming T_H17 cells with the subsequent release of IL-17A and IL-22 [58]. And indeed, inhibition of the p40 subunit that is common to IL- 12/IL-23 leads to improvement in both psoriasis and PsA [59]. Also, IL-17 inhibition leads to amelioration of cutaneous and articular manifestations of PsA [60].

But although it is generally accepted that T cells play a key role, reports from animal studies have suggested that other cell types also play a role, in particular monocytes and macrophages. Mice with a targeted deletion from the keratinocytes of Junb and c-jun, both components of the activator protein (AP)-1, developed a psoriasis-like phenotype that was also associated with erosive arthritis and periostitis, similar to that seen in humans with PsA [61]. When the affected mice were then crossed with a mouse strain that lacked T and B cells, the cutaneous manifestation of the disease persisted, however, they had a milder form of arthritis, which was not erosive. In another experiment, knockout mice with Jund and c-jun were crossed with mice that had a deletion of the components of the proinflammatory TNF signalling pathway [61]. In these new mice, a milder form of psoriasis persisted, and these mice did not develop inflammatory joint disease [61]. The significant findings from these experiments revealed that T cells and TNF signalling were not necessary for the development of cutaneous phenotypes whereas T cells were essential for the development of destructive arthritis and TNF was required for joint destruction.

Two murine models of the psoriasiform phenotype, one T-cell dependent and the other T-cell independent, revealed a significant number of macrophages within the cutaneous blocks [62]. The hyperkeratotic skin lesions improved with the deletion of macrophages. The plaque macrophages released large amounts of TNF [62]. TNF and monocyte chemoattractant protein-1 (MCP-1 also known as CC-chemokine ligand-or CCL2) acted together to stimulate monocyte migration and activation within the psoriatic plaque [62]. The hyperkeratotic lesions showed marked improvement in both models upon treatment with anti-TNF alpha drugs [62]. These studies suggest the importance of monocyte-macrophage cells as effector cells in this disease.

Monocytes can differentiate into various other cells including macrophages, osteoclasts, Langerhans cells or dendritic cells in response to environmental stimuli [63]. In histopathological analyses of enthesitis, it was found that monocytes play a pivotal role in the initiation and persistence of enthesitis [64]. Monocytes are also demonstrated in synovial tissue of psoriatic joints, and they were also found in the synovial subsynovial lining [65]. An increased number of circulating osteoclast precursors were observed in the circulation as well as in the synovial tissue of PsA patients [64]. These cells we also found in large numbers at the junction of the pannus and bone [64]. CD14+ monocytes which later develop and differentiate into osteoclasts after being exposed to monocyte

colony-stimulating factor (M-CSF) and receptor activator of NFκB ligand (RANKL), expressed by synovial cells in the inflamed psoriatic synovium, were found in large numbers [34]. Following treatment with anti-TNF drugs, the presence of osteoclasts precursors declined rapidly [66].

CD163+ macrophages have been found on immunohistochemical staining of biopsy specimens from gastrointestinal inflammation in patients with PsA and other forms of spondyloarthritides [65,67]. This transmembrane protein is part of the scavenger receptor, cysteine-rich (SRCR) superfamily. Macrophages that express this transmembrane protein receptor release significant amounts of pro-inflammatory cytokines such as IL-1 and TNF following stimulation with lipopolysaccharide as compared to CD 163- macrophages. It has also been reported in one study that CD163+ macrophages were found in the inflammatory lesions of the colon in patients with Crohn's disease and the joints of patients with spondyloarthritis but were absent in healthy controls. The finding of the presence of these cells in the colon and joints may provide a common pathophysiological link to inflammation at these two sites. Some researchers believe that the inflammatory process begins in the colon and this may be the trigger. It has also been found in murine models of uveitis that the macrophages play a significant role in initiating and perpetuating the inflammatory process in the eye [53].

Monocytes and macrophages may also play a role in the increased risk for cardiovascular disease. Lipid laden macrophages, commonly referred to as foam cells, prevent pro-atherosclerotic lipids from accumulating in the main vessels [68]. It has now been shown that monocytes can potentiate vascular disease. Specific monocyte subtypes can infiltrate the vascular endothelium and enter the atherosclerotic plaques, leading to the liberation of proinflammatory cytokines, interaction with neighbouring adipocytes, and potentiation of atherosclerotic disease. In murine models, hyperlipidaemia and hypercholesterolaemia were associated with increased numbers of circulating monocytes and cells of the Ly6C sub type which preferentially attached to TNF alpha activated endothelium and potentiating the inflammatory process [53]. In another study, mice that had an overexpression of the MCP-1 had insulin resistance with marked macrophage infiltration into the adipose tissue and hepatic steatosis [69]. All these factors, working in concert, show a dynamic relationship between pro-inflammatory macrophages, obesity, insulin resistance and atherosclerosis all of which are present in patients with psoriasis and PsA.

Associations with diabetes mellitus, hypertension, and cardiovascular risk

Patients with PsA show an increased frequency of hypertension, obesity, insulin resistance, type II diabetes mellitus and metabolic syndrome when compared to age-matched controls [70,71]. The factors mentioned above, working in concert, are in part responsible for these patients having premature atherosclerotic disease, early coronary artery disease, myocardial infarction and heart failure. Those especially at risk

for the development of premature coronary artery disease are young male patients, have severe disability resulting from PsA, and show more extensive psoriasis [71].

Several explanations might be put forward to explain these associations. First, the inflammatory process in PsA might actively mediate the development of insulin resistance, diabetes, and the metabolic syndrome, resulting in carotid disease, and cardiovascular disease, eventually manifesting itself as increased morbidity and mortality. Elaboration of pro-inflammatory cytokines leads to insulin resistance, and activation of T cells within the atheromatous plaques with activation of Th1 cytokines leads to acceleration of cardiovascular disease [58]. A second explanation might be that shared risk factors between PsA and these cardiovascular complications form the basis for this common association.
This might include shared genetic predispositions. On the environmental level, epidemiologic studies show that atherosclerosis risk factors include cigarette smoking, atherogenic lipids, hypertension, and hyperglycaemia. Several factors including a sedentary lifestyle, cigarette smoking and unhealthy dietary habits related to PsA might, therefore, explain the association with cardiovascular disease.

A third explanation for this common link between atherosclerosis and PsA, closely related to the one in the previous paragraph, might be that common systemic inflammatory mechanisms play a role. Although the cause of most rheumatological conditions is not well known, it is widely accepted that activation of the immune system and loss of tolerance leading to chronic tissue inflammation is primarily involved. A similar immunobiology is related to psoriasis, a Th1/Th17 immunological, inflammatory skin disease which may also explain the pathogenesis for PsA [72]. In general, T-cell activation promotes the release of proinflammatory cytokines and chemokines that are injurious to a large number of tissues. Similar activation of T cells and release of inflammatory mediators is involved in the pathogenesis of atherosclerosis, atherothrombotic diseases, and the various components of the metabolic syndrome, and systemic hypertension (Figure 5) [58,73].

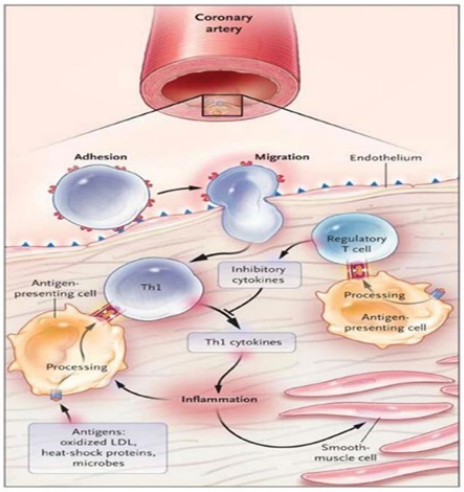

Figure 5. Effects of T-Cell Activation on Plaque Inflammation. Antigens presented by macrophages and dendritic cells (antigen- presenting cells) trigger the activation of antigen-specific T cells in the artery. Most of the activated T cells produce Th1 cytokines (e.g., interferon-γ), which activate macrophages and vascular cells, leading to inflammation. Regulatory T cells modulate the process by secreting anti- inflammatory cytokines (such as interleukin-10 and transforming growth factor β).
With permission: Göran K. Hansson. Inflammation, Atherosclerosis, and Coronary Artery Disease. N Engl J Med 2005; 352:1685-1695

Finally, another intriguing possibility is that increased CV disease risk is due to concomitant medications that are taken by patients with psoriatic arthritis. For example, use of NSAIDs, especially the selective COX II inhibiting drugs might increase the risk of hypertension or heart failure, and increase the risk of myocardial infarction in specific conditions related to PsA.
Clearly further studies are needed to unravel the association of PsA with atherosclerosis and increased cardiovascular risk. At this point in time, the link between rheumatic diseases and atherosclerosis remains a statistical association without well understood causal mechanisms.

Conclusions

The immune system is a very highly regulated network of cells and cytokines, and factors that lead to immune dysregulation are likely to cause imbalance towards the inflammatory process in the skin and joints of patients with psoriasis and PsA. Important shared mechanisms between cutaneous psoriasis and PsA include the IL-23 / Th17 pathway. IL-23 released by myeloid dendritic cells plays a significant role in the differentiation of naive CD4 T cells to committed Th17 cells. IL-23 and IL-12 share a common p40 subunit which could also be important in the immunobiology of psoriasis and PsA. As there are counterregulatory mechanisms within the different subsets of TH cells in PsA, these may be of great interest to investigate the roles in osteoclastogenesis and immunobiology of PsA.

In chapter 2, we discuss the overall assessment of PsA and the importance of incorporating the dermatological manifestations in the holistic assessment of patients of this complex disease. Composite indices and outcome measures are outlined. The treatment of PsA using traditional DMARDs and novel therapies are discussed in chapter 3. This chapter also discusses therapies that are in development.
Important advances have also been made in the clinical definition of the disease. The development of the CASPAR criteria is a step in the right direction to standardize the reporting and assessment of patients for future research. This will facilitate genetic studies and make results from different populations more comparable. Such studies may be extremely important to fine-map disease associations within disease loci. Furthermore, they may help to interpret results from studies performed in different populations. But how do these criteria perform in non-Caucasian populations, especially where the disease is relatively rare? And why is the disease rare in these populations?
In chapter 4, we discuss the clinical, biochemical and radiographic feature in our cohort. The CASPAR criteria had not been validated in a South African population previously. We undertook to validate these criteria in our cohort, and the findings are discussed in chapter 5.
In chapter 6, we describe the complete absence of African black patients with SpA/PsA in our cohort and discuss some of the reasons for its rarity.
Genetic studies support the concept that part of the disease mechanisms is shared between psoriasis and PsA. However, they also show that heritability is higher in PsA. GWAS studies have indeed identified several genes that have effect only in PsA and not psoriasis or have substantially larger effects in PsA. While the association with HLA-C*06:02 is shared, PsA has a unique and strong association with glutamine at position 45 within the antigen binding groove of the HLA-B molecule. This suggest that this variation helps to activate PsA-specific disease pathways not present in psoriasis. Additional evidence from mouse models suggests these pathways might be T-cell dependent, suggesting a role of the glutamine at position 45 in antigen presentation. Clearly more genetic and functional studies are needed to unravel the genetic associations further and elucidate the functional relevance of genes residing in the GWAS-associated regions. In chapters 7 and 8 we study two candidate genetic polymorphisms for association with PsA.
Supported by results from genetic and functional studies novel treatments, including drugs targeting IL-23 and IL-17 signaling, have been developed and show clear effects in psoriasis and PsA. Based on these insights, new drugs, e.g., targeting TYK2 and JAK, are in development. Clearly, the addition of these drugs to our armamentarium will raise new questions regarding treatment strategies. An important issue is whether we can risk stratify patients into different groups based on genetic and other risk factors, and thus tailor treatment to suit each patient individually in order to attain the best possible trade-off between effect, side-effect, risks and cost of the available treatment options. Can we predict imminent onset of disease, and thus initiate preventive treatment? Can we identify and eliminate environmental factors in genetically susceptible hosts that trigger the disease? The answers to these questions will require further studies.

References:

1. Gelfand JM, Weinstein R, Porter SB, et al. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. Arch Dermatol. 2005;141:1537–1541.
2. Brandrup F, Green A. The prevalence of psoriasis in Denmark. Acta Derm Venereol. 1981;61:344–346.
3. Ferrandiz C, Bordas X, Garcia-Patos V, et al. Prevalence of psoriasis in Spain (Epiderma Project: phase I). J Eur Acad Dermatol Venereol. 2001;15:20–23.
4. Krueger JG, Bowcock A Psoriasis pathophysiology: current concepts of pathogenesis Annals of the Rheumatic Diseases 2005;64:ii30-ii36
5. Eder L, Chandran V, Gladman DD. What have we learned about genetic susceptibility in psoriasis and psoriatic arthritis? Curr Opin Rheumatol. 2015 Jan;27(1):91-8.
6. Boyman O, Conrad C, Tonel G, et al. The pathogenic role of tissue-resident immune cells in psoriasis. Trends Immunol 28: 51–57
7. Gelfand JM, Gladman DD, Mease PJ, et al. Epidemiology of psoriatic arthritis in the population of the United States. J Am Acad Dermatol. 2005;53(4):573–577.
8. Taylor WJ. Epidemiology of psoriatic arthritis. Curr Opin Rheumatol. 2002;14:98–103.
9. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of psoriatic arthritis: A systematic review. J Rheumatol. 2008;35:1354–1358.
10. Moll JM and Wright V (1973) Psoriatic arthritis. Semin Arthritis Rheum 3: 55–78
11. Taylor W, Gladman D, Helliwell P, et.al. CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665-73.
12. Scarpa R, Ayala F, Caporaso N et al. Psoriasis, psoriatic arthritis, or psoriatic disease. J Rheumatol 33: 210–212
13. Schatteman L, Mielants H, Veys EM Gut inflammation in psoriatic arthritis: a prospective ileocolonoscopic study. J Rheumatol 22: 680–68
14. Scarpa R Scarpa R, Manguso F, D'Arienzo A, et. al. Microscopic inflammatory changes in the colon of patients with both active psoriasis and psoriatic arthritis without bowel symptoms. J Rheumatol 27: 1241–1246
15. Queiro R, Torre JC, Belzunegui Jet al. Clinical features and predictive factors in psoriatic arthritis-related uveitis. Semin Arthritis Rheum 31: 264–270
16. Paiva ES, Macaluso DC, Edwards A, et al. Characterisation of uveitis in patients with psoriatic arthritis. Ann Rheum Dis 59: 67–70
17. Durrani K and Foster CS. Psoriatic uveitis: a distinct clinical entity. Am J Ophthalmol 139: 106–111
18. Lindqvist UR, Alenius GM, Husmark T, et.al. The Swedish early psoriatic arthritis register-- 2-year follow-up: a comparison with early rheumatoid arthritis. J Rheumatol. 2008 Apr;35(4):668-73.
19. Scarpa R, Cosentini E, Manguso F et al. Clinical and genetic aspects of psoriatic arthritis "sine psoriasis." J Rheumatol 30: 2638–2640
20. Dafna D. Gladman, Philip Helliwell, Philip J. Mease, et.al. Assessment of Patients with Psoriatic Arthritis. A Review of Currently Available Measures. Arthritis Rheum 2004; 50:24–35
21. Hellgren L. Association between rheumatoid arthritis and psoriasis in total populations. Acta Rheumatol Scand 15: 316–32

22. Harrison BJ, Silman AJ, Barrett EM et al. Presence of psoriasis does not influence the presentation or short-term outcome of patients with early inflammatory polyarthritis. J Rheumatol 24: 1744–174
23. van Kuijk AW, Reinders-Blankert P, Smeets TJ, et al. Detailed analysis of the cell infiltrate and the expression of mediators of synovial inflammation and joint destruction in the synovium of patients with psoriatic arthritis: implications for treatment. Ann Rheum Dis. 2006 Dec;65(12):1551-7. Epub 2006 May 25.
24. Ritchlin C. Newer therapeutic approaches: spondyloarthritis and uveitis. Rheum Dis Clin North Am 32: 75–90
25. Elder JT, Nair RP, Guo SW, et al. The genetics of psoriasis. Arch Dermatol 1994; 130:216–224.
26. Di Lernia V, Ficarelli E, Lallas A, et al. Familial aggregation of moderate to severe plaque psoriasis. Clin Exp Dermatol 2014; 39:801–805.
27. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis 2005; 64 (Suppl 2):ii18–ii23; discussion ii 24–25
28. Rahman P, Elder JT. Genetic epidemiology of psoriasis and psoriatic arthritis. Ann Rheum Dis. 2005;64:ii37–9
29. Gladman DD, Cheung C, Ng CM, Wade JA. HLA-C locus alleles in patients with psoriatic arthritis (PsA). Hum Immunol 60: 259–261
30. Okada Y., Han B., Tsoi L.C.,et al. Fine mapping major histocompatibility complex associations in psoriasis and its clinical subtypes. Am. J. Hum. Genet. 2014;95:162–172.
31. Stuart PE, Nair RP, Tsoi LC,et al. Genome-wide Association Analysis of Psoriatic Arthritis and Cutaneous Psoriasis Reveals Differences in Their Genetic Architecture. Am J Hum Genet. 2015 Dec 3;97(6):816-36.
32. Nair R.P., Tsoi L.C., Stuart P.E., et al. Meta-analysis of psoriasis and psoriatic arthritis identifies three new susceptibility loci. J. Invest. Dermatol. 2013;133:S136.
33. Nair RP, Stuart PE, Nistor I, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. Am J Hum Genet 2006; 78:827–851
34. Korendowych E, McHugh N. Genetic factors in psoriatic arthritis. Curr Rheumatol Rep. 2005 Aug;7(4):306-12
35. Nair RP, Duffin KC, Helms C, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. Nat Genet 2009; 41:199–204.
36. Bowes J., Budu-Aggrey A., Huffmeier U., et al. Dense genotyping of immune-related susceptibility loci reveals new insights into the genetics of psoriatic arthritis. Nat. Commun. 2015;6:6046.
37. Lubberts, E. The IL-23–IL-17 axis in inflammatory arthritis Nat. Rev. Rheumatol. 11, 415–429
38. Hueber, A. J. Mast cells express IL-17A in rheumatoid arthritis synovium. J. Immunol. 184, 3336–3340.
39. Noordenbos, T. et al. Interleukin-17-positive mast cells contribute to synovial inflammation in spondyloarthritis. Arthritis Rheum. 64, 99–109
40. Van Baarsen, L. et al. Heterogeneous expression pattern of interleukin-17A (IL-17A), IL-17F and their receptors in synovium of rheumatoid arthritis, psoriatic arthritis, and osteoarthritis: possible explanation for non-response to anti-IL-17 therapy? Arthritis Res. Ther. 16, 426.
41. Moran, E. M. et al. IL-17A expression is localised to both mononuclear and polymorphonuclear synovial cell infiltrates. PLoS ONE 6, e24048.
42. Appel, H. et al. Analysis of IL-17+ cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance

than the TH17- mediated adaptive immune response. Arthritis Res. Ther. 13, R95
43. Cua, D. J. & Tato, C. M. Innate IL-17-producing cells: the sentinels of the immune system. Nat. Rev. Immunol. 10, 479–489
44. Ellinghaus E., Ellinghaus D., Stuart P.E., et al. Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. Nat. Genet. 2010;42:991–995
45. Hüffmeier U., Uebe S., Ekici A.B., et al. Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. Nat. Genet. 2010;42:996–999
46. Ashley Budu-Aggrey, John Bowes, and Anne Barto, et.al. Identifying a novel locus for psoriatic arthritis. Rheumatology (Oxford). 2016 Jan; 55(1): 25–32.
47. Christoforos V, Georgios G, Konstantinos HK, et al. Psoriasis and inflammatory bowel disease: links and risks. Psoriasis (Auckl). 2016; 6: 73–92. Published online 2016 Jul 20. doi: 10.2147/PTT.S85194
48. Danik JS, Pare G, Chasman, DI, et al. Multiple Novel Loci, Including Those Related to Crohn's Disease, Psoriasis and Inflammation, Identified in a Genome-Wide Association Study of Fibrinogen in 17,686 Women: the Women's Genome Health Study. Circ Cardiovasc Genet. 2009 Apr; 2(2): 134–141.
49. Hamilton, J. A., Cook, A. D. & Tak, P. P. Anti-colony-stimulating factor therapies for inflammatory and autoimmune diseases. Nat. Rev. Drug Discov. 16, 53–70 (2016).
50. Genetic Analysis of Psoriasis Consortium and the Wellcome Trust Case-Control Consortium. Strange A, Capon F, Spencer CC, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet 2010; 42:985–990.
51. Infante-Duarte, C., Horton, H. F., Byrne, M. C. & Kamradt, T. Microbial lipopeptides induce the production of IL-17 in TH cells. J. Immunol. 165, 6107–6115.
52. Ellinghaus E., Stuart P.E., Ellinghaus D.,et al. Genome-wide meta-analysis of psoriatic arthritis identifies susceptibility locus at REL. J. Invest. Dermatol. 2012;132:1133–1140.
53. Salvador Mérida, Elena Palacios, Amparo Navea et al. Macrophages and Uveitis in Experimental Animal Models. Mediators of Inflammation Volume 2015 (2015), Article ID 671417, 10 pages
54. Bowes J., Loehr S., Budu-Aggrey A.,et al. PTPN22 is associated with susceptibility to psoriatic arthritis but not psoriasis: evidence for a further PsA-specific risk locus. Ann. Rheum. Dis. 2015;74:1882–1885
55. Stuart P.E., Nair R.P., Ellinghaus E.,et al. Genome-wide association analysis identifies three psoriasis susceptibility loci. Nat. Genet. 2010;42:1000–1004
56. Apel M., Uebe S., Bowes J.,et al. Variants in RUNX3 contribute to susceptibility to psoriatic arthritis, exhibiting further common ground with ankylosing spondylitis. Arthritis Rheum. 2013;65:1224–1231
57. van Kuijk AWR, Gerlag DM, Vos K, et al. A prospective, randomised, placebo-controlled study to identify biomarkers associated with active treatment in psoriatic arthritis: effects of adalimumab treatment on synovial tissue. Ann Rheum Dis 2009;68:1303-1309.
58. Miossec P, Korn T, Kuchroo VK. interleukin-17 and type 17 helper T cells. N Engl J Med. 2009 Aug 27;361(9):888-98
59. Rahman P, Puig L, Gottlieb AB, et al. Ustekinumab Treatment and Improvement of Physical Function and Health-Related Quality of Life in Patients With Psoriatic Arthritis. Arthritis Care Res (Hoboken). 2016 Dec;68(12):1812-1822
60. Kavanaugh A, Mease PJ, Reimold AM et al. Secukinumab for Long-Term Treatment of Psoriatic Arthritis: A Two-Year Follow-up From a Phase III, Randomized, Double-Blind

Placebo-Controlled Study. Arthritis Care Res (Hoboken). 2017 Mar;69(3):347-355
61. Zenz R, Eferl R, Kenner L et al. Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins. Nature 437: 369–375
62. Wang H, Peters T, Kess Det al. Activated macrophages are essential in a murine model for T cell-mediated chronic psoriasiform skin inflammation. J Clin Invest 116: 2105–2114
63. Hamilton JA, Tak PP. The dynamics of macrophage lineage populations in inflammatory and autoimmune diseases. Arthritis Rheum. 2009 May;60(5):1210-21. doi: 10.1002/art.24505.
64. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature 423: 337–342
65. van Kuijk AWR, Reinders-Blankert P, Smeets TJM, et al. Detailed analysis of the cell infiltrate and the expression of mediators of synovial inflammation and joint destruction in the synovium of patients with psoriatic arthritis: implications for treatment. Ann Rheum Dis 2006;65:1551-1557.
66. Goedkoop A, Kraan M, Teunissen M, et al. Early effects of tumour necrosis factor α blockade on skin and synovial tissue in patients with active psoriasis and psoriatic arthritis. Annals of the Rheumatic Diseases. 2004;63(7):769-773. doi:10.1136/ard.2003.018085.
67. Baeten D, Møller HJ, Delanghe J, et.al. Association of CD163+ macrophages and local production of soluble CD163 with decreased lymphocyte activation in spondyloarthropathy synovitis. Arthritis Rheum 50: 1611–1623
68. Döring Y et al. Lack of neutrophil-derived CRAMP reduces atherosclerosis in mice. Circ. Res. 2012;110:1052–6.
69. Boring L et al. Decreased lesion formation in CCR2−/− mice reveals a role for chemokines in the initiation of atherosclerosis. Nature. 1998;394:894–7
70. Ogdie A, Schwartzman S, Laura C Coates, et.al. Comprehensive Treatment of Psoriatic Arthritis: Managing Comorbidities and Extra-articular Manifestations. J Rheumatol November 2014 41(11):2315-2322.
71. Mallbris L, Ritchlin CT, Ståhle M. Metabolic disorders in patients with psoriasis and psoriatic arthritis. Curr Rheumatol Rep 8: 355–363
72. Moseley, T. A., Haudenschild, D. R., Rose, L. & Reddi, A. H. Interleukin-17 family and IL-17 receptors. Cytokine Growth Factor Rev. 14, 155–174.
73. Svetlana Kondratiouk, Natalia Dalt Sova, Arthur L Klatsky, Associations of Psoriatic Arthritis and Cardiovascular Conditions in a Large Population. The Permanente Journal/ Fall 2008/ Volume 12 No. 4

Chapter 2

Assessing disease activity in psoriasis and psoriatic arthritis: impact on management and therapy

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Psoriatic arthritis (PsA) is an inflammatory arthritis that is associated with the skin disease, psoriasis [1]. Both psoriasis and PsA have a significant negative impact on the lives of affected patients. Psoriasis affects approximately 1–3% of the general population and about 30% of patients with psoriasis have PsA [2–4]. The recent development and introduction of new therapeutic agents for the treatment of all forms of psoriasis and PsA has generated renewed interest in the field of outcome assessment [5–7]. Accurate, reliable, and reproducible assessment of disease activity and change with time or therapy are important for understanding the natural history of PsA and relative effectiveness of treatments [8]. In patients with PsA, disease activity predicts the quality of life and function, development of joint damage, cardiovascular disease and mortality [9]. Moreover, in the management of rheumatic disease including PsA, immunosuppressive therapy is usually tailored to the degree of disease activity. Thus, there is a huge perceived need for the development and standardisation of outcome measures to assess disease activity and response to treatment.

The primary challenge in developing and standardising outcome measures for disease activity and response to therapy is that both psoriasis and PsA are complex conditions [10]. Although there was a general recognition of PsA as a chronic inflammatory arthritis with a variety of extra-articular manifestations, it was only in 2006 that the widely accepted classification criteria for PsA were developed through an international effort [11]. Such classification criteria aim to standardise disease definition so that patients with definite disease are included in research studies, especially clinical trials. The Classification Criteria for Psoriatic Arthritis (CASPAR) consists of established inflammatory articular disease with at least 3 points from the following features: current psoriasis (assigned a score of 2; all other elements are assigned a score of 1), a history of psoriasis (unless current psoriasis is present), a family history of psoriasis (unless current psoriasis is present, or there is a history of psoriasis), dactylitis, juxta- articular new bone formation, rheumatoid factor negativity, and nail dystrophy[11].

Beyond diagnosis and illness classification, assessing disease activity of PsA has been difficult due to the diverse manifestations of the disease. PsA is almost always associated with skin psoriasis. Approximately 70% of patients with PsA have pre-existing psoriasis, and about 15% have a simultaneous occurrence of psoriasis and PsA [12]. Nail lesions are widespread and help distinguish between patients who have PsA and those who have rheumatoid arthritis (RA), and between patients with psoriasis who have arthritis and those who do not have arthritis. Nail lesions occur in about 87% of patients with PsA [9].
Peripheral arthritis is present in most patients. Axial arthritis is seen in up to 40% of patients, but only around 2% have pure axial disease [12]. Dactylitis, defined as inflammatory swelling of the entire digit, is a typical feature affecting up to 40% of patients with PsA [12]. Magnetic resonance imaging (MRI) of digits with dactylitis has revealed synovitis, tenosynovitis, soft tissue, and bone marrow oedema [13].

Another principal manifestation is enthesitis, defined as inflammation at sites of tendon and ligament attachments. Enthesitis may be asymptomatic or painful and can affect patient's function and quality of life [14].
Other manifestations, in common with other spondyloarthritides, such as mucous membrane lesions, uveitis, urethritis, inflammatory bowel disease, and aortic root dilatation, are relatively uncommon. Heterogeneity is observed not only in disease manifestations but also in severity and course [15]. Wright described five clinical patterns among patients with PsA: distal predominant pattern, oligoarticular asymmetric, polyarticular RA-like, spondylitis, and arthritis mutilans [16]. However, it is now recognised that these patterns change over time.
The disease manifestations over time can vary from very mild psoriasis or enthesitis to widespread psoriatic plaques, disfiguring nail disease, and severe joint inflammation with destruction that can result in disability and increased mortality [15].

To standardise the assessment of PsA for the appropriate management of disease activity, the Group for Research and Assessment of Psoriasis and PsA (GRAPPA) recommends that PsA is assessed in the following five domains: peripheral arthritis, skin and nail disease, axial arthritis, enthesitis, and dactylitis [15]. It is also recommended that treatment is tailored to the most active domain with due consideration given to disease activity in other areas when choosing therapy. In the absence of a valid and reliable serological marker of disease activity in a complex rheumatic disease, such as PsA, the overall assessment of disease activity is based on the following:

a. Clinical evaluation by the physician,
b. The opinion of the patient,
c. Laboratory assessment, and
d. Imaging.

In clinical practice, rheumatologists take each of these modalities into consideration while making a judgment on how active the disease is, to recommend appropriate treatment. In clinical trials as well as clinical practice, clinicians and researchers have tended to 'borrow' measures developed for other diseases (e.g., rheumatoid arthritis, ankylosing spondylitis [AS]) and apply it to PsA without full validation. The unique characteristics of PsA and the impact of domains not assessed have been ignored. Over the past decade, there has been a general recognition of the importance of assessing all affected domains. The following section describes the recommended clinical assessment of the five domains of PsA mentioned above.

Assessment of peripheral arthritis

The American College of Rheumatology first described a 68/66 tender and swollen joint count more than 50 years ago [17]. Although first described for RA, it has been reliably used and validated for PsA. In PsA, given the involvement of the distal interphalangeal (DIP) joints, a 78/76 tender/swollen joints count has been proposed. However, it is often difficult to distinguish between the involvement of proximal interphalangeal (PIP) and DIP joints in the toes. Therefore, it has been suggested that if either the PIP or DIP of the toe is involved, it should be marked as a PIP [18]. A simpler 28 tender/ swollen joint count has been proposed to include the PIPs 1–5 and metacarpophalangeal 1–5 of the hands, wrists, elbows, shoulders, and the knees bilaterally (Table 1). However, a 28-joint count designed for RA missed 21% of patients with tender joints and 27% of patients with swollen joints in the International Group for Research and Assessment of Psoriasis and Psoriatic Arthritis Composite Exercise (GRACE) study cohort and is therefore not recommended [19].

TABLE 1: Assessment of peripheral arthritis.

Outcome measure	Strengths	Weaknesses
68/66 TJC/SJC	Includes most joints involved in PsA	Time consuming
78/76 TJC/SJC	Includes DIPs	Often difficult to differentiate synovitis of DIPs and PIPs in the feet, time consuming
28 TJC/SJC	Quick and easy	Misses many joints involved in PsA

Abbreviations: TJC: tender joint count; SJC: swollen joint count; DIP: distal interphalangeal joints; PIP: proximal interphalangeal joints.

Skin assessment

As with musculoskeletal involvement, there is marked heterogeneity in psoriasis associated with PsA. The presence of cutaneous psoriasis defines PsA. A number of instruments have been developed to measure the degree of psoriasis, although controversy about their use is still raging (Table 2). A widely used tool is the Psoriasis Area and Severity Index (PASI). The PASI is a quasi-objective measure that which scores the average redness, thickness, and scaling of the lesions (0–4 scale), weighted by the area of involvement. PASI scores range from 0 to 72, where higher scores indicate more severe disease [20]. Several researchers have objected the insensitivity of the PASI to change, especially in patients with mild disease at the lower end of the spectrum. Nevertheless, it is still widely used, primarily to monitor the degree of improvement in clinical trials.

Another key outcome measure used is the Physician Global Assessment (PhyGA), which can be done for extensive disease as well as for localised plaques [21]. The static PhyGA measures the physician's impression of disease activity at a single time point, whereas the dynamic PhyGA assesses global improvement from baseline [21]. The static rather than the dynamic PhyGA is often used for disease activity assessment. The other measure often used is the assessment of total body surface area (BSA) involved by psoriasis [21]. The BSA is a measure of the extent of involvement by psoriasis and is calculated roughly as a rule of nine, similar to the calculation used in the assessment of burns. The palm of the patients' hand is considered to represent one percent of BSA. The advantage of this system is that it is

simple to use. However, the weakness is that it has not been validated in PsA and ignores other features of psoriasis, such as erythema, thickness, and scale. Other measures include Lattice System Physician's Global Assessment (LS- PGA), the National Psoriasis Foundation Psoriasis Score, the product of PGA and BSA (PGA × BSA), the Simplified Psoriasis Index (SPI), and Self-Administered Psoriasis Area and Severity Index [22,23]. A generic patient-reported assessment commonly used is the Dermatology Life Quality Index (DLQI) that measures the psychosocial impact of skin disease [24]. The DLQI has been validated among patients with psoriasis. The DLQI has been used widely in psoriasis trials and for longer-term monitoring of patients [23].

Table 2. Outcome measures used in an assessment of skin involvement.

Outcome measure	Strengths	Weaknesses
PASI	Widely used Assesses severity and extent of psoriasis.	Does not perform well in patients with low extent of involvement, typically seen attending rheumatology clinics; time consuming
PhyGA	Can be used for extensive as well as mild disease	Subjective
BSA	Includes entire area affected by psoriasis Easy to calculate.	Does not assess severity of erythema, thickness or scales
LS-PGA	Uses a quantitative approach to global assessment by integrating the ranges BSA involved and the overall plaque morphology	Requires a computerized algorithm for scoring
BSA × PGA	Can be easily done in clinic may overcome the weakness of BSA	Needs further validation especially for those with less extensive psoriasis
DLQI	Measures impact on quality of life may be more useful in patients with limited psoriasis with severe impact on quality of life such as facial, genital, and hand psoriasis	Subjective not psoriasis specific

Abbreviations: PASI: Psoriasis Area and Severity Index; PhyGA: Physician Global Assessment; BSA: body surface area; LS-PGA: Lattice System Physician's Global Assessment; PGA: Physician's Global Assessment; DLQI: Dermatology Life Quality Index.

Assessment of nails

Nail psoriasis occurs in as many as 50% of patients with psoriasis and more than 80% of patients with PsA [25–27]. The currently commonly used outcome measure in nail involvement in psoriasis is the Nail Psoriasis Severe Index (NAPSI) [28]. This is a numeric, reproducible, objective, and simple tool for the evaluation of the nails in psoriasis. The scale is used to evaluate the severity of the nail bed and nail matrix in patients with nail involvement in psoriasis by area of involvement in the nail unit. A modified version (mNAPSI) was developed to enhance validity and feasibility of the above tool and was shown to have excellent reliability when assessed by dermatologists as well as rheumatologists [22,29]. The mNAPSI is a scoring system that takes into consideration the original NAPSI with certain modifications. Each finger is not divided into quadrants and is assessed as a whole. Onycholysis and oil drop dyschromia is scored from 0 to 3, where 0 = none and 3 = >30% of the nail), pitting from 0 to 3, where 0 = 0 pits and 3 = >50 pits), nail plate crumbling from 0 to 3, where 0 = none and 3 = >50% of the nail). Other features including splinter haemorrhages, leukonychia, red spots in the lunula, and nail bed hyperkeratosis are scored as 1 or 0 depending if these features are present or absent [29]. It was felt that these assessments would add to the sensitivity of the overall grading.
Dermatologists developed the original NAPSI in the clinic. The modifications on the original NAPSI to create the mNAPSI were made by rheumatologists, with dermatologists' input, as a tool for clinical trials. The mNAPSI may be more feasible for rheumatologists.

Axial assessment

Axial involvement occurs in about 40% of patients with PsA. Despite many shared features of axial involvement in PsA with AS, there are significant differences. The sacroiliitis in PsA appears asymmetrical, there is less male preponderance, and the spine often shows skip lesions, rather than an ascending pattern of syndesmophytes in the spine [30–32]. The disease activity is often less pronounced in patients with axial PsA as compared to AS. Unlike peripheral arthritis; it is often difficult to assess inflammation within the axial joints on clinical examination. Axial disease activity is primarily determined by patient reported degree of pain and stiffness and is thus subjective. The questionnaires that have been used were developed for use in patients with AS and have once again been borrowed from AS for use in PsA. These include the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Quality of Life (ASQoL) [33–35] (Table 3). BASDAI was found to perform similarly for axial and peripheral PsA and

did not correlate well with external indicators of disease activity, such as treatment decisions [33]. However, in patients with axial PsA,
BASDAI showed good-to-moderate discriminative ability and correlation with different constructs of disease activity [36]. The ASQoL has been used as a component in scoring the Composite Psoriatic Disease Activity Index [35]. Given its brevity and widespread use, BASDAI may be used for axial disease activity assessment, but the scores need to be interpreted with caution and in the clinical context.
MRI imaging and elevation of acute phase reactants (APRs) are often used to complement clinical assessment. There are some metrological assessments of spinal mobility. These, however, measure limitation of spinal movement in the setting of active inflammation as well as damage or irreversible change that is the end product of ongoing inflammation. The impairment of spinal mobility in AS is independently determined by both irreversible spinal damage and reversible spinal inflammation [37]. Measures of spinal mobility are reliable in PsA, but the relationship between spinal mobility, spinal disease activity, and damage has not been assessed [38]. Moreover, in PsA spinal mobility may also be restricted by other pathologies such as osteoarthritis and diffuse idiopathic spinal hyperostosis [39]. Therefore, spinal mobility assessment is not used to assess disease activity in axial PsA.

Table 3. Outcome measures of axial involvement in PsA.

Outcome measure	Strengths	Weaknesses
BASDAI	Patient reported Easy to calculate	Performs similarly in peripheral and axial PsA Did not correlate with external indicators of disease activity Subjective Not validated for PsA
ASQoL	Patient reported Easy to calculate	

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASQoL: Ankylosing Spondylitis Quality of Life.

Assessment of dactylitis

Dactylitis is a term used to describe inflammatory swelling of the entire digit including bone, tendon sheaths, articular and peri-articular tissues, and is one of the features of spondyloarthritis, and occurs in about 40% of patients with PsA. The clinical recognition of dactylitis is often difficult for the untrained and often misdiagnosed in patients with mild disease. In the case of uncertainty, an ultrasound or MRI of the digit can differentiate dactylitis from other causes of swelling of the digit. Clinically, the degree of disease activity

may be assessed by the number of digits with tender or non-tender dactylitis. The Leeds Dactylitis Index (LDI) quantifies dactylitis based on the circumference of the digit at its base/root (using a dactylometer) and the degree of tenderness [40]. Using the dactylometer increases the specificity of assessing dactylitis since to be considered as dactylitic, the digit should have a circumference greater than 10% than that of the contralateral normal digit.
The LDI while improving specificity and providing a valid and responsive method of assessing response to treatment, is not widely used due to access and feasibility issues. Clinical trials have often used simple counts of the affected digits although, in the recent PsA trial with certolizumab pegol, the LDI was used for measuring response to therapy.

Assessment of enthesitis

Enthesitis is a characteristic feature of psoriatic arthritis and plays a significant role in pathogenesis and classification of the disease. Enthesitis is defined as the inflammation of the areas of insertion of the tendons, ligaments and joint capsules to the bone. Clinically detected enthesitis is prevalent in about 25–78% of patients with PsA and maybe the initial presenting manifestation [41]. Enthesitis is clinically determined by assessing tenderness at entheseal sites. Some entheseal indices have been developed and used in clinical trials (Table 4). These include the modified Mander Enthesitis Index, the index used in the IMPACT infliximab trial, Maastricht AS Enthesitis (MASES) Index, PsA Modified MASES, the Spondyloarthritis Research Consortium of Canada (SPARCC) Index, and the Leeds Enthesitis Index (LEI). The number of entheseal sites assessed in these indices ranges from 6 to 90. Among these instruments, the LEI and SPARCC indices are the most highly rated. The LEI evaluates tenderness at six sites: the lateral epicondyles of the humerus, the medial femoral condyles, and the Achilles tendon insertion site, bilaterally. The SPARCC Index assess 18 sites: the supraspinatus insertion, medial and lateral epicondyles of the humerus, greater trochanter of the femur, the superior and inferior patellar margins, the tibial tubercle, Achilles insertion site, and plantar fascial insertion site, bilaterally. However, if both inferior patellar margin and the tibial tubercle are tender, it is only counted once, to give a maximum possible score of 16. Ultrasound and magnetic resonance imaging assessments of enthesitis may have advantages over clinical examination but are insufficiently studied in PsA. It has been shown that clinical examination may overestimate active enthesitis in PsA [42]. It was also reported that PsA-specific composite scores only partially reflect ultrasound findings [43]. Apart from the assessment of individual domains, global assessments, as well as an evaluation of laboratory and imaging markers, provide us with information on disease activity. These modalities are discussed in the following section.

Table 4. Outcome measures in enthesitis.

Outcome measure	Strengths	Weaknesses
Mander Enthesitis Index	Multiple sites assessed	Time-consuming Not feasible
MASES/PsA modified MASES	Fewer sites than Mander	Mostly axial entheses assessed
SPARCC Index	Easy to perform and validated in both PsA and AS	More time-consuming than LEI
LEI	Easy to perform and validated	Fewer entheses assessed May not be as sensitive to change as SPARCC

Abbreviations: MASES: Maastricht Ankylosing Spondylitis Enthesitis Index; SPARCC: Spondyloarthritis Research Consortium of Canada; LEI: Leeds Enthesitis Index.

Global assessments

Patient (PtGA) and physician (PhyGA) global assessments are both included in the core domain for the assessment of PsA by OMERACT [44]. Global assessments by the patient and the treating physician provide an overall assessment of disease activity and its impact that may not be captured by assessment of individual domains. When the PtGA and PhyGA disease activity were analysed within the GRACE study of the GRAPPA consortium, these measures accounted for 90% of the variability, demonstrating that these measures account for most of the variation in PsA disease activity [45]. Cauli et al. have shown that PtGA assessed using VAS is a reliable tool related to joint and skin disease activity [46].
Since disease activity in the musculoskeletal domain and the skin domain is often not congruent, the two domains may be assessed separately [46]. However, patients tend to score their disease worse than their physicians, with greater discordance for the joints than for the skin [47]. It is recommended that both PtGA and PhyGA be included in disease activity assessment as these measures are complementary.

Patient-reported outcome measures

A number of patient-reported outcome measures have been used to assess global as well as the domain-related impact of disease on quality of life in patients with PsA. The questionnaires that have assessed the quality of life and function are the Health Assessment Questionnaire (HAQ) (or modified HAQ), the Medical Outcomes Survey: Short Form 36 (SF- 36), DLQI, Psoriatic Arthritis Quality of Life (PsAQoL), and the ASQoL [48].
The HAQ is an instrument that assesses function, was originally developed for patients with RA [49]. The HAQ has been validated for patients with PsA and is related to disease activity [50]. A modified version of the HAQ that includes questions on psoriasis did not add any further information to the original HAQ in patients with PsA [51]. The SF-36 was developed to assess health status and well-being across diverse populations, and healthcare settings, and thus is a generic QoL measure but has been validated for PsA [52,53]. The SF-36 domains may be collapsed into two summary scores the physical component summary (PCS) and the mental component summary (MCS) scores. These summary scores are often reported in PsA clinical trials. The PsAQoL is a disease-specific instrument that has been developed and validated for assessing the impact on QoL of patients with PsA [54,55]. This tool has been used to measure improvements in QoL in the phase III RAPID-PsA trial with certolizumab [56]. The DLQI and ASQoL are mentioned earlier in the assessment of skin and axial disease sections, respectively.

Fatigue

Although some researchers would argue that fatigue is non-specific and occurs in many other diseases, it is important to estimate the degree of fatigue in patients with inflammatory arthritis; PsA is no exception here. Fatigue is often a manifestation of disease activity. In fact, pain, fatigue, and skin problems have been identified as domains having the highest relative importance when assessing the impact of illness by patients with PsA [57]. The degree of fatigue often parallels the level of activity in an individual patient and improvement in disease indices often leads to improvement in fatigue. Some instruments including VAS scale to measure fatigue have been proposed. Other measures include multidimensional fatigue inventory (MFI), the fatigue severity scale (FSS), the functional assessment of chronic illness therapy-fatigue scale (FACIT-fatigue), and the multidimensional assessment of fatigue (MAF). The FSS and the FACIT-fatigue have been validated in PsA using observational data [58–60]. FACIT-fatigue has also been validated in an interventional trial with adalimumab [61].

Imaging

In clinical practice, imaging is often used for diagnosis as well as to assess disease activity. Plain radiographs are used to evaluate the presence or absence of periostitis, erosions, osteolysis, subluxation and ankylosis in the peripheral joints, determine the extent of involvement of the sacroiliac joints and the joints of the spine, identify the presence of spurs at the entheses and record the presence of dactylitis [62]. Plain radiographs of the hands and feet have been scored using the Sharp score or the van der Heijde–Sharp score to monitor consequences of persistent disease activity in peripheral joints, i.e., joint damage progression. Current disease activity in the joints is best assessed using ultrasonography (US) or MRI. In peripheral PsA, US can detect both joint involvement (synovitis and erosions) and extra-articular involvement, such as bursitis, tenosynovitis, and enthesitis at the point of care [63]. US is also more sensitive than clinical examination for detecting of synovitis, tenosynovitis, and enthesitis in patients with PsA. However, the use of US in clinical trials has been hampered by a perception of observer dependence and lack of validity [64]. The Sonography of Large Joints in Rheumatology (SOLAR) score that was validated in RA allows qualitative and quantitative evaluation of large joint involvement in PsA and AS patients and may be useful for monitoring response to therapy [65]. Such scoring systems need further development and validation. For monitoring entheseal involvement in PsA, different combinations of

entheses have been suggested, but no consensus exists on a single scoring system. The Glasgow Ultrasound Enthesitis Scoring System or Madrid Sonographic Enthesitis Index scoring systems are most often used [66– 68]. Recently, new PsA ultrasound composite scores (PsASon22: 22 joints [6 MCPs, 4 PIPs of hands, 2 MTPs, 4 DIPs of hands, 2 DIPs of feet, 4 large joints] and 4 entheses [bilateral lateral epicondyle and distal patellar tendon] and PsASon13: 13 joints [2 MCPs, 3 PIPs of hands, 1 PIP of feet, 2 MTPs, 1 DIP of hands and 2 DIPs of feet and 2 large joints], and 2 entheses [unilateral lateral epicondyle and distal patellar tendon]) that includes assessment of joints as well as entheses were developed and provided sufficient convergent construct validity, sensitivity to change, reliability, and feasibility [69].

MRI may provide a more objective assessment of inflammatory activity affecting the peripheral and axial skeleton and the entheses. However, cost, discomfort, and time constraints make scanning of the entire skeletal system less feasible and prevent its more extensive use. The OMERACT MRI in Arthritis Working Group has developed an MRI scoring system for peripheral PsA in the hand, and, recently, the forefoot [63]. The PsA MRI Scoring system (PsAMRIS) was developed using the RA MRI Scoring system RAMRIS as a template. The PsAMRIS is the most validated scoring system for use in PsA and offers good intra-reader and inter-reader reliability, and sensitivity to change for inflammatory parameters [70,71]. Very little work has been done in assessing axial PsA using MRI. Whole body MRI may provide global disease activity scores and shows promise [72].

Laboratory measures of disease activity

Acute phase reactants (APRs) are commonly used to gauge the degree of systemic inflammation in a variety of inflammatory states. However, these measures perform poorly when assessing disease activity in PsA. Traditional APRs, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are elevated in only about 50% of patients with PsA despite the presence of clinically active disease [73]. Analyses of data from drug trials show that APRs are not highly specific in discriminating placebo response from treatment response [74]. These markers may, however, have prognostic value.
Elevated ESR/CRP is associated with joint damage progression as well as mortality [75,76]. In a complex disease such as PsA, it is unlikely that a single biomarker will prove sufficient. Research groups are working on identifying a panel of biomarkers that reflect disease activity.

Bringing it all together: composite disease activity measures

One could argue that in a heterogeneous disease like PsA, each domain of activity (e.g., skin or peripheral arthritis) should be assessed for activity by itself and treated appropriately keeping in consideration disease activity in other domains. This approach is often recommended in clinical practice. However, there are advantages of having a composite measure of disease activity. Such measures permit an appraisal of global disease activity at a glance, allows defining of high and low disease activity, and the creation of response criteria. Moreover, composite scores are more sensitive to change and have better discriminative ability. Disadvantages are that they are complicated to calculate and difficult to break down into their individual components [77,78]. Moreover, a single score may mask improvements in some domains and worsening in others. Therefore, when assessing treatments that do not work equally well for each of the disease manifestations, a single composite score may not detect a differential response.

There are two types of composite indices: responder indices, such as American College of Rheumatology 20% improvement (ACR20) response and PsA Response Criteria (PsARC), measure changes in disease states following an intervention, whereas indices, such as the Disease Activity Score (DAS) measure both disease activity at a single time point and changes in disease activity after treatment interventions and are thus both a static measure of disease activity and a responder index. Ideally, a composite index should combine practicability and feasibility with validity and clinical relevance and be easily applied in day-to-day treatment situations. It should provide an absolute measure of disease activity, as well as response to therapy [45].

Most of the outcome measures for psoriatic arthritis used in clinical trials have been responder indices ‘borrowed’ from RA (ACR responses). The other domains have been investigated independently using measures developed for moderate-to-severe psoriasis (PASI 75 response), or using methods developed in PsA (enthesitis, dactylitis) or ignored (e.g., axial PsA). The primary outcome measure adopted for all recent trials with biologics or small molecules has been the ACR20 response criteria. An exception was the novel joint- based measure developed for the Veterans Administration Trial of sulfasalazine that subsequently came to be known as the PsARC [79]. The DAS 28 and its variants have also been used [80]. These measures appear to function appropriately in the context of polyarticular PsA. In fact, using the data from two randomised placebo-controlled trials of tumour necrosis factor inhibitors (TNFi), it was shown that the EULAR criteria (DAS28) performed better in discriminating the active drug from placebo than the ACR20 improvement criteria, which in turn performed better than the PsARC [74].

The first PsA-specific responder index other than the PsARC that was developed using data from phase III randomised placebo-controlled trials of TNFi was the PsA Joint

Activity Index based on components of the ACR30. The PsAJAI performed better than the ACR20 and PsARC [81]. This index, however, did not explicitly include skin, entheses, or axial domains. Subsequently, some static measures of disease activity that may also be used as responder indices were developed. These include the Composite Psoriatic Disease Activity Index (CPDAI), Disease Activity in PsA (DAPSA), Psoriatic Arthritis Disease Activity Score (PASDAS), and the GRAPPA Composite Exercise (GRACE) Index.

The CPDAI was based on the GRAPPA treatment grid that recommended that disease activity be assessed as absent, mild, moderate, and severe in each of the five PsA domains (peripheral arthritis, skin, and nails, axial arthritis, enthesitis, dactylitis), and treatment be based on the most active domain considering disease activity in the other domains [15]. To calculate CPDAI, each domain of PsA is assessed using a measure of disease activity and a measure of disease impact and scored from 0 to 3 for no activity, mild, moderate, and severe activity and directly added to give a score ranging from 0 to 15 [35]. The CPDAI correlated well with patient and physician global scores and was able to differentiate between different etanercept doses in the PRESTA study [35,82]. The DAPSA is essentially Disease Activity index for Reactive Arthritis (DAREA) applied to patients with PsA [83]. The DAPSA (SJC66 + TJC68 + PtGA + pain + CRP) is a composite joint measure that incorporates full joint counts but does not assess other aspects of the disease. To overcome the perceived inadequacies of available composite measures, GRAPPA conducted the GRACE study to develop novel composite outcome measures. Five hundred and three patients were recruited and assessed at baseline, 3, 6, and 12 months. The gold standard for disease activity was the decision of the physician to change or escalate treatment for active disease. Based on the measurements obtained at baseline two outcome measures were developed: The PASDAS and the adjusted mean of the desirability function (AMDF). The latter was later modified and renamed as the GRACE Index [45]. The PASDAS is a weighted index including seven components identified on principle component analysis with weighting using logistic regression coefficients. The GRACE Index is based on the arithmetical mean of eight domain measures transformed using desirability functions [45]. In the GRACE study, these newly developed measures were compared for their ability to discriminate between subjects according to the decision to change treatment to the CPDAI, DAPSA, and DAS28. The PASDAS and AMDF performed better than other measures. Subsequently, these measures were compared retrospectively with data obtained from the GO-REVEAL study in which Golimumab 50 and100 mg once every 4 weeks was compared with placebo. This study concluded that the PASDAS and AMDF were better able to distinguish treatment effect, having larger effect sizes at 24 weeks. PASDAS, AMDF, and (modified) CPDAI better-reflected domains, such as skin, enthesitis, and dactylitis [84]. Further work has defined candidate cut-offs for low, moderate, and high disease activity as well as treatment response for these measures [85]. These need further validation.

Perhaps the more feasible PsA disease activity measure that includes measures of activity in multiple domains of psoriatic disease is the Minimal Disease Activity (MDA) criteria. The MDA is a measure of state and is proposed as a target for treatment. The criteria indicate that a patient is in MDA if he/she fulfils five of the seven following criteria: tender joint count ≤ 1; swollen joint count ≤ 1; PASI ≤ 1 or BSA ≤ 3%; patient pain VAS ≤15; patient global disease activity VAS ≤20; HAQ ≤0.5; and tender entheseal points ≤ 1 [86]. These criteria were validated in an observational cohort and retrospectively using data from phase II and III infliximab studies of PsA [87,88]. Retrospective analyses of the GO-REVEAL trial dataset also revealed that among golimumab-treated PsA patients, better long-term functional improvement, global patient assessment, and radiographic outcomes were observed when patients achieved persistent MDA [89]. The MDA criteria have now been used as a target for treatment in a randomised trial that compared a 'tight control' strategy to standard care [90]. In the tight control, arm treatment was escalated based on a standard protocol if the patient did not satisfy MDA criteria. The study showed that 'tight control' of PsA disease activity through a treat-to- target approach based on MDA significantly improves joint outcomes for newly diagnosed patients, with no unexpected serious adverse events [90].

Conclusions

Assessing disease activity in a complex disease like PsA is challenging. Over the last decade, clinicians and researchers interested in PsA have moved away from using measures borrowed from RA or AS and from assessing only one or few domains to evaluating and treating the entire spectrum of disease in the whole patient by taking into consideration all relevant domains. Newer PsA-specific domains have been developed and recently used in interventional trials. A few candidate measures show promise and further validation is required. These measures will also inform the development of 'objective' biomarker-based measures as has happened in RA [91]. Ultimately these measures should be used in regular clinical practice (as is increasingly being done in diseases, such as RA). Toward this end, knowledge translation and exchange with clinicians at the forefront of rheumatology care is essential, so that long-term outcomes such as joint damage, functional impairment, and cardiovascular disease will improve.

Expert commentary

It is now well recognised that PsA is a unique, complex inflammatory disease with varied manifestations. Disease activity assessment until recently was focused on the

evaluation of one or few domains using instruments developed for evaluation of other conditions. With the development and introduction of new therapies for both psoriasis and PsA, it was recognized that the assessment of disease activity and the available outcome measures were inadequate and did not reflect disease status of the patient as a whole. Over the past few years, available outcome measures have been evaluated, and innovative measures developed through an international collaborative effort that has involved physicians and patients. The concept of treating to target has been drawn up and implemented in an interventional trial. It is expected that better disease activity assessment and treating to target will lead to a proper evaluation of older as well as novel therapies and better long-term outcomes. Composite disease activity measures will have the greatest impact in clinical trials. But in clinical practice, the use of composite measures remains controversial, since a single score may mask improvements in some domains and worsening in others. Valid and reliable assessment of disease activity in PsA remains difficult. It is hoped that with further research involving patients, clinicians and researchers will lead to better evaluation of currently available measures and that it will result in the development of more objective blood- and imaging-based biomarkers of disease activity. The newly developed outcome measures will need to be further evaluated in formal clinical trials as well as in observational cohorts.

Five-year view

Like all in other rheumatic diseases, outcome assessment and clinical management of PsA is undergoing constant changes resulting in progressively improving short and long-term outcomes. Over the next five years, we expect that the novel outcome measures that have been developed will be fully validated and the advantages and disadvantages compared to existing measures will be better defined. These tools will lead to better designed clinical trials with novel as well as older (e.g., methotrexate) therapies. We also envisage that these tools will be made more user-friendly to the busy practising clinician with the use of mobile apps as is already happening in RA. Validated tools will also help researchers develop more ‘objective’ biomarker-based assessment tools for assessing disease activity and predicting response to therapy and joint damage. With better recognition of PsA and related conditions, and constant improvement in outcome measures the outlook for these patients is steadily improving. A better understanding of the pathogenesis of PsA and psoriasis and better assessment of disease activity will lead to the development of safer, and more effective therapies. These treatments, hopefully, will have improved outcomes with a better safety profile.

References

1. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum. 1973;3:55–78.
2. Gelfand JM, Weinstein R, Porter SB, et al. Prevalence and treatment of psoriasis in the United Kingdom: a population based study. Arch Dermatol. 2005;141:1537–1541.
3. Brandrup F, Green A. The prevalence of psoriasis in Denmark. Acta Derm Venereol. 1981;61:344–346.
4. Ferrandiz C, Bordas X, Garcia-Patos V, et al. Prevalence of psoriasis in Spain (Epiderma Project: phase I). J Eur Acad Dermatol Venereol. 2001;15:20–23.
5. Mease P. Tumour necrosis factor (TNF) in psoriatic arthritis: pathophysiology and treatment with TNF inhibitors. Ann Rheum Dis. 2002;61:298–304.
6. Gottlieb A, Antoni C. Treating psoriatic arthritis: how effective are TNF antagonists. Arthritis Res Ther. 2004;6(Suppl. 2):S31–35.
7. Vaz A, Barton J, Ritchlin C. Psoriatic arthritis: an update for clinicians. Int J Adv Rheumatol. 2004;2:126–134.
8. Mease PJ, Antoni CE, Gladman DD, et al. Psoriatic arthritis assessment tools in clinical trials. Ann Rheum Dis. 2005;64(Suppl 2):ii49–54.
9. Gladman DD, Antoni C, Mease P, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64 (Suppl 2):ii14–7.
10. Scarpa R, Oriente P, Pucino A, et al. Psoriatic arthritis in psoriatic patients. Br J Rheumatol. 1984;23:246–250.
11. Taylor W, Gladman D, Helliwell P, et al.; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665– 2673.
12. Gladman D, editor. Psoriatic arthritis. Berlin: Springer-Verlag; 2005.
13. Healy PJ, Groves C, Chandramohan M, et al. MRI changes in psoriatic dactylitis–extent of pathology, relationship to tenderness and correlation with clinical indices. Rheumatology (Oxford). 2008;47:92–95.
14. Sakkas LI, Alexiou I, Simopoulou T, et al. Enthesitis in psoriatic arthritis. Semin Arthritis Rheum. 2013;43:325–334.
15. Ritchlin CT, Kavanaugh A, Gladman DD, et al.; Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Treatment recommendations for psoriatic arthritis. Ann Rheum Dis. 2009;68:1387–1394.
16. Wright V, Moll JMH. Psoriatic arthritis. In: Wright V, Moll JMH, editors. Seronegative polyarthritis. Amsterdam: North-Holland Publishing Co; 1976. p. 169–223.
17. Deandrade JR, Casagrande PA. A seven-day variability study of 499 patients with peripheral rheumatoid arthritis. Arthritis Rheum. 1965;8:302–334.
18. Gladman DD, Mease PJ, Healy P, et al. Outcome measures in psoriatic arthritis. J Rheumatol. 2007;34:1159–1166.

19. Coates LC, FitzGerald O, Gladman DD, et al. Reduced joint counts misclassify patients with oligoarticular psoriatic arthritis and miss significant numbers of patients with active disease. Arthritis Rheum. 2013;65:1504–1509.
20. Fredriksson T, Pettersson U. Severe psoriasis: oral therapy with a new retinoid. Dermatologica. 1978;157:238–244.
21. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis. 2005;64(Suppl 2):ii65–73.
22. Chandran V, Gottlieb A, Cook RJ, et al. International multicentre psoriasis and psoriatic arthritis reliability trial for the assessment of skin, joints, nails, and dactylitis. Arthritis Rheum. 2009;61:1235–1242.
23. Chalmers RJ. Assessing psoriasis severity and outcomes for clinical trials and routine clinical practice. Dermatol Clin. 2015;33:57–71.
24. Finlay AY, Kelly SE. Psoriasis – an index of disability. Clin Exp Dermatol. 1987;12:8– 11.
25. Farber EM, Nall L. Nail psoriasis. Cutis. 1992;50:174–178.
26. Elkayam O, Ophir J, Yaron M, et al. Psoriatic arthritis: interrelationships between skin and joint manifestations related to onset, course, and distribution. Clin Rheumatol. 2000;19:301–305.
27. Williamson L, Dalbeth N, Dockerty JL, et al. Extended report: nail disease in psoriatic arthritis—clinically important, potentially treatable and often overlooked. Rheumatology. 2004;43:790–794.
28. Rich P, Scher R. Nail psoriasis severity index: a useful tool for evaluation of nail psoriasis. J Am Acad Dermatol. 2003;49:206–212.
29. Cassell SE, Bieber JD, Rich P, et al. The modified Nail Psoriasis Severity Index: validation of an instrument to assess psoriatic nail involvement in patients with psoriatic arthritis. J Rheumatol. 2007;34:123–129.
30. Hanly JG, Russell ML, Gladman DD. Psoriatic spondyloarthropathy: A long-term prospective study. Ann Rheum Dis. 1988;47:386–393.
31. Scarpa R, Oriente P, Pucino A, et al. The clinical spectrum of psoriatic spondylitis. Br J Rheumatol. 1988;27:133–137.
32. Helliwell PS, Hickling P, Wright V. Do the radiological changes of classic ankylosing spondylitis differ from the changes found in the spondylitis associated with inflammatory bowel disease, psoriasis, and reactive arthritis? Ann Rheum Dis. 1998;57:135–140.
33. Taylor WJ, Harrison AA. Could the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) be a valid measure of disease activity in patients with psoriatic arthritis?. Arthritis Rheum. 2004;51:311–315.
34. Doward LC, Spoorenberg A, Cook SA, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis. 2003;62:20–26.

35. Mumtaz A, Gallagher P, Kirby B, et al. Development of a preliminary composite disease activity index in psoriatic arthritis. Ann Rheum Dis. 2011;70:272–277.
36. Eder L, Chandran V, Shen H, et al. Is ASDAS better than BASDAI as a measure of disease activity in axial psoriatic arthritis?. Ann Rheum Dis. 2010;69:2160–2164.
37. Machado P, Landewe R, Braun J, et al. Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis. Ann Rheum Dis. 2010;69:1465–1470.
38. Gladman DD, Inman RD, Cook RJ, et al. International spondyloarthritis interobserver reliability exercise–the INSPIRE study: I. Assessment of spinal measures. J Rheumatol. 2007;34:1733–1739.
39. Haddad A, Thavaneswaran A, Toloza S, et al. Diffuse idiopathic skeletal hyperostosis in psoriatic arthritis. J Rheumatol. 2013;40:1367–1373.
40. Helliwell PS, Firth J, Ibrahim GH, et al. Development of an assessment tool for dactylitis in patients with psoriatic arthritis. J Rheumatol. 2005;32:1745–1750.
41. Ritchlin CT. Pathogenesis of psoriatic arthritis. Curr Opin Rheumatol. 2005;17:406–412.
42. Freeston JE, Coates LC, Helliwell PS, et al. Is there sub clinical enthesitis in early psoriatic arthritis? A clinical comparison with power doppler ultrasound. Arthritis Care Res (Hoboken). 2012;64:1617–1621.
43. Husic R, Gretler J, Felber A, et al. Disparity between ultrasound and clinical findings in psoriatic arthritis. Ann Rheum Dis. 2014;73:1529– 1536.
44. Gladman DD, Mease P, Strand V, et al. Consensus on a core set of domains for psoriatic arthritis. J Rheumatol. 2007;34:1159–1166.
45. Helliwell PS, FitzGerald O, Fransen J, et al. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). Ann Rheum Dis. 2013;72:986–991.
46. Cauli A, Gladman DD, Mathieu A, et al.; GRAPPA 3PPsA Study Group. Patient global assessment in psoriatic arthritis: a multicenter GRAPPA and OMERACT study. J Rheumatol. 2011;38:898–903.
47. Eder L, Thavaneswaran A, Chandran V, et al. Factors explaining the discrepancy between physician and global patient assessment of joint and skin disease activity in psoriatic arthritis patients. Arthritis Care Res (Hoboken). 2015;67:264–272.
48. Her M, Kavanaugh A. A review of disease activity measures for psoriatic arthritis: what is the best approach?. Expert Rev Clin Immunol. 2014;10:1241–1254.
49. Fries JF, Spitz P, Kraines RG, et al. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137–145.
50. Husted JA, Brian T, Farewell VT, et al. Description and prediction of physical functional disability in psoriatic arthritis: a longitudinal analysis using a Markov model approach. Arthritis Rheum. 2005;53:404–409.

51. Husted J, Gladman DD, Long JA, et al. A modified version of the Health Assessment Questionnaire (HAQ) for psoriatic arthritis. Clin Exp Rheumatol. 1995;13:439–443.
52. Ware JE, Sherbourne CD. The MOS 36-item short form Health Survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:47383.
53. Husted JA, Gladman DD, Farewell VT, et al. Validating the SF-36 health survey questionnaire in patients with psoriatic arthritis. J Rheumatol. 1997;24:511–517.
54. McKenna SP, Doward LC, Whalley D, et al. Development of the PsAQoL: a quality of life instrument specific to psoriatic arthritis. Ann Rheum Dis. 2004;63:162–169.
55. Healy PJ, Helliwell PS. Psoriatic arthritis quality of life instrument: an assessment of sensitivity and response to change. J Rheumatol. 2008;35:1359–1361.
56. Gladman D, Fleischmann R, Coteur G, et al. Effect of certolizumab pegol on multiple facets of psoriatic arthritis as reported by patients: 24-week patient-reported outcome results of a phase III, multicenter study. Arthritis Care Res (Hoboken). 2014;66:1085– 1092.
57. Gossec L, De Wit M, Kiltz U, et al. EULAR PsAID Taskforce. A patient- derived and patient-reported outcome measure for assessing psoriatic arthritis: elaboration and preliminary validation of the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire, a 13-country EULAR initiative. Ann Rheum Dis.2014;73:1012–1019.
58. Schentag C, Cichon J, MacKinnon A, et al. Validation and normative data for the 0-10 point scale version of the fatigue severity scale (FSS). Arthritis Rheum. 2000;43(Suppl 2):S177.
59. Schentag C, Gladman D. Changes in fatigue in psoriatic arthritis: disease activity of fibromyalgia. Arthritis Rheum. 2002;46(Suppl 2):S177.
60. Chandran V, Bhella S, Schentag C, et al. Functional assessment of chronic illness therapy-fatigue scale is valid in patients with psoriatic arthritis. Ann Rheum Dis. 2007;66:936–939.
61. Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double -blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005;52:3279–3289.
62. Gladman DD, Chandran V. Standardizing the monitoring of outcome measures: imaging in psoriatic arthritis. Int J Clin Rheumatol. 2011;6:77–86.
63. Poggenborg RP, Østergaard M, Terslev L. Imaging in Psoriatic Arthritis. Rheum Dis Clin North Am. 2015;41:593–613.
64. D'Agostino MA, Conaghan PG, Naredo E, et al. The OMERACT ultra- sound task force – advances and priorities. J. Rheumatol. 2009;36:1829–1832. Erratum in: J Rheumatol 2009;36:2625
65. Schäfer VS, Fleck M, Kellner H, et al. Evaluation of the novel ultra- sound score for large joints in psoriatic arthritis and ankylosing spondylitis: six-month experience in

daily clinical practice. BMC Musculoskelet Disord. 2013;14:358.
66. Balint PV, Kane D, Wilson H, et al. Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. Ann Rheum Dis. 2002;61:905–910.
67. De Miguel E, Cobo T, Munoz-Fernandez S, et al. Is the MAdrid Sonographic Enthesitis Index useful for differentiating psoriatic arthritis from psoriasis alone and healthy controls?. J Rheumatol. 2014;41:466–472.
68. Eder L, Jayakar J, Thavaneswaran A, et al. Is the MAdrid Sonographic Enthesitis Index useful for differentiating psoriatic arthritis from psoriasis alone and healthy controls?. J Rheumatol. 2014;41:466–472.
69. Ficjan A, Husic R, Gretler J, et al. Ultrasound composite scores for the assessment of inflammatory and structural pathologies in Psoriatic Arthritis (PsASon-Score). Arthritis Res Ther. 2014;16:476.
70. Ostergaard M, McQueen F, Wiell C, et al. The OMERACT psoriatic arthritis magnetic resonance imaging scoring system (PsAMRIS): definitions of key pathologies, suggested MRI sequences, and preliminary scoring system for PsA Hands. J Rheumatol. 2009;36:1816–1824.
71. Bøyesen P, McQueen FM, Gandjbakhch F, et al. The OMERACT psoriatic arthritis magnetic resonance imaging score (PsAMRIS) is reliable and sensitive to change: results from an OMERACT workshop. J Rheumatol. 2011;38:2034–2038.
72. Poggenborg RP, Pedersen SJ, Eshed I et al. Head-to-toe whole- body MRI in psoriatic arthritis, axial spondyloarthritis and healthy subjects: first steps towards global inflammation and damage scores of peripheral and axial joints. Rheumatology(Oxford). 2015;54:1039–1049.
73. Gladman DD. Natural history of psoriatic arthritis. Baillieres Clin Rheumatol. 1994;8:379– 394.
74. Fransen J, Antoni C, Mease PJ, et al. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. Ann Rheum Dis. 2006;65:1373– 1378.
75. Gladman DD, Farewell VT, Wong K, et al. Mortality studies in psoriatic arthritis: results from a single outpatient center. II. Prognostic indicators for death. Arthritis Rheum. 1998;41:1103–1110.
76. Bond SJ, Farewell VT, Schentag CT, et al. Predictors for radiological damage in psoriatic arthritis: results from a single centre. Ann Rheum Dis. 2007;66:370–376.
77. Van Der Heijde DM, Van't Hof MA, Van Riel PL, et al. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis. 1992;51:177–181.
78. van Riel P, van Gestel A, Boers M, et al. Clinical assessments in rheumatoid arthritis. In Putte LVD, Furst D and Williams H, Riel PV editors. New York: Marcel Dekker, Inc; 1998. p. 31–43.

79. Clegg DO, Reda DJ, Mejias E, et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis Rheum. 1996;39:2013– 2020.
80. Kingsley GH, Kowalczyk A, Taylor H, et al. A randomized placebo- controlled trial of methotrexate in psoriatic arthritis. Rheumatology (Oxford). 2012;51:1368–1377.
81. Gladman DD, Tom BD, Mease PJ, et al. Informing response criteria for psoriatic arthritis (PsA). II: Further considerations and a proposal–the PsA joint activity index. J Rheumatol. 2010;37:2559–2565.
82. Fitzgerald O, Helliwell P, Mease P, et al. Application of composite disease activity scores in psoriatic arthritis to the PRESTA data set. Ann Rheum Dis. 2011;71(3):358–362.
83. Schoels M, Aletaha D, Funovits J, et al. Application of the DAREA/ DAPSA score for assessment of disease activity in psoriatic arthritis. Ann Rheum Dis. 2010;69:1441– 1447.
84. Helliwell PS, Kavanaugh A. Comparison of composite measures of disease activity in psoriatic arthritis using data from an interventional study with golimumab. Arthritis Care Res (Hoboken). 2014;66:749–756.
85. Helliwell PS, FitzGerald O, Fransen J. Composite disease activity and responder indices for psoriatic arthritis: a report from the GRAPPA 2013 meeting on development of cutoffs for both disease activity states and response. J Rheumatol. 2014;41:1212–1217.
86. Coates LC, Fransen J, Helliwell PS, Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis. 2010;69:48–53.
87. Coates LC, Cook R, Lee KA, et al. Frequency, predictors, and prognosis of sustained minimal disease activity in an observational psoriatic arthritis cohort. Arthritis Care Res (Hoboken). 2010;62:970–976.
88. Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. Arthritis Care Res (Hoboken). 2010;62:965–969.
89. Kavanaugh A, Van Der Heijde D, Beutler A, et al. Patients with psoriatic arthritis who achieve minimal disease activity in response to golimumab therapy demonstrate less radiographic progression: results through 5 years of the randomized, placebo-controlled, GO- REVEAL study. Arthritis Care Res (Hoboken). 2015 Mar 16. doi:10.1002/acr.22576.
90. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet 2015;Sep30;pii: S0140-6736(15)00347-5. doi:10.1016/S0140- 6736(15)00347-5.
91. Segurado OG, Sasso EH. Vectra DA for the objective measurement of disease activity in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2014;32(5 Suppl 85):S-29–34.

Chapter 3

Treatment of psoriatic arthritis with traditional DMARDs and novel therapies: approaches and recommendations

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Abstract

Introduction: Recent advances in the therapeutics of psoriatic arthritis (PsA) have provided more options for clinicians managing PsA. The purpose of this review is to update the reader on treatment options for PsA using conventional synthetic disease modifying agents (csDMARDs) and novel therapies including tumour necrosis factor alpha inhibitors, interleukin 12/23 inhibitor (ustekinumab), the interleukin 17 antagonists including secukinumab, brodalumab, ixekizumab, and the phosphodiesterase-4 inhibitor, apremilast.

Areas covered: We reviewed published articles on the treatment of PsA. Our principal sources of data included treatment recommendations, registry studies, systematic literature reviews, major randomised controlled trials for more recently approved drugs, and abstracts from the American College of Rheumatology and EULAR meetings.

Expert commentary: An overview of the evidence for the use of various pharmacotherapeutic agents for the treatment of this heterogeneous disease was compiled. Treatment options for the different domains of PsA are also discussed.

Keywords: anti-tumour necrosis factor alpha inhibitors, apremilast, disease-modifying antirheumatic drugs, interleukin-12/23 inhibitors, interleukin-17 inhibitors, non-steroidal anti- inflammatory drugs, psoriasis, spondyloarthritis

1. Introduction

Psoriasis is a chronic inflammatory skin disease affecting about 1 to 3% of the population [1]. Approximately 30% of the patients with psoriasis have psoriatic arthritis (PsA) [2-4]. The treatment of PsA has undergone significant changes over the last two decades [5]. Treatment has evolved from the use of symptomatic non-steroidal anti-inflammatories only to the introduction of targeted therapies to modify the disease process [5]. In this review, we aim to highlight the use of traditional disease-modifying agents as well as newer developments in the treatment of PsA and to review updated safety issues with regards to the utilization of these novel therapies. Our principal sources of data include registry studies, systematic literature reviews, major randomised controlled trials for more recently approved drugs, and abstracts from the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) meetings. We performed a centralised systematic literature search for articles published on psoriatic arthritis-related therapies. The search was conducted on Medline and Embase.

2. Psoriatic Arthritis

PsA is an inflammatory musculoskeletal disease, a spondyloarthritis, associated with psoriasis [1]. PsA is a heterogeneous disease involving peripheral joints, the axial skeleton, as well as the entheses [1]. Moll and Wright described five domains of psoriatic arthritis viz. axial involvement, a symmetrical polyarthritis indistinguishable from rheumatoid arthritis, DIP joints involvement, mono- or asymmetrical oligo-articular involvement and arthritis mutilans [1]. The disease is classified according to the CASPAR criteria. There is marked heterogeneity in the presentation of patients with PsA [1]. Patients may present with a predominantly peripheral arthritis, axial arthritis, distal interphalangeal joint arthritis, arthritis mutilans, monoarthritis or a combination of the above [1]. Therapeutic options for the above joint involvement may vary according to the type of joints involved. For instance, the treatment algorithm of peripheral arthritis may be different from that of axial involvement.
Other manifestations like enthesitis and dactylitis may require a different treatment approach [6]. Of course, the activity of extra-articular manifestations such as psoriasis or uveitis would also need to be considered while choosing the appropriate therapy.

3. Drug treatment for PsA

Pharmacotherapy for PsA includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biologic therapies, newer targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs), and occasionally systemic or intra-articular corticosteroids (Table 1). Non-steroidal anti-inflammatory drugs (NSAIDS) are used for symptomatic relief. The commonly used conventional synthetic disease modifying agents (csDMARDs)-methotrexate, sulfasalazine, and cyclosporine have been the mainstay of the treatment of PsA for many years and continue to provide relief to patients with milder disease [7,8]. In 2004, leflunomide was added to our armamentarium for better control of illness [9]. Since 2000, with the introduction of TNF inhibitors, there has been a rapid progress in the available treatment of PsA with regards to the introduction of new biologic therapies with different modes of action. Targeted synthetic disease modifying agents (tsDMARDs) including the phosphodiesterase (PDE) 4 inhibitor, apremilast, have been recently introduced for the treatment of PsA. Newer agents await approval.

Table 1. Drugs used in the treatment of PsA.

NSAIDS	csDMARDs	TNFi	PDE4i	IL12/23i	IL17i
Traditional	Methotrexate	Etanercept	Apremilast	Ustekinumab	Secukinumab
Selective COX 2 inhibitors	Sulfasalazine	Infliximab			Brodalumab
	Leflunomide	Adalimumab			Ixekizumab
	Cyclosporine	Golimumab			
		Certolizumab			

NSAIDS: nonsteroidal anti-inflammatory drugs; COX: cyclooxygenase; csDMARDs: conventional synthetic disease-modifying drugs; TNFi: tumour necrosis factor alpha inhibitors; PDE4i: phosphodiesterase 4 inhibitor; IL12/23i: interleukin 12/23 inhibitor; IL17i: interleukin 17 inhibitors.

3.1 NSAIDS

Non-steroidal anti-inflammatory drugs are useful and frequently used for the symptomatic treatment of patients with PsA. However, only two RCTs with NSAIDs in PsA have been reported. It was reported that nimesulide (200 and 400 mg) was superior to placebo at 4 weeks [10]. A study comparing celecoxib to placebo demonstrated that celecoxib was efficacious at 2 weeks, but not at week 12 due to a high placebo response. [11]

3.2 Corticosteroids

Systemic corticosteroids are generally not advocated for use in PsA. The risk of pustular psoriasis when topping or tapering down corticosteroids is well-documented [12]. Intra-articular corticosteroids are effective and are generally utilized for an acute mono- or oligo-articular flare of PsA [13]. The EULAR guidelines recommend that systemic glucocorticoids may be used with caution at the lowest effective dose for the shortest possible period.

3.3 csDMARDs

The csDMARDS include methotrexate, sulphasalazine, and leflunomide.

3.3.1 Methotrexate

Methotrexate is a folic acid analogue with a variety of anti-inflammatory effects which are mediated primarily through T cells, neutrophils and monocytes/macrophages. It is believed that these cells play a central role in the pathophysiology of inflammatory arthritis and by inhibiting the action of these cells, methotrexate decreases inflammation. The anti-inflammatory effects of methotrexate may be related to an increase in extracellular adenosine and its interaction with specific cell surface receptors [14]. Via this mechanism, it is thought that methotrexate decreases the release of pro-inflammatory cytokines responsible for inflammation in PsA. Methotrexate remains a drug of choice for the treatment of PsA although questions were raised regarding its effectiveness as a disease modifying agent in PsA [15-18]. However, methotrexate remains the anchor drug in most treatment regimens.

Although methotrexate has been used for the treatment of PsA for the last two decades, the first large, double-blind, placebo-controlled study of methotrexate for PsA was published as late as 2012 [19]. The authors of that article reported that methotrexate had no significant effect on composite outcome measures of disease activity, including the DAS28, ACR20, and PsARC responses. Improvements were only demonstrated for patient's and physician's global assessment and skin scores. It must be noted that the aforementioned study had problems with the methodology, which made it difficult to take into consideration these negative results. In a subsequent observational study published, methotrexate was found to be less effective than tumour necrosis factor alpha blocking agents in inhibiting radiographic progression and joint damage [20]. In the TICOPA study, 22% of patients achieved MDA with methotrexate alone [21]. Methotrexate is effective in the treatment of cutaneous psoriasis [22]. However, methotrexate is unlikely to improve psoriatic nail disease [23]. Methotrexate is also not likely to improve enthesitis, dactylitis or axial arthritis [24-26].
Despite these findings, methotrexate continues to be used extensively in the treatment of PsA. The typical dose of methotrexate is between 7.5 and 25 mg weekly with folic acid supplementation. It has been demonstrated in rheumatoid arthritis (RA) that at doses higher than 15mg weekly, the subcutaneous administration may be more effective [27].

3.3.2 Sulfasalazine

Several studies were undertaken to investigate the benefits of sulfasalazine in PsA and psoriasis [28, 29]. Sulfasalazine was noted to be useful in the treatment of peripheral arthritis and axial involvement in PsA [30]. In this study, the primary efficacy variables were the physician's and patient's overall assessments, pain, and morning stiffness. Endpoints were analysed in the intent-to-treat and completer patient populations, the time course of

the effect was analysed in the completer patient population. 60% of the patients taking sulfasalazine improved by at least one point on a five-point scale, in contrast to 44% of patients receiving placebo. It should be stressed that the outcome measures in this trial viz. pain, morning stiffness and physician and patient global assessments are less stringent than the ACR response criteria. There has been one study showing the effectiveness of sulfasalazine in psoriasis alone [31]. Two studies reported on the use of sulfasalazine in dactylitis: No significant statistical difference was noted between the active drug and placebo [32, 33]. There was one reported study that looked at the use of sulfasalazine in enthesitis in patients with PsA [32]. However, there was no improvement in the outcome measures of enthesitis as compared to placebo. There is a lack of data in the published literature looking at radiographic progression in patients with PsA treated with sulfasalazine.

3.3.3 Leflunomide

Leflunomide is an oral disease modifying agent that is used in the treatment of RA and PsA [34]. Leflunomide reduces synovitis by inhibiting dihydroorotate dehydrogenase, an enzyme that is necessary for the production of DNA and RNA [34]. One randomised controlled study (n= 190 patients) has demonstrated the efficacy of leflunomide in PsA. In addition, two open-label trials have shown the benefit of leflunomide monotherapy versus placebo [35,36]. These studies have indicated that leflunomide is an effective disease modifying agent in both psoriasis and PsA. However, in another study, the PASI 75 response in the PsA RCT was only 17.4% [9], and there is only modest effectiveness for nail disease [37]. There is very little information on the efficacy of this drug in enthesitis and axial PsA. Leflunomide was not found to be efficacious in active ankylosing spondylitis [38]. There is a lack of published data regarding the effectiveness of leflunomide in reducing radiographic progression in patients with PsA.

3.3.4 Cyclosporine

There are no randomised trials that compared cyclosporine to placebo. An open label study showed improvement in psoriasis and PsA in 8 patients after 2 months of treatment [39]. In a 12 month randomised controlled trial, 72 patients with active PsA with an inadequate response to methotrexate were randomised to receive either cyclosporine or placebo in addition to methotrexate [40]. There were no significant differences in the both groups. However, there was a reduction in synovitis detected by ultrasound and a decrease in the psoriasis area and severity index (PASI) in the cyclosporine arm. Cyclosporine had modest efficacy for nail psoriasis [23]. There is little data on the effectiveness of cyclosporine in enthesitis, dactylitis or axial disease.

There is also no evidence in the published literature to suggest that cyclosporine reduces radiographic progression in patients with PsA.

3.3.5 Other csDMARDS

Other csDAMRDs that have occasionally been used include azathioprine, gold, and hydroxychloroquine. There is a relative dearth of published data available on the use of azathioprine, antimalarials, fumaric acid or d-penicillamine in PsA [5]. Three RCTs have indicated a modest effect of parenteral gold in PsA [5].

3.4 Biologic disease-modifying agents

Tumour necrosis factor inhibitors (TNFi) have been shown to be efficacious in the treatment of PsA. Until recently, these were the only group of biologic drugs that were available for the treatment of PsA patients who had an inadequate response to csDMARDS. Recently, new therapies including interleukin (IL) 12/23 inhibitors as well as IL-17 inhibitors have emerged for the management of psoriatic arthritis. Other targets are being evaluated (Figure 1)

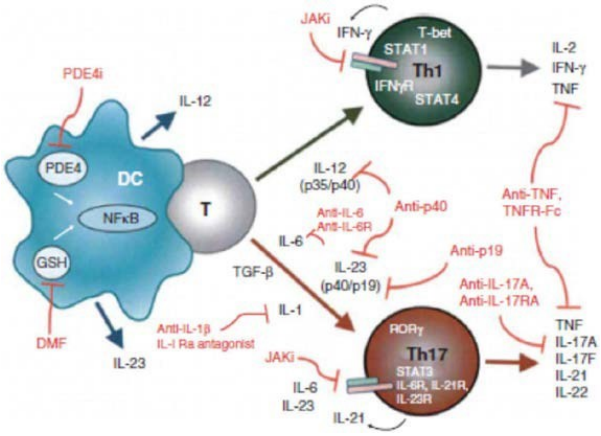


Figure 1: Therapeutic targets in psoriasis and psoriatic arthritis: The figure depicts cytokines, immune cells and signalling proteins implicated in psoriasis pathogenesis and therapeutic targeting by selected small molecules and biologics. Dendritic cells (DCs) activate naive T cells to differentiate into IFN-g+ Tbet+ Th1 cells in the presence of IL-12

or into IL-17+ RORg+ Th17 cells in the presence of IL-6, IL-1, TGF-b, and IL-23. While STAT4 (activated by IL-12) and STAT1 (activated by IFN-g+) are important for Th1 differentiation, STAT3 (activated by IL-6, IL-21, and IL-23) is required for Th17 cell differentiation. Dimethyl fumarate (DMF) and apremilast (PDE4i) modulate cytokine expression in activated DCs.
JAK inhibitors (JAKi) prevent cytokine receptor signalling. Antibodies or fusion proteins (TNFR-Fc) neutralize the indicated cytokines necessary for Th-cell differentiation or effector cytokines implicated in psoriasis/PsA pathogenesis.

Reproduced with permission from Sheane BJ, Chandran V. Investigational drugs for treating psoriatic arthritis. Expert Opin Investig Drugs 2014;23:1001–16 [41].

3.4.1 Tumour necrosis factor inhibitors (TNFi)

Tumour necrosis factor α is a key pro-inflammatory cytokine that has been targeted for the treatment of inflammatory arthritis. The benefits of inhibiting TNF α were first described in the late 1990s. All studied TNFi in PsA have demonstrated efficacy at 12 to 16 weeks for various response criteria and outcome measures including PsA response criteria (PsARC) and ACR 20, 50, 70 response criteria.

Etanercept

Etanercept is a fusion protein that is made up of two TNFα p75 receptor extracellular domains and an IgG1 Fc region. The usual dose of etanercept is 50 mg subcutaneously weekly. Etanercept has been widely studied in the treatment of PsA beginning with a single centre trial of 60 patients [41]. Patients on a stable dose of methotrexate were randomised to receive either etanercept or placebo. This trial also included methotrexate naive patients to allow assessment of oligoarticular disease to enter the trial, although the majority of the patients enrolled in this study had polyarticular disease. The primary endpoint of the study was a PsARC response with the improvement of at least two of the following criteria: improvement of tender and swollen joint count by ≥ 30%, physician and patient global improvement by at least one point on a five-point Likert scale, one of which had to be a joint assessment and no worsening of any elements. In this three-month placebo-controlled phase of the study, this response was achieved by 87% of the patients treated with etanercept as compared to 23% of the placebo group ($p<0.001$) [41]. ACR 20 response was achieved by 73% of the patients in the etanercept group as compared to

13 % of the placebo group (p<0.001).

Following the success of this initial trial, various other trials were undertaken which showed a statistically significant difference with the improvement of PsA outcome measures in the etanercept group as compared to placebo. Also, for the first time in PsA, the radiographic endpoint of a change in the modified Total Sharp Score (TSS) was evaluated, and the etanercept group showed a statistically significant reduction in radiographic progression as compared with the placebo group [41]. A subsequent study confirmed that etanercept therapy significantly improved the clinical symptoms and prevented radiographic disease progression of PsA [42]. Additionally, etanercept improved the skin lesions of psoriasis in these patients [42]. Nail psoriasis also improved significantly with etanercept treatment [23]. However, in these studies, the efficacy of etanercept on enthesitis and dactylitis was not evaluated. The PRESTA trial compared the efficacy over 12 weeks of two different etanercept regimens in treating the skin manifestations of psoriasis in patients who also have PsA [43]. This study, although not placebo controlled, demonstrated improvement in enthesitis and dactylitis with etanercept. An observational study in PsA with axial involvement as well as RCTs in ankylosing spondylitis (AS) has shown the effectiveness and efficacy of etanercept in axial disease [26].

Infliximab

During the time that the work with etanercept was progressing studies were also being done with the chimeric monoclonal antibody infliximab. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT) compared infliximab at a dose of 5 mg/ kg to placebo in patients with PsA failing on csDMARD [44]. Infliximab was superior to placebo: The proportion of infliximab-treated patients who achieved an ACR20 response at week 16 (65%) was significantly higher than the percentage of placebo-treated patients who achieved this response (10%). In a larger second trial (IMPACT II), patients were required to stay on methotrexate but had to discontinue other DMARDs [45]. This study confirmed the efficacy of infliximab. At week 14, 58% of patients receiving infliximab and 11% of those receiving placebo achieved an ACR20 response and 77% of infliximab patients, and 27% of placebo patients achieved PsARC response (both p<0.001). Significant improvement in psoriasis severity, enthesitis and dactylitis were also demonstrated. Nail psoriasis also improved with infliximab therapy [23]. Improvement in axial disease has been demonstrated in PsA [26]. Peripheral joint radiographic progression was also shown to be reduced in patients treated with infliximab [46].

Adalimumab

Adalimumab, the first fully human anti-TNF monoclonal antibody, has shown similar results as compared to the previous two biologics. Adalimumab is administered as a subcutaneous injection of 40 mg every other week. Adalimumab demonstrated a favourable risk–benefit profile in patients with PsA in the ADEPT study [47]. In this trial, patients with active PsA completed a 24-week double-blind study with either adalimumab or placebo. At 24 weeks, there was a statistically significant difference in the active treatment arm as compared to placebo in terms of inhibiting radiological damage and improvements in joint disease. An open-label extension of this trial showed similar efficacy through 48 weeks [48]. The clinical and radiographic benefits of adalimumab were sustained during long-term treatment [47]. At week 12, 58% of the adalimumab-treated patients achieved an ACR20 response, compared with 14% of the placebo-treated patients. ACR 20 responses were achieved in 58.7% of patients at week 48 and 57.3% of patients through 104 weeks. ACR 50 and 70 responses were also sustained over the two years of active treatment. No further safety concerns were reported. Improvement in psoriasis severity was also demonstrated. Adalimumab also improves nail psoriasis [23]. However, statistically significant improvements in enthesitis and dactylitis were not demonstrated with adalimumab in the ADEPT trial. Studies in AS and axial SpA have shown that adalimumab improves symptoms of axial disease [26].

Golimumab

Golimumab is also a fully human inhibitor of tumour necrosis alpha. Further to the initial 24-week trial (GO-REVEAL) of golimumab in PsA, one-year data regarding the efficacy and safety were reported [49]. In this trial, patients with active PsA with >3 tender joint count and swollen joint count were assigned to receive golimumab 50 mg subcutaneously every four weeks. Patients receiving placebo who did not have an adequate response had an early escape and crossed over to active drug at 16 weeks. At 24 weeks, patients in the placebo arm were then continued on golimumab 50 mg subcutaneously through to one-year. Analysis of the data showed golimumab inhibited structural damage progression and had a good clinical response as well as an excellent safety profile.
Improvement in enthesitis, dactylitis, psoriasis and nail disease were also demonstrated. Five-year data on the safety and efficacy of golimumab showed that this drug maintains safety and effectiveness through long-term [50]. Golimumab also improves axial symptoms in studies on axial spondyloarthritis and AS [26].

The biologics described above were all evaluated in patients not exposed to other biologic agents. Although long-term extension studies with these agents have shown reasonably sustained efficacy, data from registries have demonstrated significant failure rates. For example, data from the DANBIO registry show that almost 40% of patients switched to a second biologic drug during 10 years of follow up [51]. Response rates were lower after switching. Recent trials have thus included patients previously exposed to TNFi.

Certolizumab pegol

Certolizumab pegol (CZP) is a PEGylated Fab fragment anti-tumour necrosis factor alpha antibody approved for the treatment of PsA. The RAPID-PsA study was undertaken to evaluate the efficacy and safety of certolizumab pegol after 24 weeks of treatment [52]. In this study, patients could have had previous exposure and inadequate response to one TNFi. Patients were randomised 1:1:1 to receive placebo, or 400 mg CZP at week 0, 2 and 4 loading doses followed by either 200 mg CZP every 2 weeks or 400 mg CZP every 4 weeks, administered subcutaneously. Primary endpoint was the ACR 20 response at week 12 and modified total sharp score changes from baseline to week 24 with secondary endpoints psoriatic arthritis response criteria (PsARC) score, health assessment questionnaire disability index (HAQ-DI), psoriasis area and severity index (PASI), Leeds enthesitis index, Leeds dactylitis index and modified nail psoriasis severity index. Rapid improvements in the signs and symptoms of PsA were noted in all primary and secondary endpoints. There were no new safety concerns in the active drug arm as compared to placebo. At 12 weeks, there were significantly more patients in the active treatment arm in both the 200 and 400 mg groups that achieved ACR 20 compared with patients receiving placebo (50.0% versus 51.9% versus 24.3%). Importantly, there were no differences in the ACR responses at week 12 and week 24 in CZP patients between patients with and without prior TNFi exposure. However, it should be noted that primary failures to TNF inhibitors were excluded. The observed differences were statistically significant when active treatment arms were compared to placebo. This response was maintained through week 24. ACR 50 responses were 42.1% versus 12.5%, and ACR 70 response was 26% versus 4.4% for the active combined groups versus placebo respectively. PASI50, PASI75, PASI90 responses occurred more frequently under the active treatment at week 12 and 24 as compared to placebo. At week 24, 62.2% and 60.5% of patients treated in the certolizumab 200 mg Q2W group and certolizumab 400 mg Q4W group achieved PASI75 respectively. At week 24, 33.3% and 34.1% of the CZP 200 mg Q2W and CZP 400 mg Q4W patient groups respectively, achieved a state of minimal disease activity compared with only 5.9% of placebo patients ($p<0.001$). Axial involvement was not evaluated in this study. However, axial SpA has been shown to improve with CZP treatment [26].

Despite significant clinical response with TNFi treatment, at least 40% of patients do not get even an ACR20 response. Therefore, other targets have been investigated and are now available for the management of psoriatic disease.

3.4.2 Ustekinumab

Ustekinumab is an antibody to the p40 subunit common to both interleukin (IL)-12 and IL-23 and thus inhibits the action of both IL-12 and IL-23, important cytokines in the pathogenesis of psoriatic disease. Ustekinumab efficacy in PsA was evaluated through the PSUMMIT I and PSUMMIT II trials. Both trials had very similar designs. However, PSUMMIT I included TNFi naive patients only, whereas PSUMMIT II allowed enrollment of patients who had previously failed or had an inadequate response to TNFi [53,54]. PSUMMIT I was a phase III multicentre, randomised, double-blind, placebo-controlled study to assess the efficacy and safety of ustekinumab in patients with active PsA who had an inadequate response to disease modifying agents and/or NSAIDs [55]. Ustekinumab was dosed at week 0, 4 and then every 12 weeks, randomised to receive either 45 mg or 90 mg. The primary endpoint was a ≥ 20% improvement in ACR 20. Response rates were significantly higher in both ustekinumab 45mg and 90 mg as compared to placebo, and these responses were maintained through to week 52. In the PSUMMIT II trial, about 60% of patients were previously exposed to TNFi. Although ACR responses were similar in both PSUMMIT I and PSUMMIT II, in the PSUMMIT II trial ACR 20 responses were lower in patients who had an inadequate response to one or more anti-TNF agents.

Significant improvements in psoriasis and nail disease were also demonstrated. The PSUMMIT I trial also demonstrated significant improvement in enthesitis and dactylitis. Efficacy on axial disease needs further evaluation. In an open label single arm study, ustekinumab was associated with improvement in signs and symptoms of active AS as well as in active inflammation detected by MRI [56]. Ustekinumab was efficacious irrespective of the use of methotrexate. Response rates and adverse events did not differ in those receiving concomitant methotrexate as compared to the methotrexate naive group.
Significantly less radiographic progression was observed in the hands/feet of patients seen at week 24 in the active treatment group (combined PSUMMIT I&II) with ustekinumab as compared to placebo with mean changes in their PSA-modified vdH-S score from baseline of 0.00 to 1.51; (p= 0.003).

3.4.3 Anti-IL-17 monoclonal antibodies

Secukinumab

Secukinumab is a high affinity, human immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to and neutralises interleukin 17A. Interleukin 17 A is postulated to play a significant role in the pathogenesis of PsA. Increased levels of interleukin 17A producing cells are found in the circulation, skin, and joints of patients with PsA [57-60]. A randomised, multicenter, double-blind, placebo-controlled phase 3 study of secukinumab (FUTURE I) has been recently published [61]. The study included patients who were both TNFi naive as well as those who had a previous intolerance or had an inadequate response to TNF therapy.
Secukinumab was administered at a dose of 10mg/kg at baseline, weeks 2, 4, followed by 75 or 150 mg 4 weekly. The primary endpoint was the ACR 20 response at week 24 through to week 52. At week 24, there was a statistically significant difference between the treatment arms and placebo ($p<0.0001$). The improvement was noted through to week 52. Similar responses were seen in the ACR 50 and ACR 70 groups. ACR 20 responses in patients were similar in those with and without concomitant methotrexate therapy. There was a statistically significant reduction in radiographic progression in the active treatment group as compared to the placebo. The FUTURE II study had very similar design, the only difference being subcutaneous (weekly doses of 75, 150, 300mg of secukinumab or placebo until week 4).
Improvement in psoriasis, nail disease, enthesitis, and dactylitis were reported in the active arm. Improvement in axial disease was reported in the trials in AS [62]. The primary safety concern with inhibition of IL-17 is candida infections. Oral candidiasis was reported in four patients each in the secukinumab 150 mg and 75 mg groups. There was also one patient with oesophageal candidiasis and one patient with skin candidiasis reported in the higher dose. All cases of candidiasis responded to oral therapy [61]. Of note, there were no cases of tuberculosis reported, neither new or reactivation of latent tuberculosis [61]. A double-blind, randomised, placebo-controlled proof of concept study in patients with severe Crohn's disease showed that blockade of interleukin-17A was ineffective and also resulted in higher rates of adverse events when compared to placebo [63]. The study was terminated prematurely due to insufficient therapeutic response in the active treatment group and for the serious adverse reactions in 10 patients. 20 infections, including four local fungal infections, were seen in the secukinumab group as compared to placebo [63]. Given the increased prevalence of clinical and subclinical inflammatory bowel disease in patients with spondyloarthritis, there is concern about flares of underlying Crohn’s disease. Therefore, secukinumab is not recommended to be used in patients with active or past history of Crohn’s disease.

Ixekizumab

Ixekizumab is a humanized IgG4 monoclonal antibody that neutralizes interleukin-17A. The SPIRIT P1 trial [64] was a randomised, double-blind, placebo-controlled phase III trial that compared ixekizumab to placebo and also had an adalimumab arm. The study was not powered for direct comparison between ixekizumab and adalimumab. The doses of ixekizumab were 80 mg every two or 4 weeks. There was a statistically significant improvement in outcome measures in the ixekizumab group as compared to placebo. At 24 weeks, 62% of patients treated every 2 weeks, and 58 % of patients treated every 4 weeks with ixekizumab achieved ACR20 response compared with 30% of the placebo-treated patients. The percentage of ixekizumab treated patients who achieved ACR50 response when treated every 2 weeks or every 4 weeks were 47 % and 40%, respectively, compared with 15 % of patients treated with placebo. Furthermore, 34 % of patients treated with ixekizumab every two weeks and 23 % of those treated every four weeks experienced an ACR70 response. Only 6% of patients treated with placebo achieved this. Significant improvement in psoriasis, nail disease, enthesitis and dactylitis was reported. Axial disease was not evaluated. There was significantly less radiographic progression or structural damage in the actively treated patients in both dosing regimens, as compared to placebo, as measured by the change from baseline in the van der Heijde modified total Sharp score for PsA at 24 weeks [64].

Brodalumab

Brodalumab, a human anti-IL17R monoclonal antibody, inhibits the IL17 receptor, thus effectively blocking the activity of IL-17A, IL-17F, IL-17A/F, and IL-17E (also called IL-25). A study that investigated the safety and efficacy of brodalumab in PsA showed that brodalumab treated patients had significant ACR20 and ACR50 but not ACR70 responses. Dactylitis outcome measures and psoriasis also improved. However, there was no improvement in the enthesitis outcome measures through week 24 in all treatment groups [65]. Brodalumab also significantly improves psoriasis and nail disease. Axial disease has not been investigated. However, in May 2015, Amgen announced that it was ending its participation in co-development of the compound because of reports of patients having "events of suicidal ideation and behavioural changes."

3.4.4 Other biologics

Clazakizumab

Clazakizumab is an IL-6 monoclonal antibody with high affinity and specificity for IL-6. A phase 2b study investigating the efficacy and safety of clazakizumab in adult patients with active PsA was recently published [66]. This was a randomised, double-blind, placebo-controlled, dose ranging study in adult patients with active PsA who had an inadequate response to NSAIDs. Patients were randomised to receive clazakizumab 25 mg, 100mg, 200 mg every four weeks subcutaneously or placebo with or without methotrexate. The primary endpoint was ACR 20 response at week 16 with secondary endpoints at week 16 and 24. At week 16, ACR 20 response was statistically higher in patients on the 100 mg versus placebo (52.4% vs 29.3%; p= 0.039). In the clazakizumab 25 mg group, ACR 20 responses at week 16 were 46.3% (p= 0.101 versus placebo) and 39.0 % with the clazakizumab 200 mg (p= 0.178 versus placebo). Although the trial was not powered to look at ACR 50 and ACR 70 responses, these were numerically higher with clazakizumab compared to placebo at week 16 and 24. Clazakizumab was well tolerated, and no new safety issues were identified with respect to the pharmacology of IL-6 blockade already documented from previous clinical experience in RA. This was a first clinical trial investigating the use of IL-6 targeted therapy in PsA and suggests this may be an effective treatment for the musculoskeletal manifestations of PsA, but further studies need to be undertaken.

Abatacept

Abatacept is a selective T-cell costimulatory modulator. A six-month multicentre, randomised, double-blind, placebo-controlled phase II study investigating the safety and efficacy of abatacept has been published [67]. In the study PsA patients with an inadequate response to DMARDs including TNFi were randomised to receive placebo or abatacept at doses of 3 mg/kg every 28 days, 10 mg/kg every 28 days, or 30 mg/kg as an initial loading dose two week apart followed by 10 mg/kg every 28 days thereafter. The primary endpoint was ACR 20 criteria on day 169. Patients achieving ACR 20 responses were 19%, 33%, 48%, and 42% in the placebo, abatacept 3 mg/kg group, the abatacept 10 mg/kg and the abatacept 30/10 mg/kg groups respectively. With these dosing regimens, there was a statistically significant improvement in the ACR 20 responses in the abatacept 10 mg/kg (p= 0.006) and 30/10 mg/kg (p= 0.022) groups as compared to placebo. The 3 mg/kg group did not show any statistically significant difference from

placebo (p= 0.121). Improvement in skin psoriasis was also observed. The study shows that the dose generally used for RA (10mg/kg) may be effective in the treatment of PsA. Although abatacept has shown promise in the treatment of PsA, it has not received the necessary approval from the regulatory authorities for this indication.

3.4.5 Biosimilars

Biosimilars are biologic drugs designed to have similar active properties to ones that have been already licensed. Biosimilars are currently a hotly debated topic in rheumatology. Although some rheumatologists are cautious about their introduction in the clinical field, some are eagerly awaiting their application and approval for the treatment of common rheumatic conditions. Health economic issues play a significant role when choosing a biologic in the treatment of inflammatory arthritides. In the European Union (EU), regulatory authorities have established a framework for approving biosimilars since 2003. This framework implicates that biosimilars can only be approved centrally via the European Medicines Agency (EMA) and not nationally [68]. Examples of EMA-approved biosimilars are Benepali (etanercept), Flixabi (infliximab), Inflectra (infliximab) and Remsima (infliximab). More products are expected to come to the market soon. The lower cost of these drugs may make them more accessible especially in resource-poor settings, and inequities in terms of access may be addressed.

3.5 **Targeted synthetic disease modifying agents (tsDMARDs)**

Phosphodiesterase 4 inhibitor (PDE 4-I) Apremilast

Apremilast is an oral phosphodiesterase 4 inhibitor indicated for the treatment of psoriasis and PsA. It has been assessed in a number of phase III clinical trials in PsA (PALACE trials) [69]. Psoriatic Arthritis Long-term Assessment of Clinical Efficacy 1 (PALACE 1) compared apremilast to placebo in patients with active PsA who had an inadequate response to csDMARDS and/or biologic therapy. This was a 24-week placebo- controlled trial in which patients were randomised to receive placebo, apremilast 20 mg twice a day (BD) or apremilast 30 mg BD in a 1:1:1 fashion. The primary outcome of this study was the proportion of patients achieving a 20% improvement in the modified ACR 20 response criteria at 16 weeks. At 16 weeks, the study showed a statistically significant difference between patients receiving apremilast 20 mg twice a day (31%) and 30 mg twice a day (40%) versus placebo (19%) ($p<0.001$) with regards to the primary

endpoint, and the drug was well tolerated. The PALACE 3 study also showed statistically significant improvements with apremilast in PsA and psoriasis [70]. In this study patients with active PsA with current skin, involvement was evaluated. The design of the study was similar to PALACE1. At 24 weeks, the remaining placebo patients were randomised to receive either apremilast 20 mg BD or 30 mg BD. The efficacy and safety of apremilast was assessed at 52 weeks. At 16 weeks, significantly more patients receiving apremilast 20 mg BD (28%) and 30 mg BD (41%) achieved a 20% improvement in ACR response criteria versus placebo (18%; p= 0.0295 and p < 0.001 respectively). Apremilast was well tolerated and demonstrated an acceptable safety profile. Enthesitis was shown to improve in patients on the 30 mg but not 20 mg dose arm. Statistically significant improvement in dactylitis could not be demonstrated. A pilot study has suggested that apremilast may improve signs and symptoms of AS [71]. Apremilast also improves nail psoriasis. Most adverse events were mild to moderate in severity; the most common were diarrhoea, nausea, headache and upper respiratory tract infection. Nausea and diarrhoea in the active treatment group were highest in the first two weeks after initiation of therapy and mostly resolved within 30 days. No interruption of treatment was required, and no medical treatment intervention was needed. In total, < 2% of patients enrolled in the study discontinued due to diarrhoea of nausea throughout the 52 weeks of the study [69]. Weight loss occurred in a small percentage of patients which did not require discontinuation of treatment. Most patients maintain their weight to ≤ 5% from baseline throughout the 52 weeks of the study [70].

JAK inhibitors

Recently developed newer agents for the treatment of PsA including IL 12/23 inhibitors, IL-17 inhibitors, as well as an IL-6 inhibitor for the treatment of RA target signalling pathways that involve the Janus-Kinase (JAK) family of receptor-associated tyrosine kinases [72-74]. Activated JAKs are pro-inflammatory and recruit and activate signal transducer and activator of transcription (STAT) proteins, which in turn drive gene transcription. This JAK-STAT pathway is proinflammatory and has been shown to play a fundamental role in the pathogenesis of RA [75,76]. Tofacitinib, an oral inhibitor of JAK1 and JAK 3, is effective in psoriasis [77]. Results of RCTs in PsA are keenly awaited. Baricitinib, an oral inhibitor of JAK1 and JAK2 was also shown to be effective for psoriasis in a phase 2b study [78]. There are currently no ongoing studies with baricitinib in PsA. Although the JAK inhibitors have shown promise in the treatment of PsA, they have not received the necessary approval from the regulatory authorities for this indication.

4. The Future

Newer therapies currently in development include guselkumab, risankizumab, and tildrakizumab which target the p19 subunit of IL-23. It has been shown from phase II trials that these drugs are quite promising.

5. Treatment recommendations

The EULAR recently published its updated recommendations for treatment of PsA [79]. Over the last 2 years, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis [GRAPPA- a professional organization that includes rheumatologists and dermatologists with interest in psoriatic disease] has also undertaken an update of PsA management recommendations [11,23-26,80-82]. The new recommendations are based on several systematic literature reviews focusing on the different manifestations of PsA [11,23-26, 80-82]. The format of the new GRAPPA recommendations is much closer to the format of the EULAR recommendations since it includes overarching principles, as well as a figure giving treatment algorithms according to the predominant manifestation. Whereas, the GRAPPA recommendations encompass all domains involved in PsA, including skin and nail disease [82], the EULAR recommendations are predominantly for musculoskeletal manifestations of PsA in view of the fact that it was drawn up mainly by rheumatologist [83]. The GRAPPA recommendations are also more up to data since the trial data considered when writing up the recommendations included those available only in abstract form.

6. Approach to treatment

Since PsA may show substantial clinical heterogeneity, an assessment of disease activity requires that all aspects of the disease be assessed in order to ascertain the most active domain and to target this domain therapeutically, keeping involvement of other domains in consideration. Choosing the appropriate drug may be difficult since some drugs may not benefit all the active domains. In view of the heterogeneity of the disease process, different drugs are used for various phenotypes. EULAR recommendations define broad domains, mainly predominant peripheral arthritis, dominant axial disease, enthesitis or dactylitis or predominant skin disease (with a recommendation to refer to a dermatologist), whereas GRAPPA defines six domains (Skin, nails, peripheral arthritis, axial arthritis, enthesitis and dactylitis) and gives six flow charts for an approach to treatment. Other extra- articular manifestations, such as uveitis and IBD, also need to be considered when considering appropriate therapy for PsA.

It is well-documented that PsA is associated with a variety of comorbidities including cardiovascular disease, obesity, metabolic syndrome and type II diabetes mellitus. PsA is associated with obesity; dietary measures to lose weight should be taken. It has been demonstrated that regardless of the kind of diet, a successful weight loss of ≥5% is associated with a higher rate of achievement of MDA in overweight/obese patients with PsA who start treatment with TNF [84]. A high index of suspicion of these comorbidities needs to be maintained. Patients presenting with such comorbidities may need to be managed by a multidisciplinary team [80]. Physiotherapy plays an important role in the management of PsA, and the physiotherapist is an important cog in the wheel of the multidisciplinary team that manages these patients.

6.1 Peripheral arthritis

Treatment of peripheral arthritis is usually initiated with a csDMARD, methotrexate generally being the anchor drug [82]. Methotrexate monotherapy is generally initiated. In patients having a high disease burden, manifesting as multiple swollen and tender joints in the presence of elevated inflammatory markers, csDMARDs should be instituted as soon as possible. EULAR recommends methotrexate as the specific csDMARD of choice, whereas GRAPPA recommends that one of the csDMARDs, including methotrexate, sulfasalazine, and leflunomide may be chosen (Figure 2). Methotrexate may be the drug of choice in patients who have extensive skin lesions in addition to peripheral arthritis. Poor prognostic features include a high tender on swollen joint count, radiographic damage, and elevation of acute phase reactions. The presence of dactylitis may portend a poorer prognosis and hence requires aggressive therapy. GRAPPA (but not EULAR) recommendations in patients with poor prognosis include using biologic therapy before csDMARDs.

Should patients have an inadequate response to methotrexate monotherapy, switching to another csDMARD or combination therapy with sulphasalazine and/or leflunomide may be considered, although evidence to support this approach in PsA is lacking. Failure of csDMARDs generally requires the switch to or addition of a biologic or apremilast. TNFi is generally the first choice. Other biologics that can be considered include ustekinumab or IL-17 inhibitors (Figure 2).

6.2 Axial arthritis

Patients with predominantly axial involvement who have had an inadequate response to NSAIDs should be considered for biologic therapy [82]. Active axial involvement generally implies a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of greater than 4

points [82]. In these patients, it is appropriate to go from a NSAID to a bDMARD since csDMARDS have no proven benefits in axial disease [82]. There is limited data on the use of ustekinumab and apremilast in axial disease. In patients who have an inadequate response to one bDMARD, switching to another bDMARD should be considered (Figure 3).

6.3 Enthesitis and dactylitis

Enthesitis and dactylitis have been historically difficult to treat in patients with PsA. The diagnosis of enthesitis can be challenging in clinical practice, and several instruments have been proposed for the assessment of enthesitis. The csDMARDs have shown little benefit in enthesitis but may be of value in patients with dactylitis, and patients with severe enthesitis or dactylitis who have had an inadequate response to these drugs may require more aggressive therapy [24,25]. TNFi, ustekinumab and the IL-17A antibodies, as well as apremilast, have shown to be efficacious in improving enthesitis and dactylitis (Figure 4).

6.4 Skin and nails

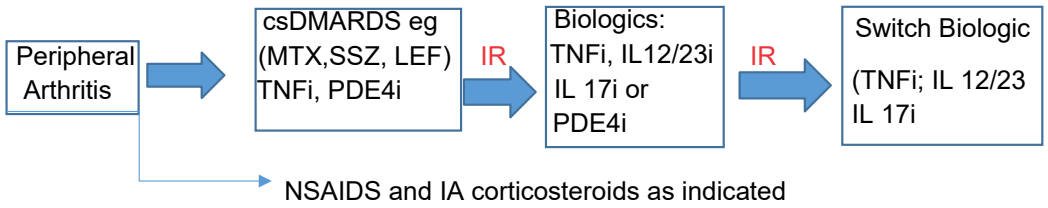
The management of skin psoriasis in PsA is usually initiated with topical therapy including keratolytics, corticosteroid creams, vitamin D analogues, emollient cream, and calcineurin inhibitors. Phototherapy or csDMARDS is often of value [82]. Nail disease is difficult to treat with traditional agents. In patients with an inadequate response to the above medications, the PDE4 inhibitor apremilast or biologic therapy may be used. Patients with PsA who have significant skin and nail psoriasis are best co-managed with a dermatologist.

7. Treating PsA to target

Treat-to-target (T2T) has become the norm in many specialities across medicine and rheumatology is no exception [85]. However, the target for treatment has been hard to define. In PsA criteria for minimal disease activity (MDA) were developed. A patient with PsA is said to be in a state of MDA if at least 5 of the following 7 criteria are achieved: Tender joint count ≤1; swollen joint count ≤1; Psoriasis Activity and Severity Index ≤1 or body surface area ≤3; patient pain visual analogue score (VAS) ≤15mm; patient global disease activity VAS ≤20mm; health assessment questionnaire ≤0.5; tender entheseal points ≤1 [86]. The TICOPA (TIght COntrol of Psoriatic Arthritis) study was the first trial to evaluate tight control in PsA with MDA as the target for treatment and showed that patients who were treated according to a T2T strategy (monthly escalation of therapy until MDA was achieved) had better articular and skin outcomes (ACR20, 50, 70 and PASI 75),

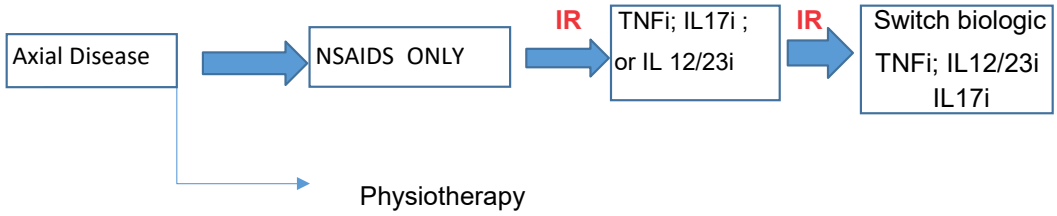
improvements in multiple patient, reported outcomes, compared to usual care [21]. However, tight control strategy was associated with an increase in adverse events due to the rapid escalation of drug therapy.

Figure 2- Flow chart for management of predominant peripheral arthritis



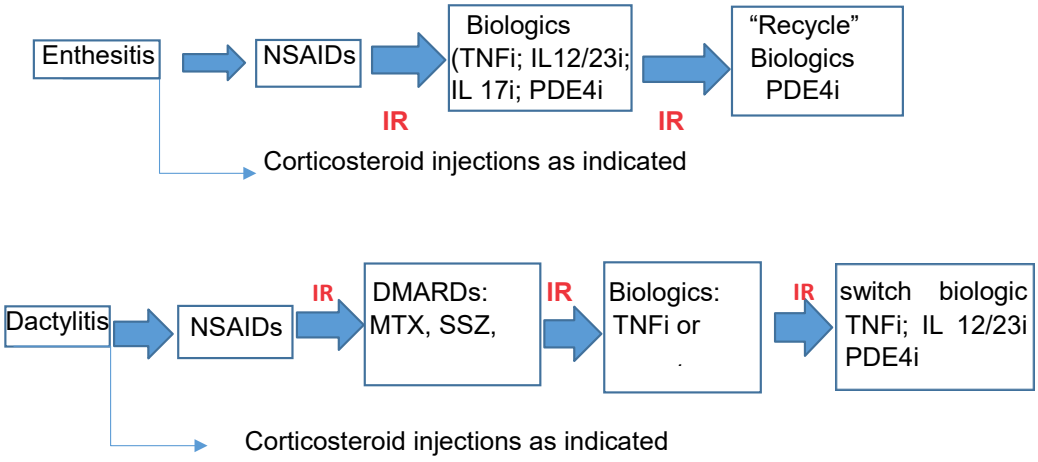
IR- inadequate response; MTX- methotrexate; SSZ- Sulfasalazine; LEF- Leflunomide; TNFi- Tumour necrosis factor inhibitor; PDE4i- apremilast; IL12/23i- Ustekinumab; IL17i- IL-17 inhibitor; IA- intra-articular

Figure 3- Flow chart for management of predominant axial arthritis



IR- inadequate response; NSAIDS- Non-steroidal anti-inflammatory drugs; TNFi- Tumour necrosis factor inhibitor; IL12/23i- Ustekinumab; IL17i- IL-17 inhibitor

Figure 4- Flow chart for management of predominant enthesitis or dactylitis



IR- inadequate response; NSAIDS- Non-steroidal anti-inflammatory drugs; TNFi- Tumour necrosis factor inhibitor; IL12/23i- Ustekinumab; IL17i- IL-17 inhibitor; PDE4i- apremilast

8. Conclusion

Rheumatologists have come a long way in the management of PsA in the last two decades. The introduction of newer therapies has changed the way we manage this disease. Early diagnosis and aggressive treatment have reduced morbidity. Our better understanding of the pathophysiology of the disease, as well as the introduction of novel therapies, have improved outcomes in patients living with PsA. It is now hoped that a holistic management of these patients with careful monitoring of extra articular manifestations and comorbidities and T2T approach will result in improved longevity and quality of life of patients with PsA. Adherence to recommendations set out by GRAPPA, and EULAR help clinicians position drug therapy appropriately.

Patients need to be assessed carefully, and the dominant domain needs to be treated aggressively. Patients who have predominant peripheral arthritis need to be commenced on early csDMARDs, in order to achieve a state of MDA. Should this not be achieved with csDMARDs, biologic therapy will need to be introduced. NSAIDs are generally first-line for axial disease. Inadequate response to NSAIDs will require the introduction of biologic therapy. Enthesitis and dactylitis are usually difficult to treat. Apremilast or biologic therapy are indicated for severe enthesitis or dactylitis. The holistic management of a patient with PsA always includes assessment of the skin and nails, even by the rheumatologist in collaboration with a dermatologist. It is generally accepted that treatment of this domain should commence with topical treatment followed by csDMARDs. If a good response is not achieved, biologics should be used.

Comorbidities should be assessed in all patients and managed with a multidisciplinary team. Particular attention should be placed on the management of obesity and metabolic syndrome. It is always important to stratify patients, and those with high inflammatory burden and poor prognostic features should be treated aggressively. It is important to identify the dominant domain and document outcome using appropriate outcome measures. It is recommended that shared decision making between the patient and physician, as well as T2T strategies, be in place, and at least a state of MDA strived for.

9. Expert Commentary

PsA is a complex inflammatory arthritis with heterogeneous manifestations. Until recently, this disease was considered to be less aggressive and more innocuous than RA. However, recently it has gained more attention due to the more aggressive nature of the disease and increased morbidity and mortality. With the availability of biologic agents targeting key molecules important in disease pathogenesis, treatment has become more aggressive to achieve minimal disease activity or remission in order

to prevent downstream joint damage and disability from the disease. Until recently, the TNFi were the only biologic treatment option licensed for the treatment of PsA. However, the introduction of IL-12/23 antagonists, IL-17 antagonists, and apremilast has opened more doors and increased treatment options for PsA. However, a large proportion of patients do not respond to biologic therapy or have secondary failure. New treatments including JAK inhibitors, biologics targeting IL-23, and dual target antibodies are actively being investigated. The introduction of biosimilars is expected to reduce the cost of therapy. Thus, the development and introduction of newer therapies have improved PsA outcomes. Rheumatologists are becoming more aware of the heterogeneity of PsA and treatment is targeted to the most active domains with disease activity in other domains being taken into consideration. The EULAR and GRAPPA recommendations have helped make choosing appropriated therapy easier.

One of the fundamental deficiencies in the management of PsA is the inability to provide holistic management to these patients including assessment and management of peripheral arthritis, axial involvement, enthesitis, dactylitis, and skin & nail involvement.
Comprehensive assessment of PsA is often challenging and time-consuming. Biomarkers for disease activity and treatment response are not available. Conventional markers such as CRP and ESR perform poorly. With improved assessment tools and outcome measures, it is hoped that these domains will be addressed sufficiently, and appropriate management instituted.

An often-overlooked aspect of treatment of PsA is the management of comorbidity. Obesity is prevalent in patients with psoriasis and PsA, and weight reduction has been shown to improve psoriasis and PsA disease activity and improve response to drug therapy. Hence, holistic management of PsA should include diet and exercise. Such treatment would be practical only with close collaboration between the rheumatologist, dermatologist, primary care physicians and allied health practitioners.

Early diagnosis, the introduction of aggressive therapy, and treat to target measures have resulted in decreased disability and improved quality of life of patients living with PsA. The realisation that early detection of disease as well as treating to target concept will lead to better control of disease activity with conventional as well as novel therapies is coming into vogue.

Recently, the association of inflammatory arthritis and psoriatic arthritis in particular, with increased cardiovascular (CVD) mortality and metabolic syndrome has gained increased attention. The management of PsA and its association with cardiovascular disease

is critical and should involve a multidisciplinary team including the rheumatologist, cardiologist, and primary care physician. Just as in the general population, cardiovascular risk factors should be sought for and addressed. A high index of suspicion for CVD should be maintained in all patients with PsA. It is recommended that lifestyle changes be made including weight loss decreased alcohol consumption and a well-balanced diet. Treatment targets for hypertension, hyperlipidaemia as well as diabetes on the same for patients with inflammatory arthritis as a general population. The systemic inflammation that is present in PsA leads to increased insulin resistance, oxidative stress, endothelial cell dysfunction and the development of premature of atherosclerosis. The primary driver of this process is inflammation, and thus decreasing the inflammatory burden using DMARDs has been hypothesised to attenuate CV risk. To date, no prospective studies are specifically examined the effect of aggressive PsA treatment regimens on the risk of cardiovascular events. These studies are eagerly awaited.

10. Five-year review

Like all rheumatic diseases, the management of PsA is evolving with the introduction of improved assessment, better outcome measures and newer therapies. The introduction of novel therapies with different modes of action gives us a broader range of therapeutic options. With the identification of new pro-inflammatory cytokines and specific therapies directed against these molecules, better disease control is anticipated. These newer treatments will hopefully have improved outcomes for all domains of illness and better safety profiles. At the same time, biosimilars are likely to make treatment less expensive and increase access to patients with moderate-to-severe disease. With more treatment options it is hoped that strategy trials integrated with validated predictive markers will be conducted so that personalized treatment that is most likely to improve outcome is provided to patients with severe disease rather than the current approach mainly based on trial and error.

11. Key issues

- PsA, an inflammatory arthritis associated with psoriasis, is a heterogeneous disease that affects multiple domains including, peripheral arthritis, axial involvement, skin and nails, entheses, and tendons.
- Treatment of this complex disease has evolved rapidly over the last decade.
- csDMARDs, once the mainstay of therapy, is now being replaced by newer targeted therapies in patients with moderate-to-severe disease.

- PsA is being treated more aggressively of late, with earlier identification and introduction of disease modifying therapy.
- TNF α inhibitors are being increasingly used in patients who had an inadequate response to csDMARDS.
- Interleukin antagonists including IL 12/23 inhibitors and IL17 inhibitors are coming into vogue for the treatment of this complex disease.
- Oral small molecules like apremilast with more specific mode of actions are being introduced.
- It is now recognised that PsA is associated with multiple comorbidities and increased morbidity and mortality.
- Multidisciplinary team approach is being advocated for improved outcomes.
- The patient with PsA needs to be treated in totality with all domains assessed and the most active treated giving adequate consideration of disease activity in other domains.
- A treat to target approach is advocated to dampen the inflammatory response and improve outcomes.
- Adherence to the EULAR and GRAPPA recommendations is supported.

References:

1. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum. 1973;3:55–78.
2. Gelfand JM, Weinstein R, Porter SB, et al. Prevalence and treatment of psoriasis in the United Kingdom: a population based study. Arch Dermatol. 2005;141:1537–1541.
3. Brandrup F, Green A. The prevalence of psoriasis in Denmark. Acta Derm Venereol. 1981;61:344–346.
4. Ferrandiz C, Bordas X, Garcia-Patos V, et al. Prevalence of psoriasis in Spain (Epiderma Project: phase I). J Eur Acad Dermatol Venereol. 2001;15:20–23.
5. Ash Z, Gaujoux-Viala C, Gossec L, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2012;71:319–26.
6. Helliwell PS, Firth J, Ibrahim GH, et al. Development of an assessment tool for dactylitis in patients with psoriatic arthritis. J Rheumatol. 2005;32:1745–

1750

7. Smolen JS, van der Heijde D, Machold KP, et al. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. Ann Rheum Dis. 2014;73:3–5.
8. Ritchlin CT, Kavanaugh A, Gladman DD et al. Treatment recommendations for psoriatic arthritis. Ann Rheum Dis. 2009; 68: 1387-94.
9. Kaltwasser JP, Nash P, Gladman D, et al. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. Arthritis Rheumatol. 2004;50:1939-50.
10. Sarzi-Puttini P, Santandrea S, Boccassini L, et al. The role of NSAIDs in psoriatic arthritis: evidence from a controlled study with nimesulide. Clin Exp Rheumatol. 2001;19:S17–S20.
11. Acosta Felquer ML, Coates LC, Soriano ER, et.al. Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. J Rheumatol. 2014; 41(11):2277- 85.
12. Brenner M, Molin S, Ruebsam K, et.al. Generalized pustular psoriasis induced by systemic glucocorticosteroids: four cases and recommendations for treatment. Br J Dermatol. 2009;161:964-6.
13. Eder L, Chandran V, Ueng J, et al. Predictors of response to intra-articular steroid injection in psoriatic arthritis. Rheumatology (Oxford). 2010;49:1367-73.
14. Montesinos MC, Desai A, Cronstein BN. Suppression of inflammation by low-dose methotrexate is mediated by adenosine A2A receptor but not A3 receptor activation in thioglycollate-induced peritonitis. Arthritis Res Ther. 2006;8(2):R53
15. Black RL, O'Brien WM, VanScott EJ, et al. Methotrexate therapy in psoriatic arthritis; double-blind study on 21 patients. JAMA. 1964;189:743–7.
16. Willkens RF, Williams HJ, Ward JR, et al. Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. Arthritis Rheumatol. 1984;27:376–81.
17. Espinoza LR, Zakraoui L, Espinoza CG, et al. Psoriatic arthritis: clinical response and side effects to methotrexate therapy. J Rheumatol. 1992;19:872–7.
18. Abu-Shakra M, Gladman DD, et al. Long-term methotrexate therapy in psoriatic arthritis: clinical and radiological outcome. J Rheumatol. 1995;22:241–5.
19. Kingsley GH1, Kowalczyk A, Taylor H, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. Rheumatology (Oxford). 2012;51:1368-77.
20. Fagerli MF, Lie E, van der Heijde D, et.al. The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study. Ann Rheum Dis. 2014;73:132-137

21. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet. 2015;19:2489-98
22. Boehncke WH, Alvarez Martinez D, et al. Safety and efficacy of therapies for skin symptoms of psoriasis in patients with psoriatic arthritis: a systematic review. J Rheumatol. 2014; 41:2301-5.
23. Armstrong AW, Tuong W, Love TJ, et al. Treatments for nail psoriasis: a systematic review by the GRAPPA Nail Psoriasis Work Group. J Rheumatol. 2014;41:2306-14
24. Orbai AM, Weitz J, Siegel EL, et al. GRAPPA Enthesitis Working Group. Systematic review of treatment effectiveness and outcome measures for enthesitis in psoriatic arthritis. J Rheumatol. 2014;41:2290-4
25. Rose S, Toloza S, Bautista-Molano W, et al. GRAPPA Dactylitis Study Group. Comprehensive treatment of dactylitis in psoriatic arthritis. J Rheumatol. 2014;41:2295-300.
26. Nash P, Lubrano E, Cauli A, et al. Updated guidelines for the management of axial disease in psoriatic arthritis. J Rheumatol. 2014;41:2286-9.
27. Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration. Ann Rheum Dis. 2014;73:1549-51.
28. Farr M, Kitas GD, Waterhouse L, et al. Sulphasalazine in psoriatic arthritis: a double- blind placebo-controlled study. Br J Rheumatol. 1990;29:46–9.
29. Gupta AK, Grober JS, Hamilton TA, et al. Sulfasalazine therapy for psoriatic arthritis: a double blind, placebo controlled trial. J Rheumatol. 1995;22:894–8
30. Dougados M, van der Linden S, Leirisalo-Repo M, et al. Sulfasalazine in the treatment of spondyloarthropathy. A randomized, multicenter, double-blind, placebo- controlled study. Arthritis Rheum. 1995;38:618–27.
31. Gupta,AK, Ellis CN, Siegel MT, et al. Sulfasalazine improves psoriasis: a double-blind analysis. Arch Dermatol 1990;126:487-93
32. Clegg DO, Reda DJ, Mejias E, et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis Rheumatol. 1996;39:2013–20.
33. Clegg DO, Reda DJ, Abdellatif M. Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondyloarthropathies: a Department of Veterans Affairs cooperative study. Arthritis Rheumatol. 1999;42:2325–9.
34. Fox RI. Mechanism of action of leflunomide in rheumatoid arthritis. J Rheumatol. 1998;53:20–6.
35. Scarpa R, Manguso F, Oriente P et al. Leflunomide in psoriatic polyarthritis: An Italian pilot study. Arthritis Rheumatol. 2001;44:S92.
36. Liang GC, Barr WG. Long term follow up of the use of leflunomide in

recalcitrant psoriatic arthritis and psoriasis. Arthritis Rheumatol. 2001;44:S121.

37. Behrens F, Finkenwirth C, Pavelka K, et al. Leflunomide in psoriatic arthritis: results from a large European prospective observational study. Arthritis Care Res (Hoboken). 2013;65:464-70
38. van Denderen JC, van der Paardt M, Nurmohamed MT, et al. Double blind, randomised, placebo controlled study of leflunomide in the treatment of active ankylosing spondylitis. Ann Rheum Dis. 2005;64:1761-4
39. Steinsson K, Jonsdottir I, Valdimarsson H. Cyclosporin A in psoriatic arthritis: an open study. Ann Rheum Dis. 1990;49:603–6.
40. Spadaro A, Riccieri V, Sili-Scavalli A, et al. Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study. Clin Exp Rheumatol. 1995;13:589–93.
41. Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet. 2000;356:385-90.
42. Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept Treatment of Psoriatic Arthritis Safety, Efficacy, and Effect on Disease Progression. Arthritis Rheumatol. 2004;50:2264-2272.
43. Sterry W, Ortonne JP, Kirkham B, et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. BMJ. 2010;340:c147.
44. Antoni CE, Kavanaugh A, Kirkham B, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: Results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheumatol. 2005;52:1227-36.
45. Antoni CE, Krueger GG, de Vlam K, et.al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 TRIAL. Ann Rheum Dis. 2005;64:1150- 7.
46. Kavanaugh A, Antoni CE, Gladman D, et al. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. Ann Rheum Dis. 2006;65:1038-43
47. Mease PJ, Ory P, Sharp JT, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis. 2009;68:702–709.
48. Gladman DD, Mease PJ, Ritchlin CT, et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial Arthritis Rheum. 2007;56:476-88.
49. Kavanaugh A, van der Heijde D, McInnes IB, et al. Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial. Arthritis Rheum. 2012;64:2504-17.

50. Kavanaugh A, McInnes IB, Philip Mease P, et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomised, placebo- controlled trial, the GO-REVEAL study. Ann Rheum Dis. 2014;0:1–6. doi:10.1136/annrheumdis-2013-204902.
51. Glintborg B, Ostergaard M, Krogh NS, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: results from the Danish Nationwide DANBIO Registry. Arthritis Rheumatol. 2013;65:1213-23.
52. Mease PJ, Fleischmann R, Deodhar AA, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis. 2014;73:48-55.
53. Ritchlin C, Rahman P, Kavanaugh A, et al. PSUMMIT 2 Study Group. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73:990-9.
54. Kavanaugh A, Puig L, Gottlieb AB, et al. Efficacy and safety of ustekinumab in psoriatic arthritis patients with peripheral arthritis and physician-reported spondylitis: post-hoc analyses from two phase III, multicentre, double-blind, placebo-controlled studies (PSUMMIT-1/PSUMMIT-2). Ann Rheum Dis. 2016 Apr 20. pii: Ann Rheum Dis-2015-209068.
55. McInnes IB, Kavanaugh A, Gottlieb AB, et al. PSUMMIT 1 Study Group Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382:780-9.
56. Poddubnyy D, Hermann KG, Callhoff J, et al. Ustekinumab for the treatment of patients with active ankylosing spondylitis: results of a 28-week, prospective, open- label, proof-of-concept study (TOPAS). Ann Rheum Dis. 2014;73:817-23.
57. Jandus C, Bioley G, Rivals JP, et al. Increased numbers of circulating polyfunctional Th17 memory cells in patients with seronegative spondylarthritides. Arthritis Rheumatol. 2008;58:2307-17.
58. Kagami S, Rizzo HL, Lee JJ, et al. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. J Invest Dermatol. 2010;130:1373-83.
59. Lin AM, Rubin CJ, Khandpur R, et al. Mast cells and neutrophils release IL-17 through extra cellular trap formation in psoriasis. J Immunol. 2011;187:490-500.

60. Noordenbos T, Yeremenko N, Gofita I et al. Interleukin-17-positive mast cells contribute to synovial inflammation in spondylarthritis. Arthritis Rheumatol. 2012; 64:99-109.
61. Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis. N Engl J Med. 2015; 373:1329-1339.
62. Baeten D, Sieper J, Braun J, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. N Engl J Med. 2015;373:2534-48.
63. Hueber W, Sands BE, Lewitzky S, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut. 2012;61:1693-1700.
64. Mease PJ, van der Heijde D, Ritchlin CT, et al. SPIRIT-P1 Study Group. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis: results from the 24-week randomised, double- blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis. 2016 Aug 23. pii:Ann Rheum Dis-2016-209709
65. Mease PJ, Genovese MC, Greenwald MW, et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. N Engl J Med. 2014;370:2295-306.
66. Mease P, Gottlieb AB, Berman A, et al. The Efficacy and Safety of Clazakizumab, an Anti-Interleukin-6 Monoclonal Antibody, in a Phase 2b Study of Adults with Active Psoriatic Arthritis. Arthritis Rheumatol. 2016 Apr 5. doi: 10.1002/art.39700.
67. Mease P, Genovese MC, Gladstein G, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. Arthritis Rheum. 2011;63:939-48.
68. GaBI Online - Generics and Biosimilars Initiative. EU guidelines for biosimilars [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [Updated 08 January 2016]. Available from: www.gabionline.net/Guidelines/EU- guidelines-for-biosimilars
69. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. 2014;73:1020-6.
70. Edwards CJ, Blanco FJ, Crowley J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). Ann Rheum Dis 2016;75:1065-1073.
71. Pathan E, Abraham S, Van Rossen E, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis. Ann Rheum Dis. 2013;72:1475-80.
72. Kirkham BW, Kavanaugh A, Reich K. IL17A: a unique pathway in immune mediated diseases: psoriasis, psoriatic arthritis, and rheumatoid arthritis..

Immunology. 2014;141:133-42
73. Novelli L, Chimenti MS, Chiricozzi A, et al. The new era for the treatment of psoriasis and psoriatic arthritis: Perspectives and validated strategies. Autoimmun Rev. 2014;13:64-9.
74. O'Shea JJ. Jaks, STATs, cytokine signal transduction, and immunoregulation: are we there yet? Immunity 1997;7:11–13.
75. Ghoreschi K, Jesson MI, Li X, et al. Modulation of innate and adaptive immune responses by tofacitinib (CP690,550). J Immunol. 2011;7:4234–43.
76. Rosengren S, Corr M, Firestein GS, et al. The JAK inhibitor CP690,550 (tofacitinib) inhibits TNF-induced chemokine expression in fibroblast-like synoviocytes: autocrine role of type I interferon. Ann Rheum Dis. 2012;71:440-7.
77. Bachelez H, van de Kerkhof PC, Strohal R, et al. OPT Compare Investigators. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. Lancet. 2015 8;386:552-61.
78. Papp KA, Menter MA, Raman M, et al. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. Br J Dermatol. 2016;174:1266-76.
79. Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis 2016;75:499-510.
80. Ogdie A, Schwartzman S, Eder L et al. Comprehensive treatment of psoriatic arthritis: managing comorbidities and extra-articular manifestations. J Rheumatol 2014; 41: 2315-22
81. Coates LC, Kavanaugh A, Ritchlin CT. GRAPPA Treatment Guideline Committee: Systematic review of treatments for psoriatic arthritis: 2014 update for the GRAPPA. J Rheumatol 2014; 41: 2273-6.
82. Coates LC, Kavanaugh A, Mease PJ. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis Rheumatol. 2016;68:1060–1071.
83. Ramiro S, Smolen JS, Landewé R, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2016;75:490-8.
84. Di Minno MN, Peluso R, Iervolino S, et al. Weight loss and achievement of minimal disease activity in patients with psoriatic arthritis starting treatment with tumour necrosis factor α blockers. Ann Rheum Dis. 2014;73:1157-62.
85. Coates LC, Helliwell PS. Treating to target in psoriatic arthritis: how to

implement in clinical practice. Ann Rheum Dis. 2016;75:640-3.

86. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis 2010;69:48-53

Part 2: CLINICAL OUTCOMES WITH BIOCHEMICAL PARAMETERS IN OUR COHORT

Chapter 4

An assessment of clinical, biochemical, and radiological features in a single centre South African psoriatic arthritis cohort.

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ABSTRACT

Objectives: To assess clinical, biochemical and radiological features in a South African cohort. Although psoriatic arthritis (PsA) is a well-documented clinical entity, epidemiologic, clinical, and radiologic studies of South African patients are sparse.

Methods: We conducted a cross-sectional assessment and prospective evaluation of the clinical, biochemical and radiological features of 384 consecutive patients with psoriatic arthritis seen at the Prince Mshiyeni Memorial Hospital rheumatology clinic between January 2007 and December 2013. Patients were assessed at enrollment and six months after enrollment. These patients were classified into five groups as described by Moll and Wright. Patients were entered into the group which best described their clinical manifestations.
Patients' clinicopathologic characteristics upon enrollment were recorded: age at the time of examination, racial background, personal and family medical history, age and symptoms at the onset of PsA, the pattern of joint involvement, joint pain and the relation between joint pain and the onset of PsA.

Results: Fifty-nine percent of patients had a polyarticular presentation indistinguishable from rheumatoid arthritis, 19% had distal interphalangeal (DIP) involvement, 9% had a spondyloarthropathy, 12% had oligoarthritis, and 1% had arthritis mutilans. The epidemiologic trends revealed in our study (male: female ratio of 1.49:1, mean age at onset of arthritis of 50.2±11.8 years, female preponderance in the polyarticular group and male preponderance in the spondyloarthropathy and oligoarticular groups) are similar to the trends published elsewhere. A notable characteristic of our cohort was the complete absence of black South Africans with PsA.

Conclusions: The complete absence of black South Africans with PsA is interesting. We anticipate that our findings will prompt genetic studies to isolate both protective and susceptibility genes for further understanding of PsA.

INTRODUCTION

Although psoriatic arthritis (PsA) is a well-documented clinical entity [1], epidemiologic, clinical, and radiologic studies of South African patients are sparse. There are, in fact, no published data regarding the prevalence and incidence of PsA in the South African population. In 1973, Moll and Wright defined PsA as an inflammatory arthritis associated with psoriasis in the absence of rheumatoid factor (RF), and it was not until 2006 that the ClASsification criteria for Psoriatic ARthritis (CASPAR) were introduced for diagnosis [1,2]. The long-recognised Moll and Wright criteria are widely accepted diagnostic criteria that divide PsA into five different types based on the patterns of joint involvement [1]:

(1) polyarticular;
(2) distal interphalangeal (DIP);
(3) spondyloarthropathy;
(4) oligoarticular; and
(5) arthritis mutilans

Some patients in the reported literature present with overlapping symptoms and thus cannot be classified into a particular group [1].

PsA is a heterogeneous disease encompassing inflammatory arthritis, enthesopathy, and new bone formation together with erosive arthropathy [3,4]. The absence of RF is well-documented in patients with PsA [5]. For a long time, PsA was considered to be a less aggressive disease than rheumatoid arthritis; however, recent studies have shown severe erosions and ankylosis in patients with PsA [6-8]. We conducted a study of PsA in a cohort of 384 South African patients and reviewed the clinical, biochemical and radiological features of the disease. Our chief goal was to document the features of PsA in South Africans and to determine the similarities and differences between features in our South African patients and features reported globally.

METHODS

Patients

Our study, which was approved by the Pharma-Ethics Independent Research Committee of South Africa, included 384 consecutive patients who were diagnosed with PsA at the Prince Mshiyeni Memorial Hospital rheumatology clinic between January 2007 and December 2013. The duration of disease symptoms varied between patients. PsA was diagnosed by one of the several consultants with a particular interest in the disorder and was based on the Moll and Wright criteria [1]. RF positivity is well documented in a small

proportion of healthy individuals and the prevalence increases with age [9]. Nevertheless, patients who were RF-positive were included in the study if they fulfilled the Moll and Wright diagnostic criteria [10]. However, patients with rheumatoid arthritis, osteoarthritis or another form of mechanical joint disease, reactive arthritis, and other seronegative arthritides or crystal-associated arthropathy were excluded from the study. Patients with evidence of collagen vascular disease were also excluded. Patients with psoriatic arthritis with secondary mechanical arthropathies were included. All study patients provided written informed consent prior to their participation.

Assessment of patient and disease characteristics

Patients' clinicopathologic characteristics, determined at the time of initial examination, were recorded. These included age and date of examination, racial background, personal and family medical history, age and symptoms at the onset of PsA, the pattern of joint involvement, joint pain and the relation between joint pain and the onset of PsA. Any extra- articular manifestations were also recorded. Peripheral joint involvement was assessed using the 68/66 tender/swollen joint count. Evaluation of axial involvement included occiput- to-wall distance, tragus-to wall distance and goniometric assessment of the range of movement of the cervical spine. The mobility of the lumbar spine was assessed by a modified Schober test, finger-tip-to-floor distance and lateral flexion of the lumbar spine.

Chest expansion evaluated thoracic spine movement. The sacroiliac joints were examined by Patrick's Faber test, anterior, posterior pelvic pressure over the anterior superior iliac spine, lateral pelvic compression, direct pressure over the sacroiliac joints and Gaenslen's test. Treatment was commenced upon enrollment and treatment strategies were recorded.

Table:1 Joint assessments

Joint involvement	Peripheral	Cerivical	Thoracic	Lumbar	Sacro-iliac
Assessment	68/66	occiput-to-wall distance	chest expansion	modified Schober test	Patrick's FABER test
		tragus-to wall distance		finger-tip-to-floor distance	anterior posterior pelvic pressure
		goniometric assessment		lateral flexion	lateral pelvic compression direct pressure on the sacroiliac joints
					Gaenslen's test

A full blood count, the erythrocyte sedimentation rate (ESR, measured by the Westergren method), C-reactive protein (CRP), urea and electrolytes, serum uric acid, serum lipids and plasma glucose concentrations were measured. Antinuclear antibodies (ANAs) were detected by immunofluorescence. Human leukocyte antigen (HLA)-B27 typing was done in all patients. Liver function tests were also performed.

Plain radiographs of the hands, feet, pelvis and lumbar spine were obtained on all patients on enrollment. The radiographs were read by one of the several radiologists with interest in inflammatory arthritis and were evaluated for erosions and new bone formation. The sacroiliac joints were assessed and described by the modified New York criteria [11].

Upon enrollment, patients were categorised into one of five clinical groups according to the Moll and Wright PsA subtypes [1]. Categorisation of these patients was based on both clinical and radiographic findings.

RESULTS

Overall patient characteristics:

Of the 384 study patients, 157 were women, and 227 were men, with a male: female ratio of 1.45:1. Most patients were referred to us by general practitioners, family practitioners or dermatologist, and a small percentage of patients (5%) were self-referred. Two hundred forty-seven of the patients were of Indian descent, and 135 were of European ancestry. Two were of mixed ancestry. Ninety-three (26.3%) of the patients had a family history of psoriasis or PsA. Mean age at the onset of psoriasis was 38.4±9.3 years, and mean age at the start of arthritis was 50.2±11.8 years. In 341 (97%) patients, psoriasis preceded arthritis. Six patients had nail changes without skin changes, and their disease was characterised by DIP involvement. Five patients had inflammatory arthritis with dactylitis and enthesopathy and a family history of psoriasis but no current evidence of psoriasis. Five patients had uveitis as the only extra-articular manifestation, and three of these five patients were HLA-B27 positive. No other extra-articular manifestations were noted in our patient cohort.

Joint distribution

All five Moll and Wright PsA subtypes were represented in our study (table 1), with polyarthritis, indistinguishable from rheumatoid arthritis, found most often (59% of cases). The next most common subtype was the DIP subtype (19%) followed by the oligoarticular type (12%); spondyloarthropathy accounted for 9% of the cases and arthritis mutilans for 1%.

Table 2. Classification of study patients (n=352) per Moll and Wright[1] PsA subtypes

PsA subtype	No. of patients	M: F ratio
Polyarticular	208	113 / 95 (1.2: 1)
DIP	67	44 / 23 (1.9: 1)
Oligoarticular	42	31 / 11 (2.8: 1)
Spondylitis predominant	32	22 / 10 (2.2: 1)
Arthritis mutilans	3	1 / 2 (1: 2)

32 patients had overlapping groups and were not included in any particular group.

[1]Moll JM, Wright V, 1973. M, male; F, female; DIP, distal interphalangeal.

Among patients in the polyarticular PsA group, metacarpophalangeal involvement was found in 82%, radiocarpal involvement in 68% and metatarsophalangeal involvement in 68%. Among patients in the oligoarticular PsA group, the knees (52%) and ankles (35%) were most frequently involved. In nine patients in this group, asymmetrical oligoarticular involvement of the lower limbs was associated with sacroiliitis. Only three patients had severe arthritis mutilans. In all three patients, the arthritis mutilans involved digits of the upper and lower limbs. Female sex was predominant in the polyarthritis group (48% women vs. 32.4% men), and male sex was dominant in the spondyloarthritis group (32.2% men vs. 18.2% women). There was also a male preponderance in the oligoarticular group with a male: female ratio of 2.8:1. Fingernail changes including pitting of the nails, onycholysis and nail dystrophy were seen in 72% of the patients.

Table: 3 Joint Involvement

	MCP	Radiocarpal	MTP
polyarticular PsA group (n=208)	170 (82%)	142 (68%)	142 (68%)

	knees	ankles
Oligo-articular (n=42)	22 (52%)	15 (35%)

Laboratory data

Results of the laboratory tests are shown in table 4. ESR elevation was noted in only 99 (28.1%) patients. The ESR elevation was greater in the polyarticular group than in the spondyloarthropathy group (mean 46 vs. 38 mm/hr). However, CRP was elevated in 243 (69.03%) of patients to a mean concentration of 15.3 mg/L (normal range: 0-8 mg/L). After six months of disease-modifying antirheumatic drug (DMARD) therapy, the mean CRP decreased to 7.1 mg/L. Results of liver function tests were normal, except hyperglobulinemia in all patients. Nineteen patients (5.4%) tested positive for RF, and 15 patients (4.2%) tested positive for anti-citrullinated peptide antibodies (ACPAs). Six patients tested positive for ANAs; however, none of these patients fulfilled the American College of Rheumatology criteria for a diagnosis of systemic lupus erythematosus.

HLA-B27 positivity was noted in 57 (16.3%) patients. 28 of these patients showed axial involvement, and 29 patients with oligo- or polyarticular disease exhibited HLA-B27 positivity. Of the patients positive for HLA-B27, 35 (62%) were of European descent; only 22 (38%) were of Indian origin.

Table 4. Results of laboratory tests in the patient cohort (n=352)

Result	No. of patients[1]	Value
ESR	99	62 (34-102) mm/hr
CRP	243	15.3 (10-38) mg/L
RF positivity	19	n/a
Anti-CCP positivity	15	n/a

[1]No. of patients: number of patients with abnormal results. Values are shown as mean (range). ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; n/a, not applicable.

Radiologic assessment

Sacroiliitis of grade 2 or higher was noted in 22 of the 27 patients with spondyloarthropathy (14 men vs. 8 women). Five patients had syndesmophytes, which were asymmetric and unilateral. The radiographic features of peripheral joint involvement included soft tissue swelling, erosion, joint space narrowing, ankylosis and new bone formation.

Treatment

Treatment was assessed at six months. All patients were DMARD naïve on enrollment. Two hundred forty-eight (70.5%) of the 352 patients were on methotrexate monotherapy at an average dose of 17.5 mg/week (range: 7.5-25 mg/week) at six months. Disease activity remained low in these patients, with a mean Simplified Disease Activity Index (SDAI) of 7.6. Sixty-five (18.5%) patients were on a combination of methotrexate and sulfasalazine; 29 patients were on triple therapy with methotrexate, sulfasalazine, and leflunomide. Only ten patients were treated with biologics. Neither hydroxychloroquine or chloroquine were used in any of the patients. Corticosteroids were only used intra-articularly for acute flares.

DISCUSSION

To the best of our knowledge, this is the first study to explore the clinical, laboratory and radiological characteristics of a relatively large cohort of South African PsA patients. Three hundred fifty-two patients diagnosed with PsA according to the Moll and Wright criteria were included. The epidemiologic trends revealed in our study (male: female ratio of 1.49:1,mean age at onset of arthritis of 50.2±11.8 years, female preponderance in the polyarticular group and male preponderance in the spondyloarthropathy and oligoarticular groups) are similar to the trends published elsewhere [12]. One notable characteristic of our cohort was the complete absence of black South Africans with PsA. Our hospital is a large regional hospital in the south of Durban, South Africa and is the only referral rheumatology centre in this region. Our catchment population is 1.6 million which is 82% African black, and our hospital outpatient attendance has an African Black percentage of 92%. At the rheumatology clinic, 63.5% of the attendees are African Black presenting with various other rheumatological problems including, RA, SLE, OA, and HIV associated arthropathy [13]. The racial distribution pattern needs to be further explored. To what degree this trend would hold true in a larger patient group remains to be determined, but it appears that there may be an absence of psoriasis/PsA in the black population. The reasons for this lack of susceptibility are not clear. It could be related to the low prevalence of HLA-B27 in this population.
Psoriasis has been noted in the HIV-positive black people.

In most of our patients, psoriasis developed before arthritis developed. The distribution of joint involvement observed in our cohort was similar to distributions published elsewhere [12].

The reason for the limited use of biologic therapy in our cohort was that PsA is not well covered by medical insurance in South Africa. Health insurance in South Africa does not reimburse PsA patients for biologic therapy.

This study of the epidemiologic, clinical, and radiologic features of a relatively large cohort of South African patients with PsA yielded data similar to data published for other populations. The complete absence of black South Africans with PsA in our cohort could be related to the low prevalence of HLA-B27 in this population. There may be yet-to-be-identified protective genes in this population group. We anticipate that our findings will prompt genetic studies to isolate both protective and susceptibility genes for further understanding of PsA.

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References:

1. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55-78.
2. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665-73.
3. O'Neill T, Silman AJ. Psoriatic arthritis. Historical background and epidemiology. Baillieres Clin Rheumatol 1994;8:245-61.
4. Gladman DD. Clinical aspects of the spondyloarthropathies. Am J Med Sci 1998;316:234-8.
5. Punzi L, Podswiadek M, Oliviero F, et al. Laboratory findings in psoriatic arthritis. Reumatismo 2007;59:52-5.
6. Gladman DD, Chandran V. Review of clinical registries for psoriatic arthritis: lessons learned? Value for the future? Curr Rheumatol 2011;13:346-52.
7. McHugh NJ, Balachrishnan C, Jones SM. Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. Rheumatology (Oxford) 2003;42:778-83.
8. Schoellnast H, Deutschmann HA, Hermann J, et al. Psoriatic arthritis and rheumatoid arthritis: findings in contrast-enhanced MRI. AJR Am J Roentgenol 2006;187:351-57.
9. Simard JF, Holmqvist,M. Rheumatoid factor positivity in the general population. BMJ 2012;345:e5841
10. Gladman DD, Shuckett R, Russell ML, et al. Psoriatic arthritis (PSA)—an analysis of 220 patients. Q J Med 1987;62:127-41.

11. van der Linden S, Valkenburg H, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
12. Gladman, DD, Antoni, C, Mease, P, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis 2005;64:14-17.
13. Maharaj,A.B and Tak,P.P. Spondyloarthritis in African Blacks. J Rheumatol 2015:42(1):139;

Chapter 5

Summary of sensitivity and specificity of psoriatic arthritis in a South African cohort according to classification criteria

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ABSTRACT

Objective: To evaluate the sensitivity and specificity of classification criteria for PsA in a South African cohort.

Methods: Data from 1168 consecutive patients with psoriatic arthritis and other chronic inflammatory arthritides were collected prospectively. Subjects were classified according to the Moll and Wright criteria, European Spondyloarthropathy Study Group (ESSG) criteria for spondyloarthritis, Vasey and Espinoza criteria, and CASPAR criteria. Patients with rheumatoid arthritis (RA) were required to fulfil the 1987 American College of Rheumatology criteria for the diagnosis of RA. Patients diagnosed with Ankylosing Spondylitis (AS) were required to satisfy the modified New York criteria for the diagnosis for AS. The sensitivity and specificity in each group of patients were compared with a clinical diagnosis made by a rheumatologist. Latent class analysis was used to calculate the criteria's accuracy and confirm their validity.

Results: In total 308 (173 males and 135 females) patients with psoriatic arthritis were entered into the study. The mean (standard deviation, s.d.) age and duration of illness were 50.2 (13.2) and 5.88 (3.78) years, respectively. Data were compared with 686 patients with RA and 174 patients with ankylosing spondylitis (AS). The ESSG criteria exhibited the lowest sensitivity followed by the Moll and Wright criteria. The sensitivity and specificity of the CASPAR criteria were 98.4% and 99.7%, respectively. This result is similar to results reported in European populations.

Conclusions: The CASPAR criteria were evaluated in a South African population, and they performed well, which is consistent with the populations for which this standard was developed. The CASPAR also exhibits increased sensitivity and specificity for classifying psoriatic arthritis compared with previously used criteria.

INTRODUCTION

Psoriatic arthritis (PsA) associated with psoriasis is an inflammatory arthritis. Approximately 1 to 3% of the general population develop psoriasis and research suggests that approximately 30% of patients with psoriasis develop PsA. The original description of psoriatic arthritis by Moll and Wright [1] in 1973 was the cornerstone of diagnosis for many years. Following this, various other criteria were developed in order to standardise the reporting of PsA [2-6]. Due to the heterogeneous nature of both the skin and joint manifestations, there has not been uniformity in reporting of these cases series. This ultimately resulted in a wide variation in reported incidence and prevalence rates.

In 2006, the ClASsification of Psoriatic ARthritis (CASPAR) criteria were developed is by a group of international experts from across the globe in order to bring about uniformity in reporting of PsA [7]. These criteria were developed from prospective studies from across the globe but mainly included Caucasian patients. The classification criteria CASPAR is listed in table 1 and provides a sensitivity of 91.4% and a specificity of 98.7%.

Epidemiological studies on South African patients in particular and African patients in general with PsA are exceedingly rare. Before the advent of human immunodeficiency virus (HIV) infection, psoriasis and PsA were extremely uncommon in the African black population. The CASPAR criteria included patients mainly from the developed world and western societies. Scores of patients of South African ethnicity were not included in the study. We, therefore, embarked to validate these criteria in South African patients with PsA, including both Caucasians as well as patients of South African Indian ethnicity.

METHODS

All of the patients with PsA attending the rheumatology clinic at two hospitals in Durban, South Africa from January 2007 to December 2012 were enrolled in the study. The diagnosis of PsA was made by a rheumatologist with a special interest in PsA. Controls were consecutive patients of the same clinic with rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Patients with rheumatoid arthritis (RA) were required to fulfil the 1987 American College of Rheumatology criteria for the diagnosis of RA [8]. Patients diagnosed with Ankylosing Spondylitis (AS) were needed to satisfy the modified New York criteria for the diagnosis of AS [9]. All of the patients enrolled were above the age of 18 years, and the study included patients of Caucasian and South African Indian ethnicity. The study did not have any patient with PsA who was categorised as African black as no African Black patients were seen with PsA as psoriasis is extremely uncommon in this population. [10].
Two patients were of mixed-race (coloured). All the patients were interviewed. After

providing informed consent, the patients were examined by a rheumatologist according to standard procedures. The examination included all of the historical information required by various criteria, including a family history. A current history of psoriasis, a family history of psoriasis, symmetrical joint disease, a current or previous history suggestive of enthesitis, a history of inflammatory back pain, and other basic demographic data were collected. Tender and swollen joint counts were recorded. Standard anteroposterior radiographs of the hands and wrists, as well as feet and pelvis, were obtained to examine them for erosions, new bone formation, and sacroiliitis. The radiographs were read by a radiologist who was blinded to the patient's clinical features. The criteria listed in Table 1 were then applied to all of the study subjects.

Table 1: Operational definition of classification of psoriatic arthritis

Name	Criteria
Moll and Wright	Inflammatory joint disease (either peripheral arthritis or spondylitis or sacroiliitis) AND psoriasis and rheumatoid factor negative
ESSG	Synovitis or inflammatory spinal pain AND psoriasis or personal history of psoriasis
Vasey and Espinoza	Psoriasis or psoriatic nail lesion AND peripheral pattern[a] or central pattern[b]
CASPAR	Inflammatory articular disease (joint, spine, or entheseal) AND 3 points from the following: (1) Current psoriasis (scores 2 points) (2) Personal history of psoriasis (if current psoriasis is absent) (3) Family history of psoriasis (if personal history of psoriasis or current psoriasis is not present) (4) Psoriatic nail dystrophy (5) A negative test for RF (6) Current dactylitis (7) History of dactylitis (if current dactylitis is not present) (8) Radiological evidence of juxta-articular new bone formation

Adapted from: Evaluation of the CASPAR criteria for psoriatic arthritis in the Chinese population. Leung YY1, Tam LS, Ho KW, Lau WM, Li TK, Zhu TY, Kun EW, Li EK. Rheumatology (Oxford). 2010 Jan;49; 1:112-5.

[a] Greater than four weeks of arthritis of the distal interphalangeal joint (DIPJ); or asymmetrical peripheral arthritis (included sausage digit); absent RF or rheumatoid nodule; or radiographic changes (pencil-in-cup deformity, whittling of terminal phalanges, fluffy periostitis, and bony ankylosis).

[b] Greater than four weeks of spinal pain and stiffness with restriction of motion, Grade 2 symmetrical sacroiliitis, or Grade 3 or 4 unilateral sacroiliitis according to the modified New York criteria.

Statistical analysis

The sensitivity and specificity of the four criteria for classifying PsA was calculated; the rheumatologist's clinical diagnosis served as the gold standard. Evaluation was done using the latent class (LC) analysis. The LC analysis is a rather simple one: it assumes that some of the parameters of a postulated statistical model differ across unobserved subgroups of the same class and that acceptance between the subgroups is compared to the gold standard, i.e., the diagnosis by a rheumatologist in this instance. This approach enables the sensitivity and specificity of each criterion within the group to be derived without actually knowing the correct diagnosis of the patient. The concordance between the clinical diagnosis and latent class model was evaluated with a κ-statistic. [11,12]

This study was reviewed and approved by the Pharma-Ethics research ethics committee of South Africa. Before entering the study, participants were informed of the nature and purpose of the study, and written consent was obtained before inclusion into the study.

RESULTS

The demographics and disease characteristics of the 308 patients diagnosed with PsA by a rheumatologist as well as 860 controls (686 RA and 174 AS subjects) are provided in Table
2. Of the 308 consecutive patients with psoriatic arthritis, 192 were South Africans of Indian descent, 114 were South Africans of European descent, and 2 were of mixed-race. None of the patients were of South African Black decent. Of the 308 patients with psoriatic arthritis, 173 were males, and 135 were female. The mean age was 50.2 years old (range 20-83 years) (Figure:1). The average duration of arthritis before diagnosis was 11.3 months (range 3-226 months). All subtypes of psoriatic arthritis were noted in the various populations. Patients with rheumatoid arthritis were older, whereas those with ankylosing spondylitis were younger but experienced a slightly longer disease duration.

Table 2: Demographic details of patients with PsA, RA, or AS on enrolment

Demographic details	**PsA** n=308	**RA** n=686	**AS** n=174
Age in years	50.2 (11.8)	56.8 (13.6)**	36 (9.6)**
M:F	1.4:1	1:3.8**	3.1:1*
Duration of disease: years	5.88 (3.78)	7.8 (8.4)*	15.8 (8.9)*
VAS –pain (0-100 mm)	58.4 (22.8)	44.8 (26.8)^	42.6 (30.1)*
MDPGA	52.8 (12.3)	43.8 (24.7) *	44.2 (28.4)*

Data shown for mean (S.D.). Statistical significance compared with PsA: *P <0.01, **P< 0.05

VAS: visual analogue scale for pain. 0= no pain; 100= maximum pain MDPGA: Physician global assessment 0= good; 100 =poor

Among the PsA cohort, 56 subjects had early PsA, which is defined as having a length of symptoms of less than 2.5 years. As expected, the patients with early PsA were younger and exhibited less damage on radiological examination; however, minimal differences in pain scores, tender joint counts, and swollen joint counts were noted in these patients compared with chronic PsA patients. (See Table 3)

Table 3: Differences between early and late PsA at inception

	Early PsA n=56	Late PsA n=252	p-value
TJC	8 (5)	10(3)	p= NS
SJC	9(6)	11(4)	p = NS
VAS	66.2(18.3)	51.3 (12.6)	p= NS
MDPGA	59.6(13.6)	45.3 (12.6)	P =NS

Data are shown for a mean (S.D.). VAS: visual analogue scale for pain. 0= no pain; 100= maximum pain. MDPGA: Physician global assessment 0= good; 100 =poor

Among the PsA cohort, 303 of the 308 subjects fulfilled the CASPAR criteria with a sensitivity and specificity of 98.4% and 99.7%, respectively. The ESSG criteria exhibited the lowest sensitivity followed by the Moll and Wright criteria. The sensitivity and specificity of the four criteria by comparing a clinical diagnosis compared to that of the latent class model are presented in Table 4.

Table 4: Summary of Classification criteria for PsA

Classification Criteria	**Clinical Diagnosis %**		**Latent Class Model %**	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
Moll and Wright	83.6	100	84.2	100
ESSG	79.3	99.8	81.3	99
Vasey and Espinoza	98	100	99	99
CASPAR	98.4	99.7	99	99

174 patients fulfilled the modified New York criteria for the diagnosis of AS. There were 129 Caucasians and 45 patients of Indian origin. Our cohort did not include any black African patients or mixed-race patients with AS. The male-to-female ratio was 3.1 : 1. The mean age was 36 years (range 22-68 years) with a mean delay in diagnosis of 62 months (range 28 - 97 months).

None of the patients with AS had either a current or history of psoriasis. Three patients in the RA group had a family history of psoriasis (0.4 %), and five patients in the AS cohort had a family history of psoriasis (2.87 %).

The breakdown of patients fulfilling the various CASPAR criteria is presented in Table 5. A good correlation between the sensitivities and specificities of the clinical diagnosis model and the latent class model was noted, thereby confirming the validity of using expert clinical diagnoses as a gold standard.

Table 5: Percentages of patients with PsA fulfilling CASPAR criteria

	PsA (n=308), %
Current psoriasis	99.3
Family history of psoriasis	26.3
Nail change	76.9
Negative RF	93.8
Dactylitis (past or present)	58.1
Juxta-articular new bone formation	38.3

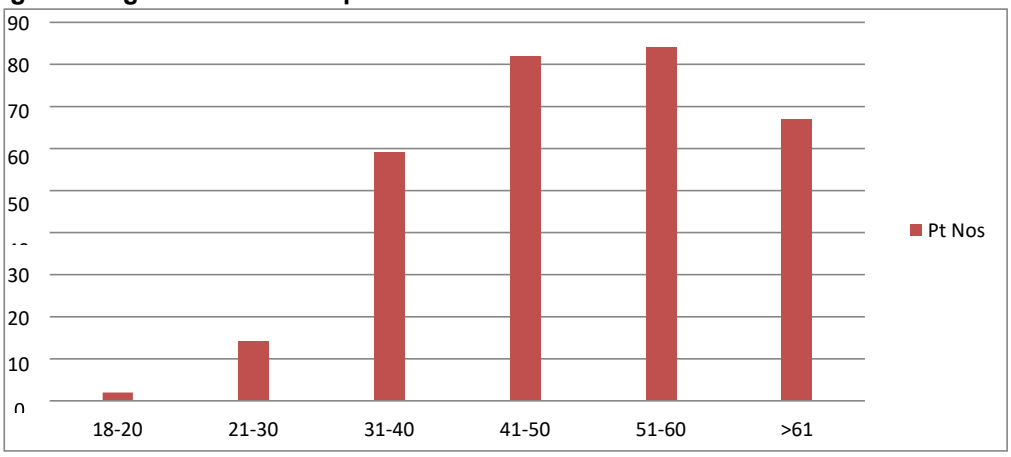
DISCUSSION

This is the first study according to our knowledge to evaluate and validate the performance of the CASPAR criteria in a South African population. Our evaluation of the CASPAR criteria in a South African cohort yielded an overall sensitivity and specificity of 98.4% and 99.7%, respectively. The sensitivity of the CASPAR criteria was superior to the previously commonly used Moll and Wright criteria. Although South African patients with PsA were included in the initial CASPAR cohort, the number of these patients was limited. It is promising that the CASPAR criteria performed well and were validated in a larger South African cohort.

Our present study has some strengths and limitations. The strengths include the fact that all possible psoriatic patients available at the time of the study were enrolled. This inclusion minimised the possibility of observer bias. The controls were unselected patients attending the same clinics. We also demonstrated good correlation using two statistical models. Our study also had a few limitations, such as being a cross-sectional study of PsA patients with a longer duration of illness attending two rheumatology clinics. This is not a multicentre study. A further limitation could be the inclusion of a small number of controls limited to RA and AS. Only 18.2% of our cohort had early PsA based on the previous definition. Chandran et al. [13,14] assessed the CASPAR criteria in early PsA patients attending a referral centre and concluded that these criteria exhibit a high sensitivity and specificity in early and late PsA.

In summary, the CASPAR criteria were developed and validated as a system for classifying PsA. These criteria performed well in a South African population and exhibited high sensitivity and specificity.

Figure 1: Age distribution of patients with PsA



References

1. Moll JMH, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55–78.
2. Bennett RM, McCarty DJ. Psoriatic arthritis. In: McCarty DJ, Hollander JL, eds. Arthritis and Allied Conditions. 9th ed. Philadelphia: Lea & Febiger 1979:645.
3. Gladman DD, Shuckett R, Russell ML, et al. Psoriatic arthritis (PsA): an analysis of 220 patients. Q J Med 1987;238:127–41.
4. Vasey FB, Espinoza LR. Psoriatic arthritis. In: Calin A, ed. Spondyloarthropathies. Orlando: Grune and Stratton 1984:151–85.
5. McGonagle D, Conaghan PG, Emery P. Psoriatic arthritis: a unified concept twenty years on. Arthritis Rheum 1999;42:1080–6.
6. Dougados M, van der Linden S, Juhlin R, et al. The European Spondyloarthropathy Study Group preliminary criteria for the classification of spondyloarthropathy. Arthritis Rheum 1991;34:1218–27.
7. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73.
8. Arnett FC1, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:3:315-24.
9. Van der Linden S, Valkenburg H, Cats A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-368.

10. Namazi M.R. Why is psoriasis uncommon in Africans? The influence of dietary factorson the expression of psoriasis. Int J Dermatol 2004;43:391-92
11. Rindskopf D, Rindskopf W. The value of latent class analysis in medical diagnosis. Stat Med 1986;5:21–7.
12. Faraone SV, Tsuang MT. Measuring diagnostic accuracy in the absence of a “gold standard.” Semin Arthritis Rheum 2004;34:575–84.
13. Chandran V, Schentag CT, Gladman DD. Sensitivity of the classification of psoriatic arthritis criteria in early psoriatic arthritis. Arthritis Rheum 2007;57:1560–3.
14. Chandran V, Schentag CT, Gladman DD. Sensitivity and specificity of the CASPAR criteria for psoriatic arthritis in a family medicine clinic setting. J Rheumatol 2008;35:2069–70.

Chapter 6

Spondyloarthritis in African Blacks: reasons for its rarity

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J Rheumatol January 2015 42(1):139

Spondyloarthritis in African Blacks

Psoriatic arthritis (PsA) appears extremely rarely in African black populations [1,2]. To the best of our knowledge, no population-based data are currently available on the prevalence and incidence of PsA in the African black population in sub-Saharan Africa, including South Africa. In South Africa, hospital-based prevalence studies, almost all of which are done in dermatology departments, show the prevalence of psoriasis to be about 2.8% to 3.5% in whites [3]. These figures are similar to those shown in other parts of the world [4]. In a study undertaken in 5 academic hospitals serving the public sector in Johannesburg, 5,355 consecutive African black patients with dermatological problems were assessed, of which 112 (2.1%) were diagnosed with psoriasis [3].

We report the complete absence of African black patients with PsA and ankylosing spondylitis (AS) at the Rheumatology Clinic, Prince Mshiyeni Memorial Hospital, Durban, South Africa, over a 5-year period between January 2007 and December 2011. This was first noted in a cross-sectional survey of 1,352 South African blacks in a study in 1975 [5]. In more recent reviews of the subject, similar findings were reported in other parts of Africa [6,7].

Of the 288 consecutive patients with PsA, 192 were South Africans of Indian descent, 94 were South Africans of European ancestry, and 2 were of mixed race. Only patients who fulfilled the ClASsification for Psoriatic ARthritis (CASPAR) criteria for a diagnosis of PsA were included in the study [8]. There were no South African black patients with PsA documented in our cohort (Figure 1). Of the 288 patients with PsA, 167 were men and 121 were women. Mean age was 51 years (range 20–83 yrs). Mean duration of arthritis before diagnosis was 11.3 months (range 3–226 mos).

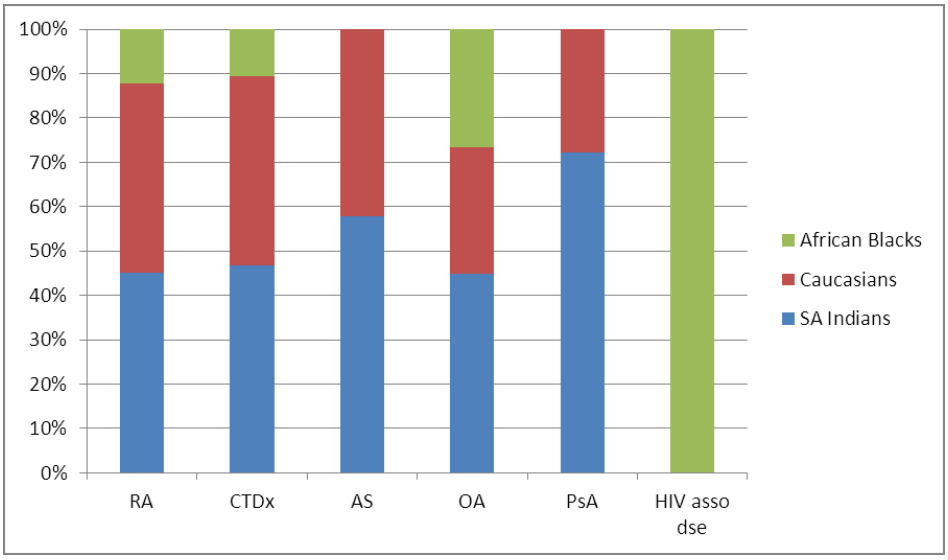
There were 248 patients with AS who fulfilled the modified New York criteria for the diagnosis of AS [9]. There were 184 whites and 645 patients of Indian origin. There were no African black patients or patients of mixed race with AS in our cohort. No African black patients were seen in our cohort of 248 patients with AS. This probably represents the low prevalence of HLA-B27 positivity among African blacks [7,10].

However, the rarity of psoriasis and psoriatic arthritis in the African black population cannot alone be attributed to the low prevalence of HLA-B27 in this population group. In West Africa, there is a disconnect between the prevalence of HLA-B27 and the prevalence of spondyloarthritis. The African black people in West Africa have a prevalence of HLA-B27 that approaches the western population. However, the prevalence of spondyloarthritis is similar to that of the rest of Africa [10]. A fair number of patients (51) with human immunodeficiency virus (HIV)-related rheumatological problems were seen; however, none of these patients had psoriasis/PsA or AS.

A recent study published in the annals of rheumatic diseases by Raychaudhuri and her group describes a vague coding allele in IFIH1 that is protective for psoriatic arthritis [11]. Although the article does not explain the presence of this protective gene in racial populations, it will be interesting to extend the study to the African black population.

A limitation of our study could be biased by inadequate health care service access by the general population. It should be noted, however, that we did see African black patients with rheumatoid arthritis, osteoarthritis, and HIV-associated musculoskeletal disease in our clinic. Taken together, the results suggest that PsA and AS may be very rare in African black patients. Our work provides the rationale for further work in independent cohorts, and if confirmed, research on risk and protective factors in African black populations to better delineate the importance of genetic and environmental factors in the pathogenesis of PsA and AS.

Figure 1. Racial breakdown of rheumatic diseases in the South African populations (%) seen at our clinic.



RA: rheumatoid arthritis; CTD: connective tissue diseases; AS: ankylosing spondylitis; OA: osteoarthritis; PsA: psoriatic arthritis; HIV asso dse: human immunodeficiency virus-associated rheumatological diseases.

References

1. Namazi MR. Why is psoriasis uncommon in Africans? The influence of dietary factorson the expression of psoriasis. Int J Dermatol 2004;43:391-2.
2. Leder RO, Faber EM. The variable incidence of psoriasis in sub-Saharan Africa. Int J Dermatol 1997;36:911-9.
3. Hartshorne ST. Dermatological disorders in Johannesburg, South Africa. Clin Exp Dermatol 2003;28:661-5.
4. Chandran V, Raychaudhuri SP. Geoepidemiology and environmental factors of psoriasis and psoriatic arthritis. J Autoimmun 2010;34:J314-21.
5. Solomon L, Beighton P, Valkenburg HA, Robin G, Soskolne CL. Rheumatic disorders in the South African Negro. Part I. Rheumatoid arthritis and ankylosing spondylitis. S Afr Med J 1975;49:1292–6.
6. Tikly M, Njobvu P, McGill P. Spondyloarthritis in sub-Saharan Africa. Curr Rheumatol Rep 2014;16:421.
7. Mijiyawa M, Oniankitan O, Khan MA. Spondyloarthropathies in sub-Saharan Africa. Curr Opin Rheumatol 2000;12:281–6.
8. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73.
9. van der Linden S, Valkenburg H, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
10. Khan MA. HLA-B27 and its subtypes in world populations. Curr Opin Rheumatol 1995;7:263-9.
11. Ashley Budu-Aggrey, John Bowes, Philip E Stuart, et al. A rare coding allele in IFIH1 is protective for psoriatic arthritis. Ann Rheum Dis 2017;0:1–4. doi:10.1136/annrheumdis- 2016-210592 published on line before print

PART 3: GENETICS of PsA in this Cohort

Chapter 7: miR-146a polymorphism influences psoriatic arthritis in South African patients.

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Abstract:

Background: Psoriasis and psoriatic arthritis (PsA) are autoimmune disorders characterized by inflammation. MicroRNA (miR)-146a plays a crucial role in regulating inflammation. A single nucleotide polymorphism in the miR-146a gene (rs2910164) aberrantly alters its gene expression and is linked with the pathogenesis of several disorders, including psoriasis and PsA. The aim of this study was to investigate whether the miR-146a SNP rs2910164 is associated with risk for PsA in South African Indian and Caucasian patients.

Methods: South African (SA) Indian (n = 84) and Caucasian (n = 32) PsA patients (total n = 116) and healthy control subjects (Indian: n = 62 and Caucasian: n = 38; total n = 100) were recruited in the study. DNA was extracted from whole blood, and patients were genotyped for the miR-146a rs2910164 using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Data for laboratory parameters were obtained from pathology reports. The consulting rheumatologist collected all other clinical data.

Results: In SA Indian patients the *miR-146a* rs2910164 C-allele frequency was significantly higher in PsA patients vs. healthy controls (35.78% vs. 26% respectively, p = 0.0295, OR = 1.59 95% CI 1.05–2.40). In SA Caucasians the C-allele frequency distribution was similar in PsA patients vs. healthy controls.

Conclusion: The rs2910164 variant C-allele may play a role in the progression of PsA in the South African Indian population.

Keywords: miR-146a rs2910164, Psoriatic arthritis, South African Caucasian and Indian population

Background:

Psoriasis is a chronic immune-mediated inflammatory skin disease triggered by a broad spectrum of genetic and environmental factors [1] and characterized by hyperproliferative keratinocytes, and aberrantly increased T lymphocyte (T-cell) activation and T-helper cell type 1 (T_H1) cytokine production [2]. Psoriasis is associated with an inflammatory arthritis, namely psoriatic arthritis (PsA) [3]. Around 30% (6-42%) of patients with psoriasis develop PsA [4-6].

MicroRNAs (miRs) are small non-coding RNAs that control gene expression at the post-transcriptional level by negatively regulating the processing, stability, and translation of mRNA. The highly conserved "seed" region of miRs, composed of 2-7 nucleotides and located at the 5'-untranslated region (5'-UTR), binds to the 3'-UTR of their target mRNA to elicit their aforementioned functions [7]. MiRs play an invaluable role in regulating physiological processes in the body, including cell cycle progression, cell differentiation, metabolism and apoptosis [8]. When miRs are aberrantly expressed, due to single nucleotide polymorphisms (SNPs) within miR encoding genes or environmental factors (pollution, teratogens, and smoking), they can also contribute towards the pathogenesis of several inflammatory disorders [9].

MiR-146a is located on human chromosome 5q34 and plays an important role in regulating immune and inflammatory response pathways [10]. MiR-146a induction is stimulated by toll-like receptors (TLRs), interleukin (IL)-1β and tumour necrosis factor (TNF)- α. They primarily target IL receptor associated kinase 1 (IRAK1) and TNF receptor associated factor 6 (TRAF6) to modulate and prevent overstimulation of inflammatory responses in the TLR/NF-κB pathways [11]. The miR-146a G/C SNP (due to a C:U miss-pairing taking place instead of a normal G:U pairing), contributes towards the pathogenesis of several inflammatory diseases, including autoimmune disorders [12], sepsis [13], cardiovascular disease [14] and diabetes [15]. This SNP is situated within the crucial stem region of pre-miRNA-146a and affects the

expression of mature miR-146a [16]. The miR-146a rs2910164 is also associated with psoriasis [17] and PsA [18]. However limited data are available.

In South Africa, psoriasis and PsA are extremely rare among the indigenous African population while such cases are more common in both the Indian and Caucasian population. The present study investigated whether rs2910164 is associated with risk for PsA in South African Indian and Caucasian patients.

Methods

Patient recruitment and sample collection

Blood samples were taken from South African Indian (n = 84) and Caucasian (n = 32) PsA patients (total n = 116) and healthy control subjects (Indian: n = 62 and Caucasian: n = 38; total n = 100 that were enrolled in the study after informed consent following ethical approval from the Pharma-Ethics Research Ethics Committee (ethics reference number: 13095660). The inclusion criteria for this study, irrespective of age and gender, were: (a) patients must be over the age of 18 years; (b) patients must have a confirmed diagnosis of PsA and must have fulfilled the Classification Criteria for PsA (CASPAR) [19] criteria; (c) Patients with all other forms of inflammatory arthritis or connective tissue disorders were excluded from this study. Patient history (age, sex, race, disease duration, HAQ scores, and medications) and height, weight were obtained by the consultant rheumatologist. Overal functional health status was assessed using the Health Assessment Questionnaire (HAQ). The HAQ Disability Index (HAQ-DI) was used to assess the level of functional ability in patients.The HAQ visual analogue (VAS) pain scale was used to assess the absence or presence of PsA related pain and its severity in patients. The HAQ VAS patient global health scale was used to assess the overall quality of life for patients where 0 = good health and 10 = poor health. HAQ score values < 0.5 and > 0.5 indicated patients had minimal functional impairments respectively moderate to severe functional impairments. The immunoglobulin M rheumatoid factor (IgM- RF) and C-reactive protein (CRP), were assessed at Lancet Laboratories (Durban, South Africa), a fully accredited South African National Laboratory.

DNA extraction

Genomic DNA was extracted from whole blood taken from PsA patients and controls using the FlexiGene® DNA isolation kit (Qiagen). Briefly, 750 µl cell lysis buffer was added to 300 µl whole blood to pellet out the mitochondria and cell nuclei, followed by the removal of contaminants such as proteins in the pellet by adding 150 µl denaturation buffer, which contained a chaotropic salt and protease enzyme, and incubating for 5 min at 65^{O}C. To this solution, 150 µl 100% isopropanol was added to precipitate out the DNA and was recovered by centrifugation. The DNA was washed in 150 µl 100% ethanol, dried at room temperature, resuspended in 15 µl hydration buffer (10 mM Tris.Cl, pH 8.5), incubated for 1 hr at 65^{O}C and stored at -20^{O}C until further use. The Nanodrop 2000 spectrophotometer (Thermo Scientific) was used to determine the purity and concentration of the DNA. All DNA samples were standardised to a concentration of 10 ng/µl.

Genotyping

The miR-146a G/C rs2910164 was genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The GoTaq® G2 Flexi DNA Polymerase PCR kit (Promega) and the CFX96 Touch™ Real-Time PCR Detection System (Bio-Rad) was used for this analysis. The 147 bp gene amplicon was amplified using 1× Green GoTaq Flexi buffer,

2.5 mM $MgCl_2$, 200 µM of each dNTP, 0.2 Units GoTaq Flexi DNA polymerase, 20 pmol of each forward (F) and reverse (R) primer sequences, and 30 ng genomic DNA template. A non-template control was run with the positive samples to assess the overall specificity of the reaction. The forward and reverse primer sequences used were 5′-CATGGGTTGTGTCAGTGTCAGAGCT-3′, and 5′-TGCCTTCTGTCTCCAGTCTTCCAA-3′, respectively. PCR conditions were: 94°C for 10 min (initial denaturation), followed by 30 cycles at 94°C for 30 sec (denaturation), 65°C for 30 sec (annealing) and 72°C for 30 sec (extension), and 72°C for 7 min (final extension). The 147 bp PCR products were electrophoresed on 1.8% agarose gel containing 2 µl GelRed and visualised using the ChemiDoc™ XRS+ Imaging System (Bio-Rad). The *Sac* I restriction enzyme (New England BioLabs) was used to digest the PCR products at 37°C for 16 hrs, electrophoresed on 3% agarose gel containing 2 µl

GelRed and visualised as mentioned above. Presence of the homozygous wild-type G-allele (GG genotype) resulted in no cleavage of the 147 bp PCR product. The homozygous variant C-allele (CC genotype) yielded two fragments of 122 and 25 bp. The heterozygous GC genotype yielded three bands of 147, 122 and 25 bp. A DNA ladder was used to determine the different genotypes accurately.

Statistical analysis

The post-hoc power analysis was used to calculate the overall statistical power of the present study [20,21]. All statistical analysis was performed using the IBM SPSS statistical software (version 24) and GraphPad Prism software (version 5.0) packages. The Student's unpaired *t*- test was used to compare the characteristics of PsA patients and the control groups (Table 1). The Chi-squared (χ^2) test and Fisher's exact test were used to analyse the genotype and allele frequencies, respectively (Table 2 and Table 3). The χ^2 test was also used to assess whether the genotype frequencies complied with the Hardy-Weinberg equilibrium. The Fisher's exact test data are represented as the relative risk ratio (RR) and odds ratio (OR) at 95% confidence intervals (CI). Data were expressed as mean ± standard error (Table 1). A *p* value less than 0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of all study subjects are shown in Table 1. There was a significant difference between patients and controls regarding age ($p = 0.0309$). Patients displayed moderate to severe functional impairments from the PsA (HAQ score =0.62 ± 0.07), and over 96% tested negative for the IgM-RF. The majority of the patients (95%) were on methotrexate (MTX), and a significant reduction in CRP levels from inclusion (18.95 ± 2.81 mg/L) to 6 months follow-up (9.68 ± 1.32 mg/L) was observed ($p = 0.0011$).

Table 1: Clinical and demographical characteristics of PsA patients and controls			
Variable[1]	**PsA patients (n = 117)**	**Controls (n = 100)**	***p* Value**
Age (years)	50.34 ± 1.14	46.23 ± 1.56	0.0309
Sex: Male, n (%) Female, n (%)	63 (54) 54 (46)	35 (35) 65 (65)	
Race: Indian, n (%) White, n (%) Mixed Race, n (%)[#]	84 (72) 32 (27) 1 (1)	62 (62) 38 (38) 0 (0)	
BMI (kg/m^2)	28.86 ± 0.50	27.85 ± 0.42	n.s.
Smoker: Yes, n (%) No, n (%)	25 (21) 92 (79)		
Disease duration (years)	6.43 ± 0.67		
HAQ score	0.62 ± 0.07		
IgM-RF: Positive, n (%) Negative, n (%)	5 (4) 112 (96)		
Drugs: MTX, n (%) SSZ, n (%) LFM, n (%) Biologics, n (%)[¶]	111 (95) 33 (28) 21 (18) 9 (8)		
CRP (mg/L): Inclusion @ 6 month	18.95 ± 2.81 9.68 ± 1.32		0.0011

[1] Presented as absolute numbers (percentage) and mean ± standard error. Comparisons for age, BMI and CRP levels were performed using the unpaired Student's *t*-test. $p < 0.05$ was considered as being significant.

Abbreviations: PsA: psoriatic arthritis, BMI: body mass index, HAQ: health assessment questionnaire, RF-IgM: rheumatoid factor-immunoglobulin M, MTX: methotrexate, SSZ: sulfasalazine, LFM: leflunomide, CRP: C-reactive protein.

[¶]Biologics: etanercept, adalimumab, and infliximab. [#]Mixed Race: Caucasian and Indian descent.

The genotype and allele frequency distribution for all PsA patients deviated from that in healthy controls. Stratified analysis showed that this was due to a significant deviation in Indian PsA patients compared to controls (GG, GC, CC: 36.90%, 54.76%, and 8.33% versus 59.68%, 35.48%, and 4.84%; p=0.0241). Indian PsA patients had a significantly higher frequency of the GC+CC genotypes (63.10% vs. 40.32%, p = 0.0075, OR = 2.53 95% CI 1.29–4.96) and variant C-allele (35.71% vs. 22.58%, p = 0.0200, OR = 1.91 95% CI 1.13–3.22) compared to healthy Indian controls. No association was noted in the Caucasian population.

Table 2: Genotype and allele frequencies for PsA patients and controls before and after stratification for race (Indians and Caucasians)				
Frequency, n (%)	**Controls**	**PsA patients**	***p* Value**	**OR (95% CI)**
Unstratified: Indians + Caucasians (PsA patients: n = 116 and controls: n = 100)				
Genotype, n (%)				
GG	52 (52)	43 (37.07)	0.06[a]	
GC	44 (44)	63 (54.31)		
CC	4 (4)	10 (8.62)		
GC+CC	48 (48)	73 (62.93)	0.03[b]	1.84 (1.07–3.17)
Allele, n (%)				
G	148 (74)	149 (64.22)	0.03[b]	1.59 (1.05–2.40)
C	52 (26)	83 (35.78)		
Stratified: Indians (PsA patients: n = 84 and controls: n = 62)				
Genotype, n (%)				
GG	37 (59.68)	31 (36.90)	0.02[a]	
GC	22 (35.48)	46 (54.76)		
CC	3 (4.84)	7 (8.33)		
GC+CC	25 (40.32)	53 (63.10)	<0.01[b]	2.53 (1.29–4.96)
Allele, n (%)				
G	96 (77.41)	108 (64.29)	0.02[b]	1.91 (1.13–3.22)
C	28 (22.58)	60 (35.71)		
Stratified: Caucasians (PsA patients: n = 32 and controls: n = 38)				
Genotype, n (%)				
GG	15 (39.47)	12 (37.50)	n.s.[a]	
GC	22 (57.89)	17 (53.13)		
CC	1 (2.63)	3 (9.38)		
GC+CC	23 (60.52)	20 (62.5)	n.s.[b]	1.09 (0.41–2.86)
Allele, n (%)				
G	52 (68.42)	41 (64.06)	n.s.[b]	1.22 (0.60–2.46)
C	24 (31.58)	23 (35.04)		

[a]Chi squared p value (controls genotypes vs. PsA patients genotypes). [b]Fisher's exact test p value (GG vs. GC+CC genotypes). [c]Fisher's exact test. A $p < 0.05$ was considered as being significant. CI: confidence interval; RR: relative risk; OR: odds ratio; PsA: psoriatic arthritis; χ^2: Chi-squared test.

Discussion

In this study, we evaluated the frequency of the miR-146a G/C rs2910164 in South African Indian and Caucasian patients with PsA compared to healthy control subjects. We observed a significantly higher prevalence of the variant C-allele in Indian PsA patients compared to healthy Indian controls (35.71% vs. 22.58% respectively, p = 0.0200, OR = 1.91 95% CI 1.13–3.22). Conversely, the variant C-allele frequency between Caucasian PsA patients and healthy controls were similar. These data suggest that Indian PsA patients with the heterozygous GC and homozygous variant CC genotypes (GC+CC) are more predisposed to developing PsA compared to patients with the homozygous wild-type GG genotype.

Functionally, when miR-146a is highly expressed, it inhibits both IRAK1 and TRAF6 resulting in concomitant reductions in pro-inflammatory cytokines (IL-2, IL-6, IL-8, IFN-γ and TNF-α) expression and CRP levels [14]. The rs2910164 C-allele dampens the overall functionality of miR-146a, leading to an upregulation in IRAK1 and TRAF6 expression, resulting in high cytokine production [13].

Previously Zhang *et al*. [17] reported that Chinese individuals homozygous for the variant CC genotype had a significantly lower risk of developing psoriasis and PsA. Chatzikyriakidou *et al*. (2010) observed an increased frequency of the GC genotype in 29 Greek PsA patients compared to 66 healthy controls (41.4% versus 27.3%). However, this difference was not significant (p = 0.394) [18]. In our Indian population, the frequency of the GC+CC genotypes and variant C-allele were significantly higher in 84 PsA patients versus 62 healthy controls, with no significant changes in genotype distribution between patients and controls. However, no association between rs2910164 and PsA were noted in the much smaller Caucasian population (Table 2).

Conclusion

This study associated the rs2910164 with increased PsA susceptibility in the South African Indian population, but not in the small Caucasian cohort. The influence of rs2910164 on miR-

146a expression and its role in the pathogenesis of PsA necessitates investigation in a bigger cohort.

List of abbreviations:

BMI: Body mass index; CI: Confidence interval; CRP: C reactive protein; C: Cytosine; DF: Degrees of freedom; G: Guanine; HAQ: Health assessment questionnaire; HWE: Hardy-Weinberg equilibrium; IL: Interleukin; IRAK1: Interleukin receptor associated kinase 1; LFM: Leflunomide; MetS: Metabolic syndrome; MicroRNA: MiR; MTX: Methotrexate; OR: Odds ratio; PsA: Psoriatic arthritis; IgM-RF: immunoglobulin M Rheumatoid factor; RR: Risk ratio; SNP: Single nucleotide polymorphism; SSZ: Sulfasalazine; TNF-α: Tumour necrosis factor alpha; TRAF6: Tumour necrosis factor-α receptor associated factor 6; UTR: Untranslated region; χ^2: Chi-squared.

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References:

1. Zeng J, Luo S, Huang Y, Lu Q: Critical role of environmental factors in the pathogenesis of psoriasis. The Journal of Dermatology 2017.
2. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB: Risk of myocardial infarction in patients with psoriasis. JAMA 2006, 296(14):1735-1741.
3. Coates LC, FitzGerald O, Helliwell PS, Paul C: Psoriasis, psoriatic arthritis, and rheumatoid arthritis: Is all inflammation the same? Seminars in Arthritis and Rheumatism 2016, 46(3):291-304.

4. Gelfand JM, Gladman DD, Mease PJ, Smith N, Margolis DJ, Nijsten T, Stern RS, Feldman SR, Rolstad T: Epidemiology of psoriatic arthritis in the population of the United States. Journal of the American Academy of Dermatology 2005, 53(4):573. e571-573. e513.
5. Alamanos Y, Voulgari PV, Drosos AA: Incidence and prevalence of psoriatic arthritis: a systematic review. The Journal of rheumatology 2008, 35(7):1354-1358.
6. Taylor WJ: Epidemiology of psoriatic arthritis. Current opinion in rheumatology 2002, 14(2):98-103.
7. Cannell Ian G, Kong Yi W, Bushell M: How do microRNAs regulate gene expression? Biochemical Society Transactions 2008, 36(6):1224-1231.
8. Bartel DP: MicroRNAs. Cell 2004, 116(2):281-297.
9. Liu X, Han Z, Yang C: Associations of microRNA single nucleotide polymorphisms and disease risk and pathophysiology. Clinical Genetics 2016:n/a-n/a.
10. Omrane I, Kourda N, Stambouli N, Privat M, Medimegh I, Arfaoui A, Uhrhammer N, Bougatef K, Baroudi O, Bouzaienne H, et al.: MicroRNAs 146a and 147b Biomarkers for Colorectal Tumor's Localization. BioMed Research International 2014, 2014:584852.
11. Saba R, Sorensen DL, Booth SA: MicroRNA-146a: A Dominant, Negative Regulator of the Innate Immune Response. Frontiers in Immunology 2014, 5(578).
12. De Felice B, Manfellotto F, Palumbo A, Troisi J, Zullo F, Di Carlo C, Sardo ADS, De Stefano N, Ferbo U, Guida M: Genome–wide microRNA expression profiling in placentas from pregnant women exposed to BPA. BMC medical genomics 2015, 8(1):56.
13. Shao Y, Li J, Cai Y, Xie Y, Ma G, Li Y, Chen Y, Liu G, Zhao B, Cui L: The functional polymorphisms of miR-146a are associated with susceptibility to severe sepsis in the Chinese population. Mediators of inflammation 2014, 2014.
14. Ramkaran P, Khan S, Phulukdaree A, Moodley D, Chuturgoon AA: miR-146a polymorphism influences levels of miR-146a, IRAK-1, and TRAF-6 in young patients with coronary artery disease. Cell biochemistry and biophysics 2014, 68(2):259-266.
15. Alipoor B, Meshkani R, Ghaedi H, Sharifi Z, Panahi G, Golmohammadi T: Association of miR-146a rs2910164 and miR-149 rs2292832 Variants with Susceptibility to Type 2 Diabetes. Clin Lab 2016, 62:1553-1561.

16. Jazdzewski K, Murray EL, Franssila K, Jarzab B, Schoenberg DR, de la Chapelle A: Common SNP in pre-miR-146a decreases mature miR expression and predisposes to papillary thyroid carcinoma. Proceedings of the National Academy of Sciences 2008, 105(20):7269-7274.
17. Zhang W, Yi X, Guo S, Shi Q, Wei C, Li X, Gao L, Wang G, Gao T, Wang L: A single-nucleotide polymorphism of miR-146a and psoriasis: an association and functional study. Journal of cellular and molecular medicine 2014, 18(11):2225-2234.
18. Chatzikyriakidou A, Voulgari P, Georgiou I, Drosos A: The role of microRNA-146a (miR-146a) and its target IL-1R-associated kinase (IRAK1) in psoriatic arthritis susceptibility. Scandinavian journal of immunology 2010, 71(5):382-385.
19. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H: Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis & Rheumatology 2006, 54(8):2665-2673.
20. Post-hoc Power Calculator: Evaluate statistical power of an existing study [http://clincalc.com/stats/power.aspx]
21. Levine M, Ensom MH: Post hoc power analysis: an idea whose time has passed? Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2001, 21(4):405-409.

Chapter 8:

The Arg72 variant of the p53 functional polymorphism (rs1042522) is associated with psoriatic arthritis in South African Indian individuals

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Abstract:

Background: Psoriasis is characterized by abnormal hyperproliferation of keratinocytes and can trigger the onset of psoriatic arthritis (PsA). Both active psoriasis and rheumatoid arthritis have both been linked with altered expression of the tumour suppressor protein p53 (p53), potentially enhancing the inflammatory process. Although a key role for p53 in inflammation is supported by integrative studies, association studies in Caucasians did not confirm this.

Objectives: To investigate whether the functional Pro72Arg variant of p53 is associated with psoriatic arthritis (PsA) in South African Indians and South African Caucasians

Methods: DNA from 84 South African Indian PsA patients and 62 controls, and from 32 caucasian PsA patients and 38 healthy controls was genotyped for the p53 Pro72Arg SNP using PCR-RFLP.

Results: The overall distribution between patients and controls did not differ significantly in the Indian and Caucasian populations. However, a significantly higher frequency of the p53 Arg72 allele was found in PsA Indian patients compared to healthy controls (42% versus 29% respectively, p = 0.03, Odds ratio 1.75). In caucasians, the frequency of the Arg allele was not increased (p=1.0).

Conclusion: Our data indicate that the p53 72Arg allele might be associated with psoriatic arthritis in the Indian population. Given the complexity of the p53 region and of p53 expression and function more detailed fine typing of the p53 region in larger patient cohorts from different ethnic backgrounds will be needed to validate and unravel this association in more detail.

Keywords: p53, Pro72Arg, Single nucleotide polymorphism, Psoriasis, Psoriatic arthritis

Introduction

Psoriasis is an autoimmune skin disorder affecting 2-3% of humans globally and initiated by several environmental and genetic factors risk factors [1]. Aberrantly elevated T lymphocyte (T-cell) activity and T-helper cell type 1 (TH1) cytokine production, and abnormal keratinocyte differentiation and epidermal hyperproliferation are considered hallmarks of this disease [2]. Approximately 30% (6-42%) of patients with psoriasis develop psoriatic arthritis (PsA) [3-5]

The tumour suppressor protein, p53 is a transcription factor involved in regulating the expression of genes that play a critical role in several cell signalling pathways [6]. p53 is encoded by the 19 kb TP53 gene located on the short arm of human chromosome 17p13.1 [6]. The activation of p53 is driven by a variety of stress signals such as DNA damage, excessive oncogene activation, hypoxia and oxidative stress [6, 7]. Once activated, p53 mediates a plethora of functions including inhibition of cell proliferation, cell cycle arrest, DNA repair, senescence and apoptosis [6, 7]. p53 also plays a significant role in metabolic pathways by regulating glycolysis [8, 9], insulin sensitivity [10], fatty acid oxidation [11] and autophagy [12]. Elevated p53 expression is also associated with the pathogenesis of inflammatory psoriasis [13, 14] and PsA [15, 16].

Single nucleotide polymorphisms (SNPs) in the p53 gene are known to alter the structure and function of p53 [17]. The proline-72-arginine (Pro72Arg) p53 SNP (rs1042522), a variant at codon 72, occurs in the proline-rich domain of p53. It arises when a guanine residue at the 72^{nd} position of the TP53 gene is converted to cytosine, resulting in the substitution of a proline (Pro) residue with an arginine (Arg) residue [16, 18]. This SNP is involved in the pro-apoptotic functions of p53 and has been implicated in several diseases including cardiovascular disease [19], rheumatoid arthritis [20], diabetes [21] and cancer [22]. Interestingly, a recent study integrating RNA-sequencing-based expression analysis and pathway analysis pointed to a key role for p53 in inflammation in rheumatoid arthritis; however, this was not supported by genome wide association studies largely performed in Caucasians [23]. Following this lead, we decided to complement on the studies done by Butt et al. [24] which were done in Caucasians, and study the association of the

Pro72Arg p53 SNP in South African Indian PsA patients and controls.

Materials and Methods

Patient recruitment and sample collection:

South African Indian and Caucasian PsA patients (n = 116) and healthy controls (n = 100) were enrolled in this study following ethical approval from the Pharma-Ethics Research Ethics Committee (ref. no. 13095660). The inclusion criteria for this study, irrespective of age and gender, were: (a) patients must be over the age of 18 years and have PsA; (b) patients must have a confirmed diagnosis of PsA and must have fulfilled the CASPAR criteria [25] (patients with all other forms of inflammatory arthritis were excluded from this study); (c) Patients with all other forms of connective tissue disorders were excluded from this study. Whole blood samples were obtained from each patient, after informed consent, and full pathology reports were generated from Lancet Laboratories (Durban, South Africa), a fully accredited South African National Laboratory.

DNA extraction:

Genomic DNA was extracted from whole blood taken from psoriasis patients and controls using the FlexiGene® DNA isolation kit (Qiagen). Briefly, 750 µl cell lysis buffer was added to 300 µl whole blood and centrifuged (10, 000xg, 20s). The supernatants were removed, and 150µl denaturation buffer consisting of chaotropic salt and protease enzyme was added to the pellet and incubated (65°C, 5 min). Thereafter, 150µl 100% isopropanol was added to precipitate the DNA which was recovered by centrifugation (10, 000xg, 3 min). The DNA was washed in 150µl 70% ethanol, dried at room temperature and resuspended in 15µl hydration buffer (10 mM Tris-Cl, pH 8.5). The samples were then incubated for 1 hr at 65°C and stored at -20°C until further use. The purity and concentration of the DNA were determined using the Nano-drop 2000 spectrophotometer. The DNA was standardised to a concentration of 10ng/µl.

Genotyping:

The p53 Pro72Arg rs1042522 SNP was genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The GoTaq® G2 Flexi DNA Polymerase PCR kit (Promega) and the CFX96 TouchTM Real-Time PCR Detection System (Bio-Rad) was used for this analysis. The 131 bp PCR product was amplified using 1× Green GoTaq Flexi buffer, 2.5 mM MgCl2, 200 µM of each dNTP, 0.2 Units GoTaq Flexi DNA polymerase, 20 pmol of each primer and 30 ng genomic DNA template. The positive DNA samples were run with a no-template DNA sample as a quality control measure against PCR contamination. Primer sequences used were: 5′-TTGCCGTCCCAAGCAATGGATGA-3′ (forward) and 5′-TCTGGGAAGGGACAGAAGATGAC–3′ (reverse). The PCR was performed using the following cycling conditions: 96°C for 12 min (initial denaturation), followed by 35 cycles at 94°C for 30 sec (denaturation), 55°C for 30 sec (annealing) and 72°C for 30 sec (extension), and 72°C for 5 min (final extension). The PCR products were then electrophoresed on 1.8% agarose gel containing 2 µl GelRed and visualised using the ChemiDocTM XRS+ Imaging System (Bio-Rad). The Bsh1236I restriction enzyme (New England BioLabs) was used to digest the PCR products at 65°C for 16 hrs. Thereafter, the restriction products were electrophoresed on 3% agarose gel containing 2 µl GelRed and visualised as mentioned above. The presence of the homozygous wild-type Pro-allele (Pro/Pro genotype) resulted in no cleavage of the 131 bp PCR product. The homozygous variant Arg-allele (Arg/Arg genotype) yielded two fragments of 81 and 50 bp. The heterozygous Pro/Arg genotype yielded three bands of 131, 81 and 50 bp. A DNA ladder was used to determine the different genotypes accurately.

Statistical analysis:

The Hardy–Weinberg equilibrium was used to test for deviation of allele/genotype frequency. All other statistical analysis was performed using the IBM SPSS statistical software (version 24) and GraphPad Prism software (version 5.0) packages. Genotype and allele frequencies were calculated using the Chi squared and Fisher's exact tests, respectively. The Kolmogorov-Smirnov and Shapiro-Wilk tests for normality followed by the one-way analysis of variance (ANOVA) test and Tukey's honest significant difference (HSD) multiple range post hoc test, and the unpaired t-test was used to analyse all data. Data were expressed as mean ± standard error. Statistical significance was determined at a *p* value less than 0.05.

Results

Demographic and clinical characteristics of all study participants are shown in table 1. A significant difference between patients and controls regarding age ($p = 0.0309$) but not BMI ($p = 0.1307$) was observed. Patients displayed moderate to severe functional impairments from the PsA (HAQ score = 0.62 ± 0.07), and over 96% tested negative for the RF-IgM. Around 95% of all patients were on methotrexate (MTX).

Table 1: Demographics and clinical parameters of patients and control subjects

	PsA patients (n = 117)	Controls (n = 100)	*p* Value
Age (years)[1]	50.34 ± 1.14	46.23 ± 1.56	0.0309*
Sex: Male, n (%)	63 (54)	35 (35)	
Female, n (%)	54 (46)	65 (65)	
Race: Indian, n (%)	84 (72)	62 (62)	
White, n (%)	32 (27)	38 (38)	
Coloured, n (%)	1 (1)	0 (0)	

[1]mean ± standard error. PsA: psoriatic arthritis

The genotype and allele frequencies of the p53 Pro72Arg SNP are shown in table 2 for patients and controls, separate for the 2 patient groups. The genotype distribution complied with the Hardy–Weinberg equilibrium in controls in both ethnic populations. There were no statistically significant differences in the total Indian patients versus controls (p = 0.08). In Indians patients with PsA showed a significantly higher frequency of the Arginine allele (p=0.03; OR=1.75). No significant deviations were observed in Caucasian patients versus Caucasian controls (p = 0.48).

Table 2: p53 Pro71Arg Genotype and allele frequencies in PsA patients and controls

Indians				Caucasians		
Frequency n (%)	PsA (n = 84)	Controls (n = 62)	*p* Value	PsA (n = 32)	Controls (n = 38)	*p* Value
Genotypes						
Pro/Pro	31 (37%)	31 (50%)	0.08	9 (28%)	17 (45%)	0.23 n.s.
Pro/Arg	36 (43%)	26 (42%)		20 (63%)	16 (42%)	

Arg/Arg	17 (20%)	5 (8%)		3 (9%)	5 (13%)	
Allele frequencies						
Pro	98 (58%)	88 (71%)	0.03	38 (59%)	50 (66%)	0.48
Arg	70 (42%)	36 (29%)		26 (41%)	26 (34%)	

PsA: psoriatic arthritis, RR: relative risk, CI: confidence interval, OR: odds ratio, DF: degrees of freedom, HWE: Hardy–Weinberg equilibrium; Pro: proline, Arg: arginine. *A $p < 0.05$ was considered as being significant.

Discussion

This study of the p53 Pro72Arg SNP in South African individuals shows that the 72Arg variant is associated with PsA in Indian patients, but not in the Caucasian population. The negative finding in the Caucasian population was not unexpected given the results done by Butt et al. [24] in large Caucasians cohorts. The discrepancy of the findings between different populations may suggest that the Pro72Arg SNP may not be involved itself, but may be increased in Indians due to linkage disequilibrium (LD) with “causative” polymorphisms nearby. These LDs and relevant allele frequencies are known to differ between populations. For instance, Beckman *et al.* (1994) found a strong correlation between the p53 Pro72Arg SNP and ethnicity, the frequency of the variant Arg allele more predominant in populations living farther away from the equator [26, 27]. If in Caucasians, the same LD does not exist a negative finding for association might be explained. Interestingly, a similar ethnic discrepancy was observed for the association of Pr72Arg with SLE in the Asian versus the Caucasian populations [20]. Further support for such a view comes from a recent study, integrating the results from RNA-sequencing-based expression analysis and pathway analysis in Caucasians [28], where the results point to p53 being a key molecule in the inflammatory process in RA, but yet the Caucasian populations studied do not show an

association of p53 polymorphisms with RA.

Overexpression of p53 has been described in psoriasis [13, 14] and PsA [15, 16] patients. P53 controls several physiological processes involved in DNA repair, cell cycle arrest and apoptosis [6, 7]. While its expression is beneficial in targeting abnormal cells for apoptosis, overexpression of p53 is considered to be detrimental regarding the growth and survival of healthy cells. However, the link between genotype and function is complicated by the fact that p53 may undergo alternative splicing of mRNA transcripts, uses alternative promotors and has alternative translation initiation sites, which also may depend upon cell type [29, 30]. Dumont *et al*. (2003) reported that the variant Arg72 allele of p53 is more efficient in inducing apoptosis [31]. Seemingly contradictory Siddique and Sabapathy (2006) reported that the Pro72 allele was most efficient in activating DNA repair [32], while it has also been reported to be a stronger inducer of G1 cell cycle arrest [32,33]. Clearly to study the exact role of these polymorphisms more in depth studies are needed to separate the effects of different isoforms of p53 in these complex molecular systems.

In conclusion, we confirm the absence of association of the P53Arg allele with PsA in Caucasians in South Africa. However, we do show an association of the P53Arg allele with PsA in the Indian population. Clearly, this should be confirmed in other Indian populations. Given the evidence that supports a key role for p53 in different rheumatic diseases, we propose that more detailed genetic studies in different ethnic groups may help us to identify causative polymorphisms and mechanisms in the chromosomal area hosting the *tp53* gene.

References:

1. Ghosh N, Singh PN, Kumar V: Novel immunobiologics for psoriasis. Indian Journal of Pharmacology 2008, 40(3):95-102.
2. Das RP, Jain AK, Ramesh V: CURRENT CONCEPTS IN THE PATHOGENESIS OF PSORIASIS. Indian Journal of Dermatology 2009, 54(1):7-12.
3. Gelfand JM, Gladman DD, Mease PJ, Smith N, Margolis DJ, Nijsten T, Stern RS, Feldman SR, Rolstad T: Epidemiology of psoriatic arthritis in the population of the United States. Journal of the American Academy of Dermatology 2005, 53(4):573. e571-573. e513.
4. Alamanos Y, Voulgari PV, Drosos AA: Incidence and prevalence of psoriatic arthritis: a systematic review. The Journal of rheumatology 2008, 35(7):1354-1358.
5. Taylor WJ: Epidemiology of psoriatic arthritis. Current opinion in rheumatology 2002, 14(2):98-103.

6. Vousden KH, Prives C: Blinded by the light: the growing complexity of p53. Cell 2009, 137(3):413-431.
7. Barlev NA, Liu L, Chehab NH, Mansfield K, Harris KG, Halazonetis TD, Berger SL: Acetylation of p53 activates transcription through recruitment of coactivators/histone acetyltransferases. Molecular cell 2001, 8(6):1243-1254.
8. Kawauchi K, Araki K, Tobiume K, Tanaka N: p53 regulates glucose metabolism through an IKK-NF-κB pathway and inhibits cell transformation. Nature cell biology 2008, 10(5):611-618.
9. Schwartzenberg-Bar-Yoseph F, Armoni M, Karnieli E: The tumor suppressor p53 down-regulates glucose transporters GLUT1 and GLUT4 gene expression. Cancer research 2004, 64(7):2627-2633.
10. Webster NJ, Resnik JL, Reichart DB, Strauss B, Haas M, Seely BL: Repression of the insulin receptor promoter by the tumor suppressor gene product p53: a possible mechanism for receptor overexpression in breast cancer. Cancer research 1996, 56(12):2781-2788.
11. Assaily W, Rubinger DA, Wheaton K, Lin Y, Ma W, Xuan W, Brown-Endres L, Tsuchihara K, Mak TW, Benchimol S: ROS-mediated p53 induction of Lpin1 regulates fatty acid oxidation in response to nutritional stress. Molecular cell 2011, 44(3):491-501.
12. Levine B, Abrams J: p53: The Janus of autophagy? Nature cell biology 2008, 10(6):637- 639.
13. Moorchung N, Vasudevan B, Kumar SD, Muralidhar A: Expression of apoptosis regulating proteins p53 and bcl-2 in psoriasis. Indian Journal of Pathology and Microbiology 2015, 58(4):423.
14. Baran W, Szepietowski JC, Szybejko-Machaj G: Expression of p53 protein in psoriasis. ACTA DERMATOVENEROLOGICA ALPINA PANONICA ET ADRIATICA 2005, 14(3):79.
15. Salvador G, Sanmarti R, Garcia-Peiro A, Rodriguez-Cros J, Munoz-Gomez J, Canete J: p53 expression in rheumatoid and psoriatic arthritis synovial tissue and association with joint damage. Annals of the rheumatic diseases 2005, 64(2):183-187.
16. Assmann G, Wagner AD, Monika M, Pfoehler C, Pfreundschuh M, Tilgen W, Roemer K: Single-nucleotide polymorphisms p53G72C and Mdm2T309G in patients with psoriasis, psoriatic arthritis, and SAPHO syndrome. Rheumatology international 2010, 30(10):1273-1276.
17. Sakamuro D, Sabbatini P, White E, Prendergast GC: The polyproline region of p53 is required to activate apoptosis but not growth arrest. Oncogene 1997, 15(8).
18. Grochola LF, Zeron-Medina J, Mériaux S, Bond GL: Single-nucleotide polymorphisms in the p53 signalling pathway. Cold Spring Harbor perspectives in biology 2010, 2(5):a001032.
19. Khan S, Phulukdaree A, Ramkaran P, Moodley D, Chuturgoon AA: The Arg72 variant of the p53 functional polymorphism (rs1042522) is associated with coronary artery disease in young South Africans of Indian ancestry. Gene 2016, 593(2):261-264.
20. Lee Y, Bae S, Choi S, Ji J, Song G: Associations between the p53 codon 72 polymorphisms and susceptibility to systemic lupus erythematosus and rheumatoid arthritis: a meta-analysis. Lupus 2012, 21(4):430-437.

21. Bonfigli AR, Sirolla C, Testa R, Cucchi M, Spazzafumo L, Salvioli S, Ceriello A, Olivieri F, Festa R, Procopio AD: The p53 codon 72 (Arg72Pro) polymorphism is associated with the degree of insulin resistance in type 2 diabetic subjects: a cross-sectional study. Acta diabetologica 2013, 50(3):429-436.
22. Proestling K, Hebar A, Pruckner N, Marton E, Vinatzer U, Schreiber M: The Pro allele of the p53 codon 72 polymorphism is associated with decreased intratumoral expression of BAX and p21, and increased breast cancer risk. PLoS One 2012, 7(10):e47325.
23. Shchetynsky K, Diaz-Gallo L-M, Folkersen L, et al. Discovery of new candidate genes for rheumatoid arthritis through integration of genetic association data with expression pathway analysis. Arthritis Research & Therapy. 2017;19:19. doi:10.1186/s13075- . 017-1220-5
24. Butt C, Peddle L, Greenwood C, Hamilton S, Gladman D, Rahman P: Association of functional variants of PTPN22 and tp53 in psoriatic arthritis: a case-control study. Arthritis research & therapy 2006, 8(1):R27.
25. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H: Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis & Rheumatology 2006, 54(8):2665-2673.
26. Siddique MM, Balram C, Fiszer-Maliszewska L, Aggarwal A, Tan A, Tan P, Soo KC, Sabapathy K: Evidence for selective expression of the p53 codon 72 polymorphs: implications in cancer development. Cancer Epidemiology and Prevention Biomarkers 2005, 14(9):2245-2252.
27. Beckman G, Birgander R, Själander A, Saha N, Holmberg P, Kivelä A, Beckman L: Is p53 polymorphism maintained by natural selection? Human heredity 1994, 44(5):266-270.
28. Shchetynsky K, Diaz-Gallo LM, Folkersen L, et al. Discovery of new candidate genes for rheumatoid arthritis through integration of genetic association data with expression pathway analysis. Arthritis Res Ther. 2017 Feb 2;19(1):19. doi: 10.1186/s13075-017- 1220-5
29. Yin Y, Stephen CW, Luciani MG, Fåhraeus R. p53 Stability and activity is regulated by Mdm2-mediated induction of alternative p53 translation products. Nat Cell Biol. 2002 Jun;4(6):462-7.
30. Marcel V, Perrier S, Aoubala M, et al. Δ160p53 is a novel N-terminal p53 isoform encoded by Δ133p53 transcript. FEBS Lett. 2010 Nov 5;584(21):4463-8. doi: 10.1016/j.febslet.2010.10.005. Epub 2010 Oct 13
31. Dumont P, Leu JI-J, Della Pietra AC, George DL, Murphy M: The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. Nature genetics 2003, 33(3):357.
32. Siddique M, Sabapathy K: Trp53-dependent DNA-repair is affected by the codon 72 polymorphism. Oncogene 2006, 25(25):3489.
33. Pim D, Banks L: p53 polymorphic variants at codon 72 exert different effects on cell cycle progression. International journal of cancer 2004, 108(2):196-199.

Chapter: 9

Summary and Discussion

Psoriatic arthritis is a chronic inflammatory immune-mediated inflammatory disease associated with a skin condition called psoriasis. It belongs to the family of spondyloarthritides. It is associated with increased morbidity and mortality and a large variety of extra-articular manifestations. Morbidity not only arises from the articular manifestations, but a significant number of patients with psoriatic arthritis also have psychological problems, in part resulting from cosmetic consequences of the disease. The clinical course of psoriatic arthritis has for a number of years been considered to be milder than that of rheumatoid arthritis, however, of late it has been shown that the effects of psoriatic arthritis can be as devastating, if not more, compared to rheumatoid arthritis.

Although current therapies are widely available in the developed world, aggressive management in developing countries is largely lacking. Treat to target paradigms have only recently come into vogue. Current therapies retard disease progression and improve symptoms but damage cannot always be prevented, and disease progression may continue without a definitive cure for the disease. Relapses are common, and many patients have an inadequate response to currently available therapies. Thus, there is a significant unmet need in the management of psoriatic arthritis.

Our understanding of the disease is improving with greater insight and newer developments in terms of the pathogenesis of psoriatic arthritis in particular, and of spondyloarthritis in general. Novel insights into the role of the IL 23 / TH 17 axis has led to new and effective therapies. The development of standardized newer criteria made the diagnosis easier and results in earlier institution of aggressive treatment. Unfortunately, biomarkers for this disease are as yet not available.

Another unfortunate occurrence is a dearth of published literature on psoriatic arthritis from the African continent. A minefield of data can be found on this continent waiting to be tapped. In South Africa, we have a unique situation in which we have three population groups viz. Caucasians, people of Indian descent, and the African black population. The prevalence of psoriatic arthritis in the former two categories equals that published in literature from the Western countries. However, very little is known about why the African black population does not develop psoriatic arthritis and spondyloarthritis until they become HIV infected and become immune-compromised. Better understanding whether this population group has a lack of a predisposing gene or the presence of a protective gene and the epigenetic effects of HIV on spondyloarthritis will improve our understanding of psoriatic arthritis in general and in this population group in particular.

Epidemiological studies in psoriatic arthritis from the African continent are largely lacking. Hopefully, our current data will provide an impetus for more epidemiological studies to be undertaken and published with greater focus on the burden of this disease in Africa. Validation of the Caspar criteria in our population is a step in the right direction.

In **chapter 1** we provide a general introduction into the pathogenesis of psoriatic arthritis with regards to the immunobiology of the disease. The importance of the various pro-inflammatory cytokines, IL-23/ TH 17 axis as well as the genetic factors that modulate the disease process is discussed. We also give an overview of clinical presentation and the CASPAR criteria.

Chapter 2 discusses the different assessments done in psoriasis and psoriatic arthritis. The assessment measures the severity of the illness and dictates the need to parallel the severity of the disease with the aggressiveness of therapy. Conventional DMARDs and newer modalities of treatment with treat to target strategies are discussed in **chapter 3**. Approaches and recommendations by EULAR and GRAPPA are covered in this section. This gives a brief overview of all the therapies available at the current time, as well as emerging therapies and a look into the future of the management of psoriatic arthritis. Also discussed in this chapter is the emergence of biosimilars which are bound to take part of the market in the near future. This chapter outlines current recommendations and discusses therapies with newer modes of action.

Chapter 4 gives a brief overview of the clinical features, biochemical parameters and radiological features in our cohort. This is the first time a study of this nature has been published from South Africa. It is important because it gives us the basis for future studies and an essential foundation on which to build on. The findings of the clinical, biochemical and radiological features in the SASCEPA cohort is similar to that in the published literature.

In **chapter 5**, we validated the CASPAR criteria in a South African population. This was the first time that this was undertaken in a South African population with mixed ethnicities. The Caspar criteria performed well in our cohort and the data compared to that in the published literature.

The most striking feature is a complete absence of African Black patients in our cohort. This rarity is discussed in **chapter 6**. It was noted that the prevalence of rheumatoid arthritis and other inflammatory arthritides in the African population was equal to that of published literature. The rarity of spondyloarthritis in African black people cannot be solely attributed to the low prevalence of HLA-B27 in this community group. It is a well-known fact that the prevalence of HLA-B27 in the African black population is low, however, in West Africa, the prevalence of HLA-B27 approaches that of Western populations but the prevalence of spondyloarthritis is similar to that of the rest of Africa. The disconnect between HLA-B27 positivity and the prevalence of spondyloarthritis in African black populations in Western Africa has not been elucidated. A recently published article in the Annals of Rheumatic Diseases by Soumya Raychaudhuri and his co-workers identified a rare coding allele in IFIH1 to be protective for PsA. This needs to be further explored in the African population as it will provide valuable information regarding the rarity

of spondyloarthritis in this population group.

In **chapters 7, and 8** we studied the polymorphisms in miR146a and P53 in our population groups and found fascinating data, stressing how important it is to perform these genetic studies in different ethnic groups to try and isolate susceptibility and protective genes. In chapter 7, we studied the association of miR-146a rs2910164 with psoriatic arthritis in South African Indian and Caucasian population and concluded that the rs2910164 variant C-allele may play a role in the progression of PsA in the South African Indian population. The Arg72 variant of the p53 functional polymorphism (rs1042522) was investigated in chapter 8, and our findings show that it is associated with psoriatic arthritis in South African Indian individuals.

This is the first time that a study of psoriatic arthritis of this nature has been undertaken in a South African population. We anticipate that this will provide an impetus for future studies to be conducted in this field and drive the research agenda forward. There is a huge vacuum with regards to data from the African continent in the area of psoriatic arthritis.

Chapter 10

Samenvatting

Artritis psoriatica is een immuungemedieerde inflammatoire ziektedie geassocieerd is met de huidziekte psoriasis. De ziekte behoort tot de familie van de spondylartritiden. De ziekte is geassocieerd met een verhoogde morbiditeit en mortaliteit en een grote verscheidenheid aan extra-articulaire manifestaties. Morbiditeit van deze ziekte is niet alleen te wijten aan ontsteking en aantasting van de gewrichten maar ook aan psychologische effecten door de cutane manifestaties. Er werd jarenlang gedacht dat het beloop van artritis psoriatica milder was dan dat van reumatoïde artritis. Recentelijk werd echter duidelijk dat artritis psoriatica een ernstig beloop kan hebben dat vergelijkbaar is met reumatoïde artritis en soms zelfs ernstiger. De meest effectieve therapieën zijn beschikbaar in de westerse wereld, maar deze agressieve behandelstrategieën zijn grotendeels niet beschikbaar in de ontwikkelingslanden. Het treat-to-target paradigma is pas recentelijk doorgedrongen in de ontwikkelingslanden. De huidige behandelingen vertragen progressie van ziekte en bestrijden symptomen, maar schade is soms onontkoombaar. De ziekte schrijdt voort zolang er geen genezing beschikbaar is. Opvlammingen van ziekteactiviteit komen veel voor en vele patiënten hebben een inadequate reactie op de beschikbare therapieën. Er is derhalve een belangrijke onvervulde behoefte aan betere therapieën voor deze ziekte.
Hiertoe is het belangrijk dat we beter inzicht krijgen in de pathogenese van artritis psoriatica en in bredere zin van de spondyloartritiden.

Het begrip van de rol van de IL23/Th17 heeft geleid tot nieuwe therapieën. De ontwikkeling van gestandaardiseerde nieuwe criteria maakt de diagnose eenvoudiger en maakt het mogelijk om eerder met agressieve therapieën te beginnen. Helaas zijn betrouwbare biomarkers voor artritis psoriatica nog niet beschikbaar. Een ander probleem is het gebrek aan data over artritis psoriatica van het Afrikaanse continent. Een grote hoeveelheid data is beschikbaar, maar deze data worden tot nu toe onvoldoende geanalyseerd en gebruikt. In Zuid-Afrika bestaat de unieke situatie dat er drie verschillende etnische populaties zijn (de Kaukasische populatie, de populatie van Indiase afkomst en de oorspronkelijke Afrikaanse populatie). De prevalentie van artritis psoriatica in de eerste twee populaties is gelijk aan die in de beschikbare literatuur uit de Westerse landen.

Het blijft echter onduidelijk waarom artritis psoriatica niet de oorspronkelijke Afrikaanse populatie treft, behalve als zij HIV-besmet raken en immunogecompromiteerd zijn. Als we te weten komen of deze populatie beschermt is door genen of dat de ziekte ontstaat door een epigenetisch effect ten gevolge van de HIV infectie dan zouden we artritis psoriatica in het algemeen, en in deze populatie in het bijzonder, beter begrijpen.

Epidemiologische studies gericht op artritis psoriatica op het Afrikaanse continent ontbreken grotendeels. Wij hopen dat onze huidige data een impuls geven voor het uitvoeren van meer epidemiologische studies waardoor de last van deze ziekte meer

aandacht krijgt in Afrika. Validatie van de CASPAR criteria in onze populatie is in ieder geval een stap in de goede richting.

In **hoofdstuk 1** bespreken we algemene klinische aspecten en de pathogenese van artritis psoriatica. Hierbij ligt de nadruk op de immunobiologie van de ziekte. Het belang van de verschillende pro-inflammatoire cytokines, de IL23/Th17 as en de genetische factoren die de ziekte moduleren worden besproken. Verder besteden we aandacht aan de klinische manifestaties en de CASPAR criteria.

Hoofdstuk 2 bespreekt verschillende manieren om ziekteacitiviteit vast te stellen bij psoriasis en artritis psoriatica. Het beoordelingsinstrument helpt om de ernst van de ziekte systematisch vast te stellen en de therapie daarop af te stemmen. Conventionele DMARDs, nieuwere therapieën en treat-to-target strategieën worden beschreven in **hoofdstuk 3**.
Richtlijnen van EULAR en GRAPPA worden ook behandeld in dit hoofdstuk. Dit geeft een kort overzicht van alle beschikbare behandelingen op dit moment en biedt een blik op de toekomstige behandelingen van artritis psoriatica. Dit hoofdstuk behandelt ook de opkomst van biosimilars waarvan verwacht wordt dat zij een impact zullen hebben op de behandeling van de ziekte.

Hoofdstuk 4 geeft een kort overzicht van de klinische kenmerken, biochemische parameters en radiologische kenmerken van ons cohort. Dit is de eerste studie uit Zuid-Afrika die over dit onderwerp gepubliceerd is. De studie is belangrijk omdat hiermee de basis wordt gelegd voor toekomstige studies en we hierop verder kunnen bouwen. De klinische, biochemische en radiologische kenmerken van het SASCEPA cohort zijn vergelijkhaar met reeds gepubliceerde studies. In **hoofdstuk 5** valideerden we de CASPAR- criteria in een Zuid-Afrikaanse populatie. Dit was de eerste keer dat dit werd ondernomen in een Zuid-Afrikaanse populatie met gemengde etniciteiten. De CASPAR-criteria voldeden goed in ons cohort vergeleken met de gegevens die in de literatuur zijn gepubliceerd. Het meest opvallende is de afwezigheid van de oorspronkelijke Afrikaanse bevolking in ons cohort artritis psoriatica patiënten. Deze bevinding wordt verder uitgewerkt in **hoofdstuk 6.**. We vonden dat de prevalentie van reumatoïde artritis en andere inflammatoire artritiden in de oorspronkeljke Afrikaanse bevolking vergelijkbaar is met gepubliceerde gegevens in andere populaties. Het feit dat artritis psoriatica nauwelijks voorkomt in de oorspronkelijke Afrikaanse populatie kan niet volledig toegeschreven worden aan de lage prevalentie van HLA-B27 in deze populatie. Het is bekend dat de prevalentie van HLA-B27 laag is in de oorspronkelijk Afrikaanse populatie. Echter in West-Afrika is de prevalentie van HLA-B27 bijna gelijk aan die in de Westerse populatie, terwijl de prevalentie van spondyloartritis gelijk is aan die in de rest van Afrika. Het verschil tussen de prevalentie van HLA-B27 en spondyloartritis in de oorspronkelijke Afrikaanse populatie in West-Afrika is vooralsnog niet opgehelderd. Een recente publicatie in de Annals of Rheumatic Diseases door Soumya Raychaudhuri et al. beschrijft een zeldzaam

coderend allel in IFIH1 dat beschermend is voor artritis psoriatica. Of dit een rol speelt, moet verder onderzocht worden in toekomstige studies.

.

In **hoofdstukken 7, 8** onderzochten we de genetische polymorfismen in miR146a en p53 in onze populatie. De resultaten gaven inzicht in het belang van het uitvoeren van deze genetische studies in verschillende populaties om gevoeligheid en beschermende genen te isoleren. In hoofdstuk 7 bestudeerden we de associatie van miR-146a rs2910164 met psoriatische artritis in de Zuid-Afrikaanse Indiase en Kaukasische bevolking en kwamen tot de conclusie dat het rs2910164-variant C-allel een rol kan spelen in de progressie van PsA in de Zuid-Afrikaanse Indiase bevolking. De Arg72-variant van het p53-functionele polymorfisme (rs1042522) werd onderzocht in hoofdstuk 8 en onze bevindingen tonen aan dat het geassocieerd is met psoriatische artritis bij Zuid-Afrikaanse Indiërs

Dit is de eerste keer dat een studie over artritis psoriatica is uitgevoerd in een Zuid-Afrikaanse populatie. We verwachten dat dit een impuls geeft aan toekomstige studies in dit onderzoeksveld. Er is immers een vacuüm met betrekking tot data over artritis psoriatica van het Afrikaanse continent.

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2. EDUCATIONAL QUALIFICATIONS

(a)	Dundee High School Matriculation Exemption	1977
(b)	Institute of Medical Sciences Banaras Hindu University Varanasi INDIA	
	Bachelor of Medicine and Bachelor of Surger	1986
(c)	College of Medicine of South Africa	
	Higher Diploma in Internal Medicine	1998
	Awarded Gold Medal for Outstanding Performance	
(d)	Fellow of the College of Physicians of South Africa FCP (SA)	2001
(e)	Fellowship in Rheumatology of the College of Physicians Of South Africa	2003

3. PROFESSIONAL AFFILIATIONS

(a) South African Medical and Dental Council Since 1990
(b) College of Medicine of South Africa 1998
(c) South African Rheumatology and Arthritis Association - 2002
(d) GRAPPA – International Group for Research and Assessment for Psoriasis and Psoriatic Arthritis
(e) ACR/EULAR guideline committee on PMR
(f) ILAR (International League of Associations of Rheumatology) Committee on drawing up recommendations for the treatment of psoriatic arthritis in . resource- poor settings/developing countries
(g) ASAS (Assessment of Spondyloarthritis International Society) – FULL . MEMBER
(h) Member of International Psoriasis and Arthritis Research Team (IPART)

4. AWARDS

(1) Awarded United Nations Scholarship (UNESCO) To study Medicine In 1981
(2) Awarded Y K SEEDAT Gold Medal by The College of Physicians of South Africa for the best candidate in The Higher Diploma in Internal Medicine in 1998
(3) Awarded Pharmacia/Pfizer Rheumatology Travel Scholarship for South Africa for 2002
(4) Recipient of Uttar Pradesh Pravasi Bharatiya Ratna Award 2017, Government of Uttar Pradesh, India.

5. CONFERENCE PAPERS:

(1) Profile of Rheumatic Diseases in Indian and Black South Africans in Durban KwaZulu Natal, South Africa-SOUTH AFRICAN RHEUMATISM AND ARTHRITIS ASSOCIATION meeting, Johannesburg 2003
(2) Astra Zeneca Research DAY 2003 – Nelson R Mandela School of Medicine, University of Natal, DURBAN Profile of Rheumatic Diseases in Indian and Black South Africans in Durban, KwaZulu Natal, South Africa
(3) Medicine UPDATE 2004- LUPUS in the New Millennium- Treatment Update
(4) Pharmacological Heritage of Ancient India- its Influence on Modern Medicine. Seminar on Ancient India's Contribution to Medical Science and Values. RAMAKRISHNA CENTRE OF SOUTH AFRICA 06 February 2005
(5) Vinod Gathiram Memorial Lecture 2011: Treatment of Rheumatoid Arthritis- from pret-a-porter to houte courtier
(6) 1st Annual Congress of the Faculty of Consulting Physicians of South Africa- The Inflammatory Continuum - CVS Effects. ICC, Cape Town, 2012
(7) Pfizer Pain Forum 2012- Cape Town – Rheumatoid Arthritis
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(9) Management of HIV associated Arthropathy ANNUAL WORKSHOP ON ADVANCED CLINICAL CARE - AIDS, Durban; 10/2014

(10) APLAR 2015 Assessment of Peripheral arthritis in Psoriatic Arthritis. Chennai, India 09/2015
(11) Indian Rheumatology Annual Meeting, IRACON 2017, Assessment of Psoriatic Arthritis
(12) KZN Specialist Network 2017: Indications for biologic therapy: A physician's perspective. Durban, 28 October 2017.
(13) Norvatis masterclass: challenges and opportunities in the diagnosis of psoriatic arthritis. Cape Town 25 November 2017
(14) Norvatis masterclass: comorbidities in Spondyloarthritis. Cape Town 25 November 2017.
(15) IRACON 2017. Indian rheumatology Association annual conference Assessment of peripheral arthritis in patients with psoriatic arthritis. Lucknow. 30 November-3 December 2017

6. Member of International committees:

(a) GRAPPA – International Group for Research and Assessment for Psoriasis and Psoriatic Arthritis
(b) ACR/EULAR guideline committee on PMR
(c) ILAR (International League of Associations of Rheumatology) Committee on drawing up recommendations for the treatment of psoriatic arthritis in resource-poor settings/developing countries
(d) ASAS (Assessment of Spondyloarthritis International Society) – FULL MEMBER
(e) Member of International Psoriasis and Arthritis Research Team (IPART)

PUBLICATIONS:

(1) AFPL-19. Profile of rheumatic diseases among Africans and Indians at King Edward VIII Hospital in Durban A. B. Maharaj · M. Y. Akhalwaya · N. Patel · G. M. Mody Apr 2007 · Clinical Rheumatology

(2) AFPL-25. Extrapulmonary tuberculosis in rheumatic diseases in the absence of biological agents G. M. Mody · N. Patel · A. B. Maharaj Apr 2007 · Clinical Rheumatology

(3) Recognising Rheumatoid Arthritis- Update June 2012.

(4) Suboptimal management of rheumatoid arthritis in the Middle East and Africa: could the EULAR recommendations be the start of a solution? El Zorkany B, Alwahshi HA, Hammoudeh M, Al Emadi S, Benitha R, Al AwadhiA, Bouajina E, Laatar A, El Badawy S, Al Badi M, Al-Maini M, Al Saleh J,Alswailem R, Ally MM, Batha W, Djoudi H, El Garf A, El Hadidi K, El Marzouqi M,Hadidi M, Maharaj AB, Masri AF, Mofti A, Nahar I, Pettipher CA, Spargo CE,Emery P. Clinical Rheumatology 32 (2): 151 (2013)
PMID: 23274756

(5) ACR/ARHP Poster Session B: Vasculitis II (1662)
Developing Guidelines for Polymyalgia Rheumatica: Prioritisation of Outcome Measures – Perspective of Patients, General Practitioners and Rheumatologists. Yogesh Singh, MD, DM(Presenter); Christian Dejaco, MD, PhD; Sarah Mackie, MBBS; Daniel Ching; Artur Bachta; Ajesh Maharaj; et al.

(6) Comprehensive Treatment of Psoriatic Arthritis: Managing Comorbidities and Extra-articular Manifestations. A Ogdie, S Schwartzman, Laura C Coates, L Eder, Ajesh B Maharaj, D Zisman, S Raychaudhuri, Soumya Reddy, Arthur F Kavanaugh, Philip J Mease, Christopher T Ritchlin, Elaine Husni. J Rheumatol November 2014 41(11):2315-2322;
PMID: 25362717

(7) Unusual Cause of Limited Elbow Movement in a Patient with Psoriatic Arthritis AJESH B. MAHARAJ and VINOD CHANDRAN J Rheumatol 2014;41(12):2482-2483
PMID: 25452180

(8) Spondyloarthritis in African Blacks AJESH B. MAHARAJ and PAUL P. TAK J Rheumatol January 2015 42(1):139;
PMID: 25554810

(9) Pancytopenia in a Patient with Psoriatic Arthritis Treated with Methotrexate and Concomitant Lithium. AJESH B. MAHARAJ and VINOD CHANDRAN J Rheumatol March 2015 42(3):557
PMID: 25729049

(10) Summary of Sensitivity and Specificity for Psoriatic Arthritis in a South African Cohort according to Classification Criteria. Ajesh B. Maharaj, Jayandran Govender, Kasthurba Maharaj, Michelle Rajkaran and Paul P. Tak J Rheumatol 2015; 42; 960-962 PMID: 25877500

(11) Drs. Maharaj and Chandran reply AJESH B. MAHARAJ and VINOD CHANDRAN J Rheumatol 2015;42;1062 PMID: 26034234

(12) 2015 Recommendations for the Management of Polymyalgia Rheumatica A European League Against Rheumatism/American College of Rheumatology Collaborative Initiative
Christian Dejaco, Yogesh P. Singh, Pablo Perel, Andrew Hutchings, Dario Camellino, Sarah Mackie, Andy Abril, Artur Bachta, Peter Balint, Kevin Barraclough, Lina Bianconi, Frank Buttgereit, Steven Carsons, Daniel Ching, Maria Cid, Marco Cimmino,Andreas Diamantopoulos, William Docken, Christina Duftner, Billy Fashanu, Kate Gilbert, Pamela Hildreth, Jane Hollywood, David Jayne, Manuella Lima, Ajesh Maharaj, Christian Mallen, Victor Martinez-Taboada, Mehrdad Maz, Steven Merry, Jean Miller, Shunsuke Mori, Lorna Neill, Elisabeth Nordborg, Jennifer Nott, Hannah Padbury, Colin Pease, Carlo Salvarani, Michael Schirmer, Wolfgang Schmidt, Robert Spiera, David Tronnier, Alexandre Wagner, Madeline Whitlock, Eric L. Matteson, and Bhaskar Dasgupta Arthritis and Rheumatology 09/2015; 67(10):2569-2580. DOI:10.1002/art.39333
PMID: 26352874

(13) 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative
Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, Abril A, Bachta A, Balint P, Barraclough K, Bianconi L, Buttgereit F, Carsons S, Ching D, Cid M, Cimmino M, Diamantopoulos A, Docken W, Duftner C, Fashanu B, Gilbert K, Hildreth P, Hollywood J, Jayne D, Lima M, Maharaj A, Mallen C, Martinez-Taboada V, Maz M, Merry S, Miller J, Mori S, Neill L, Nordborg E, Nott J, Padbury H, Pease C, Salvarani C, Schirmer M, Schmidt W, Spiera R, Tronnier D, Wagner A, Whitlock M, Matteson EL, Dasgupta B.Ann Rheum Dis. 2015 Oct;74(10):1799-807. doi: 10.1136/annrheumdis-2015-207492.
PMID: 26359488

(14) Assessing disease activity in psoriasis and psoriatic arthritis: impact on management and therapy
V Chandran, AB Maharaj. Expert Rev Clin Immunol May 2016; 12(06): 572-583
DOI:10.1586/1744666X.2016.1146133
PMID: 26807494

(15) McArdle's Disease Presenting with Acute Renal Failure
Ajesh B Maharaj, Vinod B Patel. South African Medical Journal 2016;106(5):469.
DOI:10.7196/SAMJ. 2016.v106i5.10348
PMID: 27138678

(16) Psoriatic arthritis (PsA): an assessment of clinical, biochemical and radiological features in a single centre South African cohort. Ajesh B. Maharaj*, Michelle Rajkaran, Jayandran Govender, Kasthurba Maharaj, Niek de Vries, Paul-Peter Tak. South African Medical Journal 2016; 106(6) 630-3. doi: 10.7196/ SAMJ. 2016. V106i6.10347.
PMID: 27245733

(17) Treatment of psoriatic arthritis with traditional DMARDs and novel therapies: approaches and recommendation. Ajesh B Maharaj; V Chandran Expert Rev Clin Immunol. 2017 Apr;13(4):319-331. doi: 10.1080/1744666X.2017. 1257939. PMID: 27826996

(18) MiR-146a G/C rs2910164 variations in South African Indian and Caucasian patients with psoriatic arthritis. Ajesh Maharaj, Pragalathan Naidoo, Terisha Ghazi, Naeem Abdul, Shanel Dhani, Taskeen Docrat, Prithiksha Ramkaran, Paul Tak and Niek de Vries, Anil Chuturgoon
Published online: BMC Medical Genetics (2018); doi.org/10.1186/s 12 881-018-0565-1

In Press:

(19) Treatment of enthesitis, dactylitis and nail lesions in psoriatic arthritis
Ajesh B Maharaj, F Paruk, Current Treatment Options in Rheumatology

(20) Comorbidities of Psoriatic Arthritis and their impact on management.
Ajesh Maharaj, Vinod Chandran. Expert Rev Clin Immunol

Invited Manuscripts/Reviews:

(1) Assessing disease activity in psoriasis and psoriatic arthritis: impact on management and therapy
V Chandran, AB Maharaj. Expert Rev Clin Immunol May 2016; 12(06): 572-583
DOI:10.1586/1744666X.2016.1146133
PMID: 26807494

(2) Treatment of psoriatic arthritis with traditional DMARDs and novel therapies: approaches and recommendation. Ajesh B Maharaj; V Chandran Expert Rev Clin Immunol. 2017 Apr;13(4):319-331 doi: 10.1080/1744666X.2017. 1257939. PMID: 27826996

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(8) Pain Forum – Cape Town: The Coxib Debate – Truth vs. Hype 2013
(9) Management of HIV associated Arthropathy ANNUAL WORKSHOP ON ADVANCED CLINICAL CARE - AIDS, Durban; 10/2014
(10) APLAR 2015 Assessment of Peripheral arthritis in Psoriatic Arthritis. Chennai, India 09/2015
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