

For reprint orders, please contact:
reprints@futuremedicine.com

Treatments for psoriatic arthritis

Neil John McHugh

Royal National Hospital for
Rheumatic Diseases,
Upper Borough Walls,
Bath, BA1 1RL, UK
Tel.: + 44 122 578 7048;
neil.mchugh@rnhrd-tr.swest.
nbs.uk

The effectiveness of antitumor necrosis factor treatment for psoriatic arthritis has invigorated research into the many dimensions of this intriguing condition. Awareness of the need for better outcome measurements and for the evaluation of traditional treatments, many borrowed from the field of rheumatoid arthritis, has spurred new initiatives and collaborations. Insights into the pathogenic pathways can be explored by studying changes in the involved tissue following effective interventions, such as cytokine blockade. The heterogeneity of disease expression poses challenges for those interested in studying the genetics involved. The presence of disease pathology at separate sites in the same individual, including involvement of the skin, synovium and the entheses, offers unique opportunities to investigate tissue-specific mechanisms of inflammation. Patients with psoriatic arthritis can expect improvements in their wellbeing from newer approaches to treatment, which should be aimed at effective remission for both skin and joint disease.

Psoriatic arthritis (PsA) is an inflammatory synovitis and/or enthesitis that may occur in nearly 30% of individuals with skin psoriasis. The exact prevalence is uncertain, mainly because of the application of varying definitions for the disease, different population settings (e.g., community vs hospital), the lack of a specific diagnostic biomarker and the presence of subclinical unrecognized disease. An incidence of approximately 6 per 100,000 has been reported in some studies, with a population prevalence of 1 per 1000 [1,2]. Original notions that PsA is a benign form of arthritis have been reconsidered in the light of studies that demonstrate progressive joint damage, loss of function and enhanced mortality in patients followed in hospital clinics [3,4]. Therefore, the need for effective treatments for patients at risk of a poor outcome is apparent.

Most treatments for PsA have been carried over from experience in rheumatoid arthritis (RA). However, there are several features that make PsA a distinct entity that does not guarantee a similar therapeutic response to that seen in RA. There are important genetic and pathological differences between PsA and RA that need consideration (Table 1). PsA itself is a heterogeneous disorder that can affect one or multiple peripheral joints, has a predilection to enthesitis and may also affect the spine, causing spondylitis either alone or together with peripheral joint involvement. Historically, PsA has been classified into five subgroups [5], although these groups may often overlap and, with time, one group may evolve to another. Also, a broader classification would encompass less common conditions,

such as synovitis, acne, pustulosis, hyperostosis and osteolysis (SAPHO), which may share important pathogenic features with PsA, such as enthesopathy [6]. Another important issue is the presence of concomitant skin psoriasis that may influence the choice of treatment. Although there may be common pathogenic mechanisms operating between skin psoriasis, synovitis and enthesitis in the same patient, there are clear differences in the pattern of response at these sites to certain medications.

The advent of targeted treatments, such as cytokine blockade, has brought the need to develop a more rational approach to the treatment of PsA and better ways of assessing outcome into focus. Herein, the unique genetic and pathological features that may have a bearing on the treatment of PsA are reviewed, the effectiveness of newer versus conventional treatments is compared and consideration is given to future approaches to therapy.

Pathological features

The presence of a predominant T-cell infiltrate is a central feature in the immunopathogenesis of PsA, enthesitis and psoriasis. A greater oligoclonality of CD8⁺ T cells than CD4⁺ T cells has been demonstrated in psoriatic fluid [7] and CD8⁺ cells predominate in epidermal lesions of psoriasis [8], suggesting a role for major histocompatibility complex (MHC) Class I-driven immune reactions. Therapeutic responses to methotrexate correlate with the suppression of nonclonal T-cell populations that may have more of a regulatory role [9]. Treatments aimed at

Keywords: anti-TNF, cytokine therapy, entheses, psoriatic arthritis, psoriasis, synovium

future
medicine

Table 1. Key genetic and pathological differences between psoriatic and rheumatoid arthritis.

Psoriatic arthritis	Rheumatoid arthritis
Association with MHC Class I haplotype (HLA-Cw6)	Association with MHC Class II haplotype containing DR4 'shared epitope'
Low frequency of rheumatoid factor and anti-CCP levels [43]	High frequency of rheumatoid factor and anti-CCP levels
Increased synovial vascularity	Increased synovial lining layer thickness
Increased infiltration of CD163 ⁺ macrophages in synovial sublining [10]	Increased frequency of intracellular citrullinated proteins in synovium [10]

CCP: Citric citrullinated peptide; HLA: Human leukocyte antigen; MHC: Major histocompatibility complex.

suppressing or anergizing activated T cells have a good rationale, as do those that may influence T-cell adhesion and recruitment to inflammatory sites.

Synovial tissue from PsA patients has less lining layer thickness and greater vascularity than that seen in RA [10], suggesting angiogenic factors, such as vascular endothelial growth factor (VEGF), may be attractive targets for therapy. VEGF and other vascular growth factors are increased in psoriatic synovium [11,12]. There are increased levels of macrophage-derived cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1, 6 and 8 and Th1-derived cytokines, such as IL-2 and interferon- γ in the synovial fluid and membranes of affected joints [13]. IL-18 may also have an important pathophysiological role and is increased in PsA serum and synovial tissue [14]. Mediators of cartilage degradation and tissue remodeling, such as matrix metalloproteinase (MMP)1 and 3 are also increased in psoriatic joints.

The receptor activator of nuclear factor (NF)- κ B ligand (RANKL) is found on osteoblasts, stromal cells, T cells and synoviocytes and binds to RANK, a TNF-like receptor that is present on osteoclasts. Osteoprotegerin is a soluble decoy receptor that can deactivate RANKL and inhibit osteolysis and osteoclast precursors in peripheral blood. The RANKL–RANK system is an important regulatory system for bone remodeling. An attractive model has been proposed that may explain the distinctive spectrum from osteolysis to new bone formation that occurs within psoriatic joints, based on observations including increased expression of RANKL on synovial lining cells [15]. Furthermore, part of the effectiveness of anti-TNF agents in PsA may be explained by down-regulation of TNF-mediated osteoclast recruitment and activation. The transcription factor NF- κ B has a pivotal role in osteoclastogenesis and inflammation-related bone loss.

Box 1. Genes within the MHC region on chromosome 6 that may be associated with psoriatic arthritis.

HLA-Cw6

Ancestral haplotypes containing HLA-Cw6
 AH13.1 (A30; B13; Cw6; DR7; DQ2)
 AH47.1 (A3; B47; Cw6; DR7; DQ2)
 AH57.1 (A1; B57; Cw6; DR7; DQ2)

Tumor necrosis factor- α

Lymphotoxin- α

MICA

MICB

Corneodesmosin

SEEK-1

OTF-3

HCR

HCR: Alpha-helix coiled-coil rod homolog; MHC: Major histocompatibility complex; MICA: MHC Class 1 chain-related gene A; MICB: MHC Class 1 polypeptide-related sequence B; OTF: Octamer transcription factor.

Genetic factors

There may be an interplay of several genetic factors controlling immune responses and inflammatory mediators that influence the susceptibility of an individual developing arthritis in addition to psoriasis alone. The strongest known association with psoriasis is with human leukocyte antigen (HLA)-Cw6 and many candidate genes along an extended ancestral haplotype containing Cw6 (Box 1). Reported associations with TNF promoter polymorphisms and *MICA* genes are of interest, but difficult to differentiate from other genes on the same haplotype [16]. However, it is conceivable that polymorphisms in genes such as TNF, IL-1, -6 and other proinflammatory cytokines may influence the likelihood of responses to the biological therapies. Understanding the role of the innate immune system in the development of PsA may lead to new insights into treatment. There have been reports of associations of PsA with genes that

are involved with innate immunity, such as *CARD15*, that determine responsiveness to bacterial lipopolysaccharide [17], and killer cell immunoglobulin-like receptors (KIR) that are present on natural killer (NK) cells and form part of the early immune defense mechanisms [18].

Traditional treatments for PsA

The evidence base for the use of most of the traditional treatments for PsA is scarce and mostly based on assumptions that PsA will respond in a similar manner to that seen in RA. For reasons touched upon previously, such notions are open to challenge. Nonetheless, there are probably sufficient studies backed by clinical experience to support the continued use of nonsteroidal anti-inflammatory drugs (NSAIDs) with appropriate gastric protection as a reasonable starting point for symptom relief (note that there have been no published studies of cyclooxygenase (cox) II inhibition for PsA). The risk of a psoriasis flare related to a buildup of leukotrienes in the skin with NSAID use is reported but not commonly encountered. The use of intra-articular corticosteroid injections is based on expert opinion as there have been no clinical trials. Similarly, there have been no studies of oral corticosteroids, which are thought to be contraindicated because of the risk of severe psoriasis flare with corticosteroid withdrawal. It is unlikely that agents such as oral or intramuscular gold, penicillamine or antimalarials will be used widely in the future for PsA. The place of other, more traditional disease modifying agents needs at least a brief mention.

Sulphasalazine, methotrexate & cyclosporin

There is a paucity of evidence for the effectiveness of most of the commonly used disease-modifying agents for PsA [19]. There have been more studies of sulphasalazine than of other agents. At best, sulphasalazine has a modest effect on improving joint symptoms and does not appear to halt radiological progression. Considering the widespread use of methotrexate in PsA, there is little published evidence from clinical trials. Cyclosporin is used more commonly for the treatment of psoriasis than PsA, and is more often used in cycles of treatment for psoriasis that may be less appropriate for the control of arthritis. All these agents have significant problems with toxicity, including gastrointestinal side effects for sulphasalazine, liver toxicity for methotrexate and renal toxicity for cyclosporine. Overall, it seems likely that the

prolonged use of these agents in patients with persistently active disease will be superseded by more targeted therapies that become available over the next 5–10 years.

Newer treatments

Leflunomide

Leflunomide is licensed for use in adults with active PsA. It is an isoxazol derivative that in its active form inhibits dihydro-orotate dehydrogenase, a mitochondrial enzyme essential for the *de novo* synthesis of pyrimidines. It preferentially inhibits the activation and proliferation of T lymphocytes that, as noted previously, are important in the pathogenesis of both psoriasis and PsA. Modest efficacy has been demonstrated in PsA with some improvement in psoriasis [20], but further studies on psoriasis would be helpful, as would information regarding the prevention of radiological progression. The main limitations to its use are gastrointestinal side effects, liver toxicity and hypertension. Leflunomide would be a good choice as a comparator with TNF antagonists in future clinical trials.

Mycophenolate

Mycophenolate mofetil (MMF) inhibits inosine monophosphate and the subsequent *de novo* guanine synthesis necessary for DNA replication in lymphocytes but not neutrophils. MMF is most commonly used to prevent organ-graft rejection and is gaining more widespread use for maintaining disease remission in a range of autoimmune disorders. Small studies in PsA have been promising [21]. MMF is converted rapidly to its active metabolite, mycophenolic acid, which may have fewer gastrointestinal side effects than MMF.

Bisphosphonates

In addition to their potent action as inhibitors of osteoclastic bone resorption, bisphosphonates have anti-inflammatory effects that may be due to the downregulation of proinflammatory cytokines and inhibition of antigen presentation by macrophages, which may make them useful agents in PsA. Indeed, early studies of pamidronate infusion have shown some efficacy in patients with ankylosing spondylitis [22]. Furthermore, refractory cases of SAPHO have responded to pamidronate infusion [23]. Further studies of bisphosphonates in patients with PsA, especially those with osteolysis, would be of considerable interest.

Biological treatments

TNF antagonists

TNF- α is a potent proinflammatory immunomodulatory cytokine that is produced mainly by monocytes/macrophages. Cytokines such as TNF- α play a pivotal role in the pathogenesis of PsA. Recent studies with TNF- α antagonists have shown that TNF- α blockade is an effective treatment for both PsA and psoriasis [24–29]. Histologically, anti-TNF treatment is associated with a reduction of synovial layer thickness, vascularity, cell adhesion molecules (e.g., vascular cell adhesion molecule [VCAM]-1, intracellular cell adhesion molecule [ICAM]-1 and E-selectin), inflammatory cell infiltration and growth factors (e.g., VEGF) [30].

Currently, there are three TNF- α antagonists licensed for use in patients with active PsA who have not responded to traditional treatment. Etanercept (Emberel[®]) is a recombinant molecule comprising part of the human TNF receptor plus the constant region of human immunoglobulin (Ig)G. The licensed dose is 25 mg twice weekly, administered subcutaneously. Infliximab (Remicade[®]) is a chimeric human–murine monoclonal antibody directed against TNF- α . It is licensed (for use in combination with methotrexate) at a dose of 5 mg/kg, administered by intravenous infusion at 0, 2, 6 and 8-weeks thereafter. Adalimumab (Humira[®]) is a fully humanized recombinant monoclonal antibody directed against TNF- α . The licensed dose is 40 mg every other week, given subcutaneously. All anti-TNF antagonists have proven efficacy in reducing the signs and symptoms of joint inflammation, improving quality-of-life measures and slowing radiological progression, and they are also effective in improving psoriasis. There have been no head-to-head comparisons of anti-TNF agents. A summary of findings at a common end point time from relevant studies is shown in Table 2. Another anti-TNF- α antagonist, oncept, is a

recombinant human p55 TNF-binding protein that can be administered subcutaneously at a dose of 50 or 100 mg/week and has been shown to be effective in a Phase II study [31].

It is likely that TNF antagonists will be much more widely used for the treatment of PsA. As treatment is expensive, more information on cost effectiveness is urgently needed, with economic modeling encompassing quality-of-life measures for both joint disability and skin disease. Another issue is whether there is justification for switching patients to an alternative anti-TNF antagonist should the first agent be ineffective. Experience from RA suggests that there is a good rationale for doing so, most likely based on differences in pharmacokinetics and mechanisms of action. For instance, etanercept is able to neutralize TNF- β (lymphotoxin- α), whereas infliximab and adalimumab are directed selectively at TNF- α . Conversely, infliximab is able to lyse TNF-producing cells *in vitro*, whereas etanercept does not [32] and infliximab may also act by disrupting cognate CD40/CD40L-dependent cognate interaction between T cells and the microvasculature [33]. Such differences may explain why conditions such as Crohn's disease are more amenable to treatment with infliximab than etanercept. Further studies investigating the effectiveness of sequential therapy are needed.

Other cytokine inhibitors

Anakinra is an IL-1 receptor antagonist administered daily by subcutaneous injection that ameliorates synovitis and prevents joint erosion in RA but has not been evaluated in PsA. Similarly, studies of other anticytokine blockade therapies, such as those directed against IL-6, -12, -15 and -18, have been undertaken in RA and may prove effective for PsA. Conversely, IL-10 is an anti-inflammatory cytokine that inhibits the production of IL-1 and TNF- α .

Table 2. Outcome data at 24 weeks from recent anti-TNF studies in PsA (active vs placebo).

Outcome measure [44]	Etanercept [25] (n = 205)	Infliximab [27] (n = 200)	Adalimumab [29] (n = 313)
PsARC	70 vs 23%	70 vs 32%	60 vs 23%
ACR20	50 vs 13%	54 vs 15%	57 vs 15%
HAQ score (%change)	54 vs 6%	-0.2 vs 0.5%	-0.4 vs -0.1%
PASI-75 (score)	23 vs 3%	60 vs 1%	42 vs 0%

ACR20: American College of Rheumatology response criteria, 20% improvement in composite measures; HAQ: Health assessment questionnaire; n: Number of patients; PASI-75: Psoriasis area severity index, 75% improvement; PsA: Psoriatic arthritis; PsARC: PsA response criteria; TNF: Tumor necrosis factor.

Recombinant human IL-10 administered daily over 28 days to patients with PsA was associated with the suppression of Type I cytokine production *in vitro*, decreased markers of endothelial cell activation and decreased T-cell and macrophage infiltration of synovial tissue [34]. There was a modest improvement in skin, but not articular, measures of outcome; however, the study was of short duration.

Antilymphocyte treatments

T-cell activation requires engagement of the T-cell receptor with the MHC and a second co-stimulatory signal delivered by interaction of several ligand–receptor pairs. Agents targeted at blocking the co-stimulatory signal may have the consequence of inducing T-cell anergy or apoptosis and have been actively pursued as a strategy for treating T-cell driven diseases such as PsA and psoriasis. Co-stimulatory pathways include the interaction of leukocyte function-associated antigen (LFA)-3 with CD2, ICAM-1 with LFA1 and CD80/CD86 with CD28/cytotoxic T-lymphocyte antigen (CTLA)4. Biological therapies for blocking all three pathways are available and have been used in trials of PsA and/or psoriasis.

Alefacept

Alefacept is a humanized fusion protein of LFA-3 with Fc fragments of IgG₁ that has been approved for the treatment of psoriasis. By binding to CD2 on T cells, it blocks CD2 engagement with LFA-3 on antigen-presenting cells (APCs). The IgG₁ portion binds to FcγRIII IgG receptors on NK cells, resulting in the apoptosis of T cells that express high levels of CD2. A small, open-label study suggested that alefacept may be an effective agent for PsA [35]. In a more recent, larger, Phase II study, the combination of alefacept with methotrexate was more effective than methotrexate alone for both peripheral arthritis and psoriasis [36]. In the former study, there was a decline in CD4, CD8 and CD68 positive macrophages within the synovial lining. An expected decline in peripheral blood CD4 counts occurs and needs monitoring. Intermittent courses are given to allow the recovery of CD4 counts, which correlate with activity of the psoriasis.

Efalizumab

Efalizumab is humanized form of a murine antibody directed against the CD11a subunit of LFA-1. By binding LFA-1 on memory T cells, efalizumab inhibits LFA-1 engagement with

ICAM-1 and thus T-cell activation, as well as the migration of T cells into tissue. Efalizumab when given at its licensed weekly dose of 1 mg/kg by subcutaneous injection, is effective for moderate-to-severe psoriasis, with approximately a third of patients becoming clear after 12 weeks [37,38]. Preliminary studies of PsA showed less benefit, but further studies are awaited.

Abatacept

CD28 is an activating receptor on T cells that engages CD80 (B7–1) and CD86 (B7–2) on APCs, although with less affinity than the inhibitory receptor CTLA-4. Abatacept is a soluble receptor composed of CTLA-4 and the Fc fragment of IgG. It blocks the interaction of CD80 (B7–1) and CD86 (B7–2) with CD28 on T cells and may also have a CD28-independent mechanism of action that causes inhibition of lymphocyte activation and T-cell death. Abatacept has been an effective treatment in trials of RA, for which it is now approved, and has shown benefit in an open-label study of psoriasis [39].

Rituximab

The effectiveness of targeting B cells in psoriasis or PsA has not been evaluated. Rituximab is a human–mouse, chimeric, monoclonal antibody directed against the B-cell CD20 antigen and causes rapid and specific B-cell depletion. Rituximab does not deplete mature plasma cells but may diminish antigen-presenting B cells that support the activation of autoreactive T cells. Such a mechanism may well be effective in PsA given the evidence for oligoclonal expansion of T cells in psoriatic synovial tissue.

Emerging therapies

Biological therapies are expensive to manufacture and need to be administered by injection, with the possibility of adverse reactions. An alternative approach is to inhibit the enzymes that generate proinflammatory cytokines with smaller molecules. Two such approaches under development are for the metalloproteinase TNF- α converting enzyme (TACE) and the cysteine protease caspase-1 (IL-1 β converting enzyme, [ICE]) [40]. Inhibitors of these enzymes may provide less expensive, orally bioavailable agents in the future. Another target that seems attractive for therapy in PsA is the RANKL–RANK signaling pathway and the associated transcription factor NF- κ B that play a pivotal role in osteoclast differentiation and activation. In particular, RANKL production by activated T cells and subsequent signal

Executive summary**Pathological features & genetic factors of psoriatic arthritis**

- Psoriatic arthritis (PsA) affects approximately 30% of individuals with psoriasis and is usually a progressive condition, associated with significant morbidity in those patients needing treatment in a hospital setting.
- Distinctive clinical and radiological features separate PsA from other forms of arthritis, such as the frequent involvement of distal interphalangeal joints, enthesal inflammation, osteolysis and a tendency to bony ankylosis of both peripheral and axial joints.
- Key pathological features include enhanced synovial vascularity, T-cell infiltration of synovium with evidence of CD8 oligoclonality and the upregulation of macrophage-derived cytokines.
- The receptor activator of nuclear factor κ B (RANK)–RANK ligand (L) system that regulates bone remodeling may play a critical role via osteoclast recruitment and activation, and interaction with proinflammatory cytokines such as tumor necrosis factor (TNF)- α .
- Genetic associations with major histocompatibility complex (MHC) Class I alleles, MHC class 1 chain-related gene A, killer cell immunoglobulin-like receptor polymorphisms and *CARD* genes may point to an involvement of the innate immune response in pathogenesis.

Traditional treatments

- The evidence base for the use of traditional medications, including nonsteroidal anti-inflammatory agents, corticosteroids and disease-modifying agents, is not well established because of a lack of well-controlled clinical trials. Sulphasalazine, methotrexate, cyclosporine and more recently leflunomide constitute the most widely used traditional disease-modifying agents and have generally modest efficacy and frequent toxicity.

Newer emerging treatments

- The advent of anti-TNF antagonists, such as etanercept, infliximab and adalimumab, has provided an important advance in effective treatment for both PsA and psoriasis.
- Other novel therapies are emerging that need further evaluation and include cytokine blockade, targeting T-cell trafficking and activation, B-cell ablation, inhibition of osteoclast recruitment and activation, and small molecule inhibitors.

Future perspective

- Challenges for the immediate future are the development of better methods for assessing disease outcome, including all dimensions of involvement, accurate profiles for those patients at risk of severe outcome and evidence-based algorithms for treatment.

transduction leading to NF- κ B activation is likely to be an important mechanism accounting for the bone remodeling and resorption that occurs in psoriatic joints. Suppression of NF- κ B activation may account partially for many of the therapeutic effects of traditional disease-modifying agents such as sulphasalazine and corticosteroids. However, specific and selective inhibition of kinases, such as inhibited(I) κ B kinase, that are involved in NF- κ B activation pathways is possible with peptide kinase inhibitors [41], and may be very effective for therapy in bone resorbing inflammatory disorders such as PsA.

Combination therapy

In contrast to RA there have been very few studies looking at combination therapy in PsA. In one recent study, 72 patients with an incomplete response to methotrexate were randomized to receive either cyclosporine in addition to methotrexate or placebo plus methotrexate [42].

Patients on cyclosporine had significant clinical improvements from baseline in swollen joint count and C-reactive protein levels that were not evident in the placebo group. Many of the studies of anti-TNF antagonists in PsA have allowed patients to remain on conventional disease-modifying agents, such as methotrexate, and more data on additive efficacy are needed. Part of the rationale for using a conventional disease-modifying agent, such as methotrexate, with monoclonal anti-TNF drugs has been to lessen the chance for the development of antichimeric antibodies, which may be associated with a greater chance of an infusion reaction, although this seems less of a problem in patients with psoriasis.

Conclusion & future perspective

The concept of an early, aggressive approach aimed at inducing complete remission in PsA should be achievable with the advent of more effective treatments. Mechanisms for measuring

disease activity and remission in all dimensions, including peripheral joint disease, enthesopathy, spinal disease and skin psoriasis, will be of fundamental importance and may well include the use of new imaging modalities, as clinical observation alone is unlikely to be sensitive enough. Composite measures to reflect the total impact of therapy on skin and joint disease will require closer collaboration between the health professions involved. Better knowledge of risk factors for adverse outcomes in any individual may include the use of biomarkers, genetic

profiling, microarray and proteomic technology, and will provide additional insights into pathogenesis and treatment. Recent breakthroughs using effective biological agents for psoriasis and PsA have set a new benchmark. No doubt the concurrent or sequential use of multiple agents dependent on the stage and patterns of disease, and including strategies such as cytokine blockade, lymphocyte depletion, antiosteoclast therapy, angiogenesis inhibition and small peptide inhibitors, is a challenging agenda for the future.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

- Kaipainen-Seppänen O: Incidence of psoriatic arthritis in Finland. *Brit. J. Rheumatol.* 35, 1289–1291 (1996).
- Shbeeb M, Uramoto KM, Gibson LE, O'Fallon WM, Gabriel SE: The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982–1991. *J. Rheumatol.* 27(5), 1247–1250 (2000).
- Gladman DD, Antoni C, Mease P, Clegg DO, Nash P: Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann. Rheum. Dis.* 64(Suppl. 2) S14–S17 (2005).
- McHugh NJ, Balakrishnan C, Jones SM: Progression of peripheral joint disease in psoriatic arthritis. *Rheumatology* 42, 778–783 (2003).
- Moll JM, Wright V: Psoriatic arthritis. *Semin. Arthritis Rheum.* 3, 55–78 (1973).
- McGonagle D, Conaghan PG, Emery P: Psoriatic arthritis: a unified concept twenty years on. *Arthritis Rheum.* 42, 1080–1086 (1999).
- Promotes the concept that the enthesitis is the primary site of pathological involvement in the different patterns of psoriatic arthritis.**
- Costello PJ, Winchester RJ, Curran SA *et al.*: Psoriatic arthritis joint fluids are characterized by CD8 and CD4 T cell clonal expansions appear antigen driven. *J. Immunol.* 166(4), 2878–2886 (2001).
- Krueger JG, Bowcock A: Psoriasis pathophysiology: current concepts of pathogenesis. *Ann. Rheum. Dis.* 64(Suppl. 2), S30–S36 (2005).
- Curran S, Winchester R, Costello P *et al.*: Methotrexate therapy reduces polyclonal T-cell infiltration in the psoriatic arthritis synovium, revealing expanded CD4 and CD8 T-cell clones. *Arthritis Rheum.* 42, S372 (1999).
- Kruithof E, Baeten D, De Rycke L *et al.*: Synovial histopathology of psoriatic arthritis, both oligo- and polyarticular, resembles spondyloarthropathy more than it does rheumatoid arthritis. *Arthritis Res. Ther.* 7(3), R569–R580 (2005).
- Recent study that further emphasizes important differences in histopathology between spondyloarthropathy and rheumatoid arthritis.**
- Ritchlin CT: Pathogenesis of psoriatic arthritis. *Curr. Opin. Rheumatol.* 17(4), 406–412 (2005).
- Veale DJ, Ritchlin C, Fitzgerald O: Immunopathology of psoriasis and psoriatic arthritis. *Ann. Rheum. Dis.* 64(Suppl. 2), S26–S29 (2005).
- Ritchlin C, Haas-Smith SA, Hicks D *et al.*: Patterns of cytokine production in psoriatic synovium. *J. Rheumatol.* 25, 1544–1552 (1998).
- Rooney T, Murphy E, Benito M *et al.*: Synovial tissue interleukin-18 expression and the response to treatment in patients with inflammatory arthritis. *Ann. Rheum. Dis.* 63(11), 1393–1398 (2004).
- Ritchlin CT, Haas-Smith SA, Li P, Hicks DG, Schwarz EM: Mechanisms of TNF- α - and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J. Clin. Invest.* 111(6), 821–831 (2003).
- Demonstrates a mechanism whereby the receptor activator of nuclear factor κ B (RANK)–RANK ligand(L) system may play a key role in the pathogenesis of psoriatic arthritis.**
- Korendowycz E, McHugh N: Genetic factors in psoriatic arthritis. *Curr. Rheumatol. Rep.* 7(4), 306–312 (2005).
- Rahman P, Bartlett S, Siannis F *et al.*: CARD15: a pleiotropic autoimmune gene that confers susceptibility to psoriatic arthritis. *Am. J. Hum. Genet.* 73(3), 677–681 (2003).
- Martin MP, Nelson G, Lee JH *et al.*: Cutting edge: susceptibility to psoriatic arthritis: influence of activating killer Ig-like receptor genes in the absence of specific HLA-C alleles. *J. Immunol.* 169(6), 2818–2822 (2002).
- Ties in data incriminating genes involving innate immunity with well-established associations of psoriasis with major histocompatibility complex Class I genes.**
- Soriano ER, McHugh NJ: Systematic review of therapies for peripheral joint disease in psoriatic arthritis. *J. Rheumatol.* (2006) (In Press).
- 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 Rheum.* 150(6), 1939–1950 (2004).
- Grundmann-Kollmann M, Mooser G, Schraeder P *et al.*: Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. *J. Am. Acad. Dermatol.* 42(5 Pt 1), 835–837 (2000).
- Maksymowych WP, Jhangri GS, Fitzgerald AA *et al.*: A six-month randomized, controlled, double-blind, dose–response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal anti-inflammatory drug-refractory ankylosing spondylitis. *Arthritis Rheum.* 46(3), 766–773 (2002).
- Amital H, Applbaum YH, Aamar S, Daniel N, Rubinow A: SAPHO syndrome treated with pamidronate: an open-label study of 10 patients. *Rheumatology* 43(5), 658–661 (2004).
- Mease PJ, Goffe BS, Metz J *et al.*: Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 356, 385–390 (2000).
- First randomized controlled trial to demonstrate efficacy of antitumor necrosis factor blockade in psoriatic arthritis.**

25. Mease PJ, Kivitz AJ, Burch FX *et al.*: Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum.* 50(7), 264–272 (2004).
26. 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 Rheum.* 52(4), 1227–1236 (2005).
27. Antoni C, Krueger GG, de Vlam K *et al.*: Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann. Rheum. Dis.* 64(8), 1150–1157 (2005).
28. Kavanaugh A, Antoni C, Krueger GG *et al.*: Infliximab improves health-related quality of life and physical function in patients with psoriatic arthritis. *Ann. Rheum. Dis.* 65(4), 471–477 (2005).
29. 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.* 52(10), 3279–3289 (2005).
30. Canete JD, Pablos JL, Sanmarti R *et al.*: Antiangiogenic effects of anti-tumor necrosis factor α therapy with infliximab in psoriatic arthritis. *Arthritis Rheum.* 50(5), 1636–1641 (2004).
31. Nikas SN, Drosos AA: Onercept. *Serono. Curr. Opin. Investig. Drugs* 4(11), 1369–1376 (2003).
32. Van den Brande JM, Braat H, van den Brink GR *et al.*: Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. *Gastroenterology* 124(7), 1774–1785 (2003).
33. Danese S, Sans M, Scaldaferrri F *et al.*: TNF- α blockade down-regulates the CD40/CD40L pathway in the mucosal microcirculation: a novel anti-inflammatory mechanism of infliximab in Crohn's disease. *J. Immunol.* 176(4), 2617–2624 (2006).
34. McInnes IB, Illei GG, Danning CL *et al.*: IL-10 improves skin disease and modulates endothelial activation and leukocyte effector function in patients with psoriatic arthritis. *J. Immunol.* 167(7), 4075–4082 (2001).
35. Kraan MC, van Kuijk AW, Dinant HJ *et al.*: Alefacept treatment in psoriatic arthritis: reduction of the effector T cell population in peripheral blood and synovial tissue is associated with improvement of clinical signs of arthritis. *Arthritis Rheum.* 46(10), 2776–2784 (2002).
36. Mease PJ, Gladman DD, Keystone EC: Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* 54(5), 1638–1645 (2006).
37. Lebowitz M, Tyring SK, Hamilton TK *et al.*: A novel targeted T-cell modulator, efilizumab, for plaque psoriasis. *N. Engl. J. Med.* 349(21), 2004–2013 (2003).
38. Smith CH, Anstey AV, Barker JN *et al.*: British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. *Br. J. Dermatol.* 153(3), 486–497 (2005).
39. Abrams JR, Kelley SL, Hayes E *et al.*: Blockade of T lymphocyte costimulation with cytotoxic T lymphocyte-associated antigen 4-immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. *J. Exp. Med.* 192(5), 681–694 (2000).
40. Le GT, Abbenante G: Inhibitors of TACE and caspase-1 as anti-inflammatory drugs. *Curr. Med. Chem.* 12(25), 2963–2977 (2005).
41. Ruocco MG, Karin M: IKK β as a target for treatment of inflammation induced bone loss. *Ann. Rheum. Dis.* 64(Suppl. 4), S81–S85 (2005).
42. Fraser AD, van Kuijk AW, Westhovens R, *et al.*: A randomised, double blind, placebo controlled, multicentre trial of combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis. *Ann. Rheum. Dis.* 64(6) 859–864 (2005).
43. Korendowycz E, Owen P, Ravindran J, Carmichael C, McHugh N: The clinical and genetic associations of anti-cyclic citrullinated peptide antibodies in psoriatic arthritis. *Rheumatology* 44(8), 1056–1060 (2005).
44. Gladman DD, Helliwell P, Mease PJ *et al.*: Assessment of patients with psoriatic arthritis: a review of currently available measures. *Arthritis Rheum.* 50(1), 24–35 (2004).

Affiliation

- Neil John McHugh
Royal National Hospital for Rheumatic Diseases,
Upper Borough Walls, Bath, BA1 1RL, UK
Tel.: + 44 122 547 3432;
Fax: + 44 122 547 3435;
neil.mchugh@rnhrd-tr.swest.nhs.uk