

Psoriatic arthritis: state of the art review

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ABSTRACT

Psoriatic arthritis (PsA) accounts for around 20% of referrals to the early arthritis clinic and presents a significant diagnostic and management challenge. Early diagnosis is important to prevent long term functional disability and to ensure optimal management of arthritis and key comorbidities. From the rheumatologist's perspective, the differential diagnosis includes rheumatoid arthritis, gout and other inflammatory arthritides. Once diagnosed, it is essential to assess the disease fully, including arthritis, enthesitis, dactylitis, skin/nail disease and axial involvement. Using this information, appropriate treatment can be planned using therapies that are effective at treating the relevant domains of disease. Despite poor data, traditional disease-modifying anti-rheumatic drugs are commonly used and have been effective in observational studies. Following tumour necrosis factor inhibitors, which have proven excellent efficacy in multiple domains of PsA, new biologics are available or in development and will improve treatment options for people with refractory PsA.

Introduction

In 1964, psoriatic arthritis (PsA) was recognised as a separate disease by the American Rheumatism Association (now the American College of Rheumatology), and is now included as a member of the spondyloarthropathy spectrum.¹ PsA was initially defined by Moll and Wright as 'an inflammatory arthritis in the presence of psoriasis with a usual absence of rheumatoid factor',² but newer more robust classification criteria are discussed in this article.³

Why is it important to recognise PsA?

Although PsA was thought initially to be a relatively benign disorder, registry data has shown the destructive and progressive nature of the disease;⁴ it has a similar impact on quality of life and functional ability as in rheumatoid arthritis.⁵

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In recent years, the additional burden of increased mortality and significant cardiovascular comorbidity has also been identified.⁶ Despite this, identification and treatment are still not optimal. There are significant delays in diagnosis for the majority of patients (typically, in screening studies, up to 50% of established cases have not previously been identified).⁷ Delay in diagnoses of 6 and 12 months have been shown to impact on long-term joint damage and functional disability.^{8,9}

Diagnosis

PsA is a heterogeneous condition with musculoskeletal involvement, including arthritis, enthesitis, dactylitis and axial involvement as well as potential skin and nail disease. Different patterns of involvement of PsA can mimic different inflammatory arthritides.

For the rheumatologist, a patient presents with inflammatory arthritis and the differential diagnosis can include rheumatoid arthritis, crystal arthropathies and other inflammatory arthritides. When differentiating from rheumatoid arthritis, particularly in polyarticular PsA, there are a number of features

Key points

Psoriatic arthritis is an heterogeneous disease with multiple musculoskeletal and dermatological manifestations

Early recognition and treatment are likely to result in better long-term outcomes

Almost 50% of cases in primary care and secondary care clinics are unrecognised

There are significant metabolic comorbidities and increased cardiovascular morbidity and mortality

Traditional disease-modifying drugs have a modest benefit but new biologic agents, including the TNF inhibitors, are effective for most of the manifestations of the disease

KEYWORDS: Assessment, diagnosis, psoriatic arthritis and treatment ■

Table 1. Differentiating rheumatoid arthritis (RA) and psoriatic arthritis (PsA)

Features	PsA	RA
Number of joints involved	30–50% with oligoarthritis	Predominant polyarthritis
Joint involvement	Any joint, including distal interphalangeal joints	Usually distal interphalangeal joint sparing
Enthesitis	Typical, clinically present in 60–80%	Not typical
Dactylitis	Present in 30%	Not typical
Axial involvement	Axial spondyloarthritis phenotype	Erosive cervical disease
Skin/nail disease	Psoriasis in 80%, nail disease in 60%	Background population risk or lower
Serology	Usually RF and CCP negative	Usually RF and/or CCP positive
Typical radiographic changes	Periosteal new bone formation (uncommon especially in early disease)	Erosion and osteopenia

CCP = cyclic citrullinated peptide; RF = rheumatoid factor

that can help (Table 1). The CASPAR (Classification Criteria for Psoriatic Arthritis) criteria (Table 2) include a number of features typical of PsA such as psoriasis, nail disease, dactylitis and negative serology.

Given that 10–15% of patients develop arthritis prior to psoriasis, one additional issue is the potential presence of PsA sine psoriasis. In this situation, other features – including a family history of psoriasis, typical musculoskeletal involvement and negative serology – can help to differentiate PsA. Sometimes the psoriasis is ‘hidden’ and not readily identified in areas such as the scalp, nails, flexural areas and natal cleft (Fig 1). Of interest, these are the phenotypes of psoriasis most likely to be associated with the development of PsA.¹⁰

In contrast, for dermatologists and GPs caring for people with psoriasis, the key question is whether patients have an inflammatory arthritis rather than osteoarthritis or mechanical joint pain. Further work is ongoing to define the features of inflammatory musculoskeletal disease as quoted in the stem of the CASPAR criteria.¹¹ Generally, laboratory tests are unhelpful: markers of systemic inflammation, such

as the C-reactive protein or erythrocyte sedimentation rate, may be elevated in only 50% of cases and low titre rheumatoid factor and anti-cyclic citrullinated peptide may be found in up to 10% of cases.⁴ Current National Institute for Health and Care Excellence guidance for the management of psoriasis suggests that the Psoriasis Epidemiology Screening Tool patient-completed screening questionnaire¹² (www.bad.org.uk/healthcare-professionals/forms-downloads) should be used annually to identify PsA.¹³

Multidisciplinary/multispecialty care

PsA patients require input from the multidisciplinary rheumatology team. Specialist rheumatology nurses review and co-manage patients with PsA regularly in the UK. Physiotherapists, occupational therapists, podiatrists and other healthcare professionals are key to optimising outcomes for patients.

By the nature of spondyloarthritis, patients with PsA often require multispecialty care. Alongside rheumatology, the most

Table 2. The CASPAR criteria for classifying psoriatic arthritis

Inflammatory articular disease (joint, spine or entheses), with three or more points from the following:

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

*Current psoriasis scores 2 points. CASPAR = Classification Criteria for Psoriatic Arthritis; ELISA = enzyme-linked immunosorbent assay

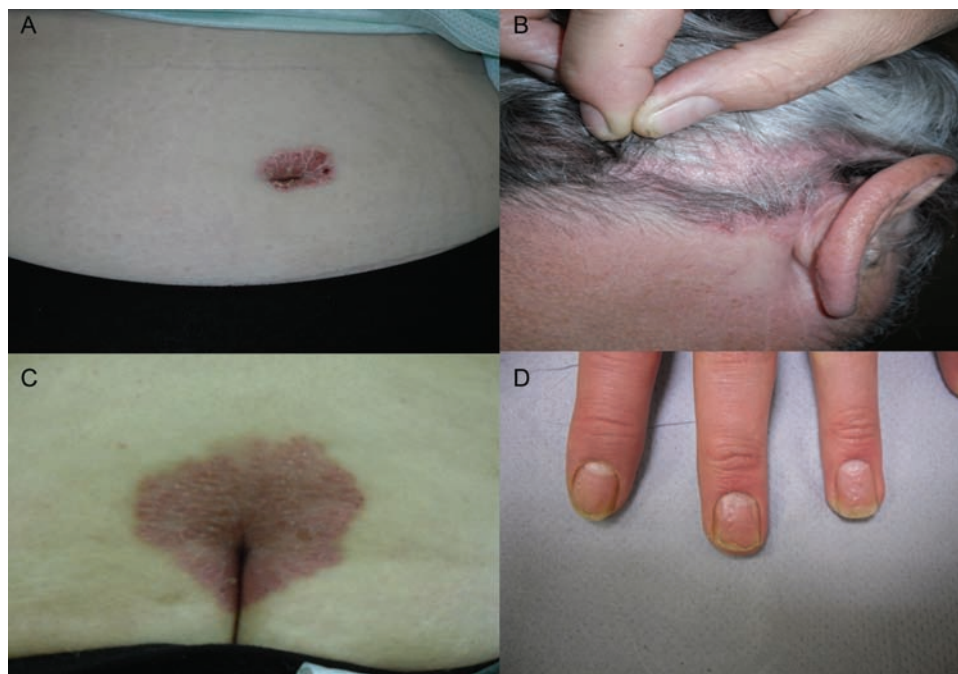


Fig 1. Typical 'hidden' psoriasis in peri-umbilical area (A), scalp (B), natal cleft (C) and nails (D).



Fig 2. Dactylitis in the hands (right second and fourth digits and left second digit) and feet (right third digit and left fourth digit).

obvious specialty is dermatology as around 80% of patients with PsA have active skin psoriasis. A number of centres now run combined clinics where patients can be simultaneously reviewed by both rheumatologists and dermatologists, an approach that is favoured by patients.¹⁴ PsA can be associated with uveitis and inflammatory bowel disease, requiring appropriate specialty care.

The other key comorbidity in PsA is the higher cardiovascular risk significantly contributed to by the high risk of metabolic syndrome. It has been found that 40% of PsA patients fulfil the diagnosis for metabolic syndrome¹⁵ and effective management of this is key to minimising morbidity and mortality.

Monitoring and assessing disease activity

The different manifestations of PsA mean that a number of assessments are required to fully appreciate disease activity. Rheumatologists need to move beyond the 28 joint count used routinely in rheumatoid arthritis as the more variable arthritis involvement in PsA is not well identified using this measure.¹⁶ It is recommended that a full 68/66 joint count is performed, including the foot and ankle. Assessment of key entheses, such as the Achilles tendon and lateral epicondyles, as well as examination for dactylitis (inflammation of the fingers and toes (Fig 2)) are important. Patients should be questioned further about back pain and any inflammatory back pain should be further investigated. Joint damage is highly variable in PsA but has been shown to be predicted by baseline joint damage, high acute phase response (C-reactive protein/erythrocyte sedimentation rate) and a higher number of actively inflamed joints.¹⁷

While rheumatologists are not required to make a full assessment of skin and nail disease, being aware of the patterns of these is important. An ability to quantify these, for example

using a psoriasis area and severity index or body surface area, can help with accurate assessment and appropriate therapeutic options for patients.

Pharmaceutical therapy

New treatment recommendations for PsA were updated in 2015 by both the European League Against Rheumatism (EULAR)¹⁸ and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis.¹⁹ Both of these recommendations are evidence-based and both broadly suggest a similar 'step up' approach to therapy. This approach uses therapies sequentially starting with simple therapies such as non-steroidal anti-inflammatory drugs for pain or topical therapies for psoriasis, followed by single disease modifying drugs (DMARDs), then combinations of standard DMARDs, and finally biologic drugs if patients fail to respond to the previous treatment.

The majority of patients referred are already taking non-steroidal anti-inflammatory drugs and these are symptomatically useful with appropriate cautions about side effects. In the initial stages, corticosteroids are used to settle inflammatory disease rapidly, often given as intra-articular or intra-muscular injections. Expert opinion is that intra-articular steroid injections may be used in persistent mono- or oligoarthritis.¹⁹ Observational evidence showed that 41% of joints improved at 3 months following use of corticosteroids, although 33% of these relapsed subsequently.²⁰ Oral steroids are not recommended, in part because of possible skin 'rebound' when they are withdrawn.

Methotrexate remains the most common first-line DMARD therapy, despite controversies. The methotrexate in PsA (MIPA) trial²¹ is the only powered placebo-controlled trial to assess methotrexate in PsA and did not achieve the primary outcome. The only significant difference was seen in patient and physician global visual analogue scores.²¹ However, there were methodological flaws with this paper, including slow recruitment, low target doses of methotrexate and a high drop-out rate.²² Supplementary data suggest a marked reduction in disease activity in the polyarticular group (≥ 5 active joints) but this was not formally tested.²¹ Observational data from the tight control of PsA (TICOPA) study²³ found an ACR20 (American College of Rheumatology 20% improvement criteria) score of 40.8% at 12 weeks with methotrexate, as well as some effect on enthesitis and dactylitis.

Sulfasalazine has been the subject of a number of studies. A Cochrane review²⁴ confirmed a significant but small effect against placebo with no effect on enthesitis. Leflunomide is the most well researched of the DMARDs for PsA, with a placebo-controlled randomised controlled trial of 190 patients.²⁵ However, leflunomide is not commonly used in clinical practice.

Tumour necrosis factor (TNF) inhibitors were the first licensed biologics in PsA (adalimumab, certolizumab, etanercept, golimumab and infliximab) and are now commonly used. NICE has recommended these treatments for PsA in cases where patients have failed at least two standard DMARDs and when they have at least three tender and three swollen joints.²⁶

Etanercept was the first TNF inhibitors shown to have a significant response in PsA, with 87% of patients achieving a response according to PsA response criteria compared with 23% of placebo treated patients.²⁷ The IMPACT (Identification

and Management of Psoriasis Associated Comorbidity) studies confirmed a significant improvement in arthritis and skin disease when taking infliximab, but they were also the first studies to show efficacy for enthesitis and dactylitis.^{28,29} Adalimumab, golimumab and certolizumab have been shown to have similarly significant benefit on arthritis, psoriasis, enthesitis and dactylitis^{30–32} as well as on radiographic damage. Although drug survival on TNF inhibitors does fall over time, registry studies have shown efficacy with second- and third-line TNF inhibitors, supporting drug switching in PsA.³³ In recent months, biosimilars for both infliximab and etanercept have become available in the UK. Their licensing studies showed similar pharmacodynamics, pharmacokinetics and efficacy to the reference product but these were performed in patients with rheumatoid arthritis and ankylosing spondylitis only.

In recent years, new biologics with alternative modes of action have also been tested in PsA. Ustekinumab is an IL-12/23 inhibitor that is used commonly for psoriasis and has been shown to be effective for arthritis, skin, enthesitis and dactylitis.³⁴ Despite no head-to-head studies, it is felt to be slightly less effective than TNF inhibitors for musculoskeletal manifestations despite being superior for skin disease. Ustekinumab is now approved by NICE for treatment of PsA, but only as a second-line therapy.

Given basic science data highlighting the importance of the Th17 pathway in PsA, a number of new therapies targeting this pathway are in development. Secukinumab, a monoclonal antibody to IL-17A, has excellent efficacy in psoriasis with superiority to both etanercept³⁵ and ustekinumab.³⁶ Secukinumab has also been shown to have good responses in PsA^{37,38} but there are no head-to-head comparator studies. A second IL-17A inhibitor, ixekizumab, has also reported good responses in PsA with similar efficacy to an internal adalimumab control arm.³⁹ Development of another IL-17 receptor antagonist, brodalumab, which showed early promising efficacy, was halted because of safety concerns (events of suicidal ideation). It is felt that the short-term efficacy of these IL-17 inhibitors is similar to that of TNF inhibitors for musculoskeletal manifestations. Newer therapies targeting the Th17 axis are also in development and have shown promising early results.

Another new therapy available for PsA is apremilast, a phosphodiesterase-4 inhibitor. The efficacy of apremilast seems lower than biologics, particularly for higher levels of response.⁴⁰ However, its favourable safety profile, with no regular blood monitoring required and no hepatotoxicity, can be an advantage in practice.

The advent of newer mode of action therapies has provided additional choice for clinicians who can choose optimal therapies based on their efficacy for different musculoskeletal and skin manifestations and their side effect profile.

Therapeutic strategies

There is very little evidence to guide how these therapies should be used. The newest data for treatment strategy in PsA is from the Tight Control of PsA (TICOPA) trial; the study recruited 206 patients with early PsA who were randomised 1:1 to receive either tight control or standard care. The tight control patients were reviewed every 4 weeks and their treatment was escalated to achieve minimal disease activity. The standard

care patients were seen every 12 weeks and were treated with no set protocol.⁴¹ The TICOPA study confirmed a significant benefit with tight control in terms of peripheral arthritis, skin disease and patient reported outcomes.⁴² As a result of this study, the first recommendation of the updated 2015 EULAR recommendations for the management of PsA is that 'treatment should be aimed at reaching the target of remission or, alternatively, minimal/low disease activity, by regular monitoring and appropriate adjustment of therapy'.¹⁸

The drugs used within the TICOPA study still followed a broadly 'step up' approach in keeping with current recommendations. This remains the default approach as it reduces costs associated with biologic therapies and because there is no evidence to date that a more aggressive treatment strategy improves outcome.

Conclusions

PsA is a common, disabling and frequently undiagnosed arthropathy for which effective treatments are available. Early detection and treatment are likely to improve the outcome. For assessment and therapy, it should be appreciated that this is a heterogeneous disease best managed with a multispecialty and multidisciplinary team. The era of targeted biologic drugs has transformed the treatment landscape for this disease but more research is required on different treatment strategies. ■

Conflicts of interest

The authors declare a potential conflict of interest, having received grant support and/or honoraria for consultations and/or for presentations as indicated:

- > LCC – Abbvie, Amgen, Boehringer Ingelheim, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, Sun Pharma and UCB.
- > PSH – Abbvie, Amgen, Boehringer Ingelheim, Janssen, Eli Lilly, MSD, Novartis, Pfizer and UCB.

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