Understanding psoriatic arthritis

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Previously, psoriatic arthritis was considered an uncommon, generally benign variant of ankylosing spondylitis or rheumatoid arthritis, with few therapeutic options. It is now recognized as a distinct, potentially serious disorder that can be effectively managed with a number of new agents.

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Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis, generally classed as a spondyloarthropathy. It shares features of rheumatoid arthritis and ankylosing spondylitis, but is also characterized by distinctive features of its own.

The first case of PsA to be described was probably that by Baron Jean Alibert in 1818, but it was not until seminal publications by Verna Wright in the late 1950s (Wright, 1959) that the condition was accepted as a distinct disease. The concept of PsA as a distinct disease, however, is not yet universally accepted. This is because it shares so many clinical features with other disorders and a clear pathogenetic basis has not yet been determined (Berthelot, 2003). Insights into the pathogenesis and the management of psoriatic arthritis have been revolutionized by recognition of the key role of tumour necrosis factor alpha (TNF-alpha). This review discusses the key clinical features, biology and genetic basis, and examines the evidence base for drug treatment of this disease.

CLINICAL FEATURES

The diversity of clinical manifestations and overlap with other disorders often make PsA difficult to separate accurately from other arthropathies. There are currently seven different diagnostic classification criteria, although preliminary analysis of a large dataset from the Classification of Psoriatic Arthritis (CASPAR) study group suggests that the criteria of Vasey and Espinoza (1984) have the greatest sensitivity and specificity (*Table 1*) (Helliwell and Taylor, 2005). Such criteria, however, are designed for groups of patients in research situations and not for individual patients in the context of clinical care. Nevertheless, they are often useful reminders of the key features of PsA.

The characteristic features of PsA are an oligoarthritis onset, involvement of finger and toe distal interphalangeal joints, including great toe interphalangeal joints, asymmetric sacroiliitis, dactylitis, enthesitis, inflammatory spinal symptoms (although these may be absent even with typical radiological signs of spondylitis), and psoriasis. The skin manifestations are poorly correlated with osteoarticular manifestations, being minor or even absent at presentation. About 10% of patients will develop skin disease at around the same time of arthritis and about 10% after the development of arthritis (Roberts et al, 1976). The prevalence of PsA is around 100 per 100 000 population and incidence is around six per 100 000 population per year (Shbeeb et al, 2000), although epidemiological data are difficult to interpret in the absence of a validated case definition. Females are equally affected as males and, beyond childhood and before the eighth decade, the effect of age is relatively minimal with similar incidence rates

TABLE 1.
Criteria proposed by Vasey and Espinoza (1984)

Criteria I plus one from either Criteria II or III	
Criteria I: Psoriatic skin or nail involvement	
Criteria II: Peripheral pattern	Pain and soft-tissue swelling with or without limitation of movement of the distal interphalangeal joint for over 4 weeks
	Pain and soft-tissue swelling with or without limitation of motion of the peripheral joints involved in an asymmetric peripheral pattern for over 4 weeks. This includes a sausage digit
	Symmetric peripheral arthritis for over 4 weeks, in the absence of rheumatoid factor or subcutaneous nodules
	Pencil-in-cup deformity, whittling of terminal phalanges, fluffy periostitis and bony ankylosis
Criteria III: Central pattern	Spinal pain and stiffness with the restriction of motion present for over 4 weeks
	Grade 2 symmetric sacroiliitis according to the New York criteria
	Grade 3 or 4 unilateral sacroiliitis

From Vasey and Espinoza, 1984.

from early adulthood through to the seventh decade (Harrison et al, 1997).

PsA was once considered a relatively benign condition, except for a small group with a very destructive arthritis mutilans, but it is now known that a majority of patients experience a chronic, progressive course (Kane et al, 2003). There is a great deal of interest in altering the natural history by inhibiting TNF-alpha (Mease et al, 2000).

PATHOPHYSIOLOGY

The genetics of PsA is complex and difficult to untangle from the genetics of psoriasis alone (Barton et al, 2001). The first twin study was reported recently and surprisingly showed no evidence for a genetic basis of this disease, with no difference in probandwise concordance between monozygotic and dizygotic twins (Pedersen et al, 2004). A number of earlier studies, however, showed an increased frequency of several genes in PsA. The controls in many such case-control studies have been persons without psoriasis, so it has been very difficult to distinguish the genetic contribution to PsA separately from that to psoriasis. Several putative genetic associations have subsequently been shown to be in linkage dis-equilibrium with HLA-Cw*0602, a well-established genetic association with psoriasis. Furthermore, cytokine gene polymorphisms in PsA have been shown to associate with severity of disease rather than presence of disease (Balding et al, 2003).

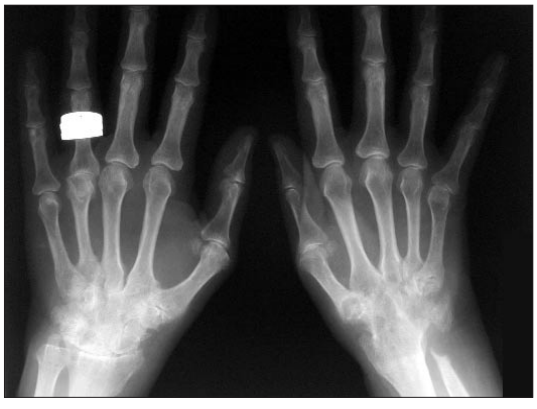

Figure 1. Joint osteolysis and bony ankylosis throughout the right carpus and wrist.

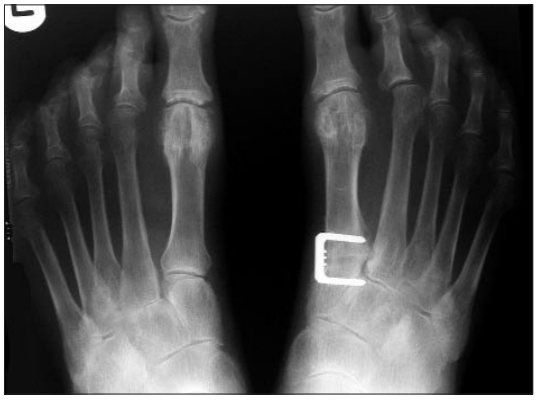

Figure 2. Right great toe interphalangeal joint erosive change and juxta-articular new bone formation giving a typical 'mouse-ear' appearance.

The twin study suggests a greater role for environmental factors in the development of PsA, and this is of particular interest since trauma has often been reported to precede the onset of PsA more often than in other arthropathies. Biomechanical stressing of cultured keratinocytes results in liberation of increased amounts of interleukin-1, a potent proinflammatory cytokine (Lee et al, 1997). Furthermore, there is strong evidence from magnetic resonance imaging studies that inflammation is often located at the ligament–capsule–tendon–bone interface, the enthesis (McGonagle et al, 1998; 1999), a site subject to significant mechanical traction.

Synovial, entheseal and skin histopathology and histochemistry have demonstrated several differences in the pathology of PsA compared with rheumatoid arthritis. A recent study, published only in abstract form (Chappell et al, 2004), suggested distinctive clustering of serum cytokines in different inflammatory rheumatic diseases, suggestive of distinct pathogenic mechanisms. In this study, the serum cytokine profile in PsA was characterized by eotaxin, CCL4/MIP-1beta, IL-12(p40), CCL3/MIP-1alpha, IL-6, and CCL2/MCP-1. There is also a distinctive vascular pattern of the synovium in PsA seen at arthroscopy, associated with increased levels of endothelial cytokines such as vascular endothelial growth factor (Reece et al, 1999).

A characteristic radiological feature of PsA is the expression of both bone resorption and new bone formation (Taylor et al, 2003), sometimes at the same joint (*Figures 1–2*). Proliferative changes are manifest as ankylosis, juxta-articular new bone formation, non-marginal syndesmophytes and irregular enthesophytes. Resorption is manifest as joint osteolysis (pencil-in-cup sign), entheseal erosion or distal phalangeal tuft erosion.

PROGNOSIS

The natural history of PsA has mainly been studied using cohorts of patients seen at clinics with a special interest in the condition. This introduces the significant possibility of referral bias. Such studies suggest that PsA is associated with a significant risk of structural joint damage (Gladman et al, 1990; Kane et al, 2003) and even premature mortality (Wong et al, 1997). Community-based studies have not shown a mortality risk (Shbeeb et al, 2000), but do suggest different outcomes for patients with early inflammatory arthritis if they also have psoriasis (Morgan et al, 2004).

The most important risk factors for an adverse prognosis are high levels of acute phase reactants (McHugh et al, 2003) and radiological damage at baseline (Gladman et al, 1998).

TREATMENT

There are few randomized controlled trials of treatment in PsA and until relatively recently there was only evidence for sulfasalazine as an effective therapy, despite the widespread and apparent utility of methotrexate (MTX) (Clegg et al, 1996; Jones et al, 1997). The most commonly-used drug, MTX, has been inadequately studied in PsA. A single randomized controlled trial of weekly intravenous MTX has shown no evidence of benefit, although a UK study is currently enrolling patients into a more robust placebo-controlled trial (contact Dr Gabrielle Kingsley, http://www.controlled-trials.com/isrctn/trial/%7C/0/54376151.html). Despite the lack of evidence, MTX is widely used and is generally found to be a useful drug, both for arthritis and skin disease. Although MTX is fairly well tolerated, there are a number of potential side effects that include nausea, mouth ulcers, hepatic fibrosis, pneumonitis and cyto-penias. Hepatotoxicity may be more common in patients with psoriasis, although the data on this is a little conflicting.

It is unclear whether guidelines for monitoring potential MTX hepatotoxicity should be aligned with the Psoriasis Task Force (Roenigk et al, 1988) that recommend periodic routine liver biopsies, or with the American College of Rheumatology guideline (Kremer et al, 1994) for its use in rheumatoid arthritis. This recommends monitoring mainly with monthly aspartate transaminase and albumin and only to perform liver biopsies if screening blood tests are abnormal (Kremer et al, 1994). This approach appears to be safe in rheumatoid arthritis, except possibly for people with diabetes, where reliance on transaminases alone may be insufficient reassurance (Erickson et al, 1995). Ciclosporin has been shown to be effective in psoriasis and also PsA, often studied in combination with MTX (Mazzanti et al, 1994; Fraser et al, 2004). The main concern about this drug is the risk of renal impairment, but this risk can be minimized with regular blood pressure and serum creatinine checks. Leflunomide, a novel pyrimidine synthesis inhibitor has also been found effective in a randomized controlled trial (Kaltwasser et al, 2004). *Table 2* summarizes conventional treatment for PsA.

The only drug to obtain licensing for treatment of PsA by the Food and Drug Agency (USA) is etanercept, based on very good evidence for effi-

TABLE 2.
Non-biologic drugs in the treatment of psoriatic arthritis

Name	Regimen	Evidence of efficacy (PsARC rate in active *vs* placebo)	Adverse effects
Sulfasalazine	2–4 g daily in two divided doses	57.8% *vs* 44.6% at 36 weeks (Clegg et al, 1996)	Nausea, rash, abnormal liver enzymes, agranulocytosis
Methotrexate (MTX)	10–25 mg once weekly	No supportive evidence from randomized controlled trials	Nausea, mouth ulcers, hepatic fibrosis, cytopenias pneumonitis, agranulocytosis
Leflunomide	20 mg daily	58.9% *vs* 29.7% at 24 weeks (Kaltwasser et al, 2004)	Diarrhoea, alopecia, hypertension, abnormal liver enzymes, peripheral neuropathy
Ciclosporin	3–5 mg/kg in 2 divided doses	A review of non-randomised studies suggested benefit (Olivieri et al, 1997); a randomized controlled trial of ciclosporin in addition to MTX showed an effect only for joint ultrasound indices (Fraser et al, 2004)	Hypertension, renal impairment, gum hypertrophy, peripheral neuropathy
Azathioprine	2–3 mg/kg	A single very small study (six patients) showing an effect size of 2.2 (Levy et al, 1972)	Nausea, abnormal liver enzymes, agranulocytosis, possible risk of malignancy
Sodium aurothiomalate	50 mg intramuscular injection weekly to monthly	One study showed possible benefit but the results were ambiguous (Palit et al, 1990)	Rash, proteinuria, aplastic anaemia, nitritoid reaction

PsARC = Psoriatic arthritis response criteria

cacy in terms of controlling disease activity and, more recently, radiological damage. It appears that anti-TNF therapy is truly disease-modifying, with evidence that infliximab (Antoni et al, 2004) and etanercept (Mease et al, 2004) slow or even reverse radiological damage over time.

The development of anti-TNF treatment has been an important advance in PsA. Both the osteoarticular and skin compartments are very responsive to anti-TNF therapy. Etanercept (Mease et al, 2000) and infliximab (Antoni et al, 2003) have been effective in randomized controlled trial with composite index response rates of 87% and 78% at 12 and 16 weeks, respectively. One potential concern with the use of anti-TNF agents that is relatively unique to psoriasis is the possibility of excessive exposure to UV radiation in a treatment context (psoralens and longwave ultraviolet radiation); increasing the risk of skin cancers, which may possibly be exacerbated by anti-TNF treatment. It is also important to note that the pivotal studies for the efficacy of anti-TNF therapy only required inadequate response to non-steroidal anti-inflammatory agents, and not to standard diesease-modifying anti-rheumatic drug treatment. For instance, less than half of patients studied by Mease et al (2000) were taking MTX.

The British Society for Rheumatology have developed a guideline for anti-TNF alpha therapy in PsA (McHugh, 2004) (*Table 3*). It is suggested that an adequate therapeutic trial of two standard disease-modifying anti-rheumatic drugs be tried first and if three or more tender and swollen joints remain, then etanercept is indicated. For continuation of therapy, the patients need to demonstrate a satisfactory PsA response criteria at 12 weeks.

TABLE 3.
British Society for Rheumatology guidelines for anti-TNF alpha therapy in adults with psoriatic arthritis

Failure to respond to standard therapy	Treatment for 6 months or longer of two or more drugs (separately or in combination); Methotrexate, sulfasalazine, ciclosporin or leflunomide except in cases of drug toxicity		
Active disease	At least three tender and three swollen joints on two separate occasions at least 1 month apart (dactylitis counted as one active joint)		
Caution for patients with:	History of >1000 joules cumulative dose of psoralens and longwave ultrviolet radiation, especially if subsequently treated with ciclosporin		
	HIV/AIDS		
	Congestive cardiac failure		
	Pregnancy or breast-feeding		
	Active infection (including chronic leg ulcers, previous tuberculosis, recent septic arthritis, recurrent chest infections, indwelling urinary catheter		
	Malignancy or pre-malignancy (except basal cell carcinoma, remote history – more than 10 years)		
	Demyelinating disease		
Response to therapy	Improvement in two factors (with at least one being a joint score) with worsening of none of the following four factors:	Patient global assessment (0–5 Likert scale)	
		Physician global assessment (0–5 Likert scale)	Improvement is a decrease by at least one unit; worsening is an increase of at least one unit
		Tender joint count (78 joints)	
		Swollen joint count (76 joints)	Improvement is a decrease by at least 30%; worsening is an increase by at least 30%
Withdrawal of therapy	Malignancy		
	Severe drug-related toxicity		
	Pregnancy (temporary)		
	Severe intercurrent infection (temporary)		
	Surgical procedures (temporary)		
	Failure to achieve psoriatic arthritis response criteria at 3 months		

CONCLUSIONS

The advent of anti-TNF alpha therapy has revolutionized the management of PsA, suggesting a central role for TNF alpha. The standard of evidence for the newer agents has been far in advance of the older agents, but the poor evidence base does not allow a clear judgment to be made for the relative efficacy of methotrexate and the biologics, especially for first-line therapy.

Further randomized controlled studies with active comparators are required to define the best indications for biologics. The role of genetics in the pathogenesis of PsA has been thrown into doubt by the first twin study (abstract only) and this will intensify efforts to identify relevant environmental factors. HM

Conflict of interest: none

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KEY POINTS

- Psoriatic arthritis is a distinct arthropathy characterized by oligoarticular onset, dactylitis, enthesitis, distal interphalangeal joint involvement, psoriasis, bone osteolysis and proliferation.
- The cytokine tumour necrosis factor-alpha is over-expressed in skin and synovial lesions. Inhibition of this cytokine is an effective treatment of psoriatic arthritis.
- The genetic basis for psoriatic arthritis is perplexing, with no evidence for a genetic influence from the first twin study reported recently.
- Low-dose oral weekly Methotrexate is commonly used for treating psoriatic arthritis but there are no randomized controlled trials to support this practice.