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Traditional and Newer Therapeutic Options for Psoriatic Arthritis

An Evidence-Based Review

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Contents

Abstract

Psoriatic arthritis (PsA) is a destructive form of inflammatory arthritis that occurs in about one-third of patients with psoriasis. The pathogenesis of PsA includes genetic and immunological factors. A review of the currently available therapies reveals that traditional disease-modifying medications have provided only marginal relief from joint inflammation in patients with PsA, and have not been successful in controlling the disease and preventing joint damage. On the basis of current understanding of the pathogenesis of joint destruction in PsA, several new medications have been introduced, including anti-tumour necrosis factor (TNF) agents and agents that interfere with T-cell function. Most of these medications have been found to be effective in both psoriasis and PsA. Recent

randomised controlled trials suggest that at least anti-TNF agents may help prevent progression of joint destruction.

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis, usually seronegative for rheumatoid factor.[1] PsA was identified as a unique form of arthritis distinguished from rheumatoid arthritis by the absence of rheumatoid factor, the presence of asymmetric distribution, distal joint involvement, dactylitis, enthesitis and spondyloarthritis. There is currently no widely accepted validated classification for PsA; however, an international effort is under way to address this issue. The exact prevalence of PsA is unknown and estimates have varied from 0.04% to 1.2%.[2] The prevalence of PsA among patients with psoriasis has varied from 6% to 42%. Recent studies suggest that some 30% of patients with psoriasis develop PsA.[3] If the prevalence of psoriasis is 1–3% of the population, the prevalence of PsA may be as low as 0.3% or as high as 1%.

PsA includes both peripheral joint and axial involvement. While the peripheral arthritis may affect any joint, it commonly affects the distal interphalangeal joints. Generally, the arthritis tends to be asymmetric, in a 'ray' distribution, affecting all joints of one digit, as opposed to all joints of the same level at both hands, which is common in rheumatoid arthritis. There is often a reddish-bluish discoloration over the affected joint. Dactylitis, or 'sausage digit', occurs in 48% of patients and is associated with radiological changes.[4] Enthesitis, often at the Achilles tendon or plantar fascia insertion into the calcaneous, is also common in PsA. Both sacroiliitis and spondylitis occur in about 40% of patients, but are less severe than in ankylosing spondylitis, as the sacroiliitis tends to be less painful clinically and less severe radiologically, and the spinal involvement tends to skip vertebral bodies and be asymmetric.[5]

Over the past 2 decades it has become clear that PsA may be severe and progressive.[6-8] More active disease at presentation, and the number of inflamed joints at each visit, as well as the degree of damage at each visit, predict future clinical damage in patients with PsA.[9] Reduced quality of life and functional disability similar to that in patients with rheumatoid arthritis have been documented in PsA.[10,11] Traditional therapies have not provided adequate control and prevention of damage in these patients. Moreover, patients with PsA are at an increased risk of death compared with the general population, with a standard mortality ratio of 1.62.[12] Mortality risk is related to disease severity, measured by the number of damaged joints and a high erythrocyte sedimentation rate (ESR) at presentation to the clinic.[13] Thus, it is important to make the diagnosis early and treat aggressively to prevent these untoward outcomes in patients with PsA.

A MEDLINE search for therapies in PsA was carried out with emphasis on randomised controlled trials where available. In addition, the American College of Rheumatology (ACR) and the European League of Associations of Rheumatology (EULAR) websites were searched to identify trials presented at recent meetings. Websites of companies known to have carried out recent randomised controlled trials in PsA were also searched. This review concentrates on the therapeutic options for patients with PsA with emphasis on evidence from randomised controlled trials. In order to understand the reasons for the choice of therapy in PsA, the pathogenesis of the disease is briefly reviewed.

1. Pathogenesis of Psoriatic Arthritis (PsA)

Neither the aetiology nor the pathogenesis of PsA has been fully elucidated. Genetic factors clearly play an important role, as evidenced by family investigations showing familial aggregation,[14] association studies showing a role for the HLA region on the short arm of chromosome 6,[15,16] and genome scans which have identified several genes in psoriasis and PsA.[17,18] Since we cannot change the genetic makeup of the patients, this information has

not yet been helpful in designing new therapies for PsA. However, genes at the HLA region may be relevant to disease expression in PsA, since the presence of HLA-B27 with HLA-DR7, the presence of HLA-B39, and the presence of HLA-DQw3 in the absence of HLA-DR7 were associated with progression of clinical damage, whereas HLA-B22 was protective of damage in a large cohort of patients with PsA followed prospectively.[19] Environmental factors such as infection and trauma may also be relevant to the development of PsA.[1] However, we cannot modify the environmental encounters of our patients either.

On the other hand, we may be able to interfere with some of the immunological factors thought to contribute to the development and perpetuation of PsA. In particular, the role of T cells and their cytokines in the development of joint destruction in PsA has targeted those elements in the development of new therapeutic modalities for PsA. The pathology of skin and joint lesions in PsA is that of an inflammatory reaction, and there is evidence for autoimmunity as well, perhaps mediated by complement activation.[20] The inflammatory nature of the joint lesions in PsA is demonstrated by synovial lining cell hyperplasia and mononuclear cell infiltration.[21] The presence of higher amounts of T helper-1 (T_h1) cytokines (tumour necrosis factor [TNF]-α, interleukin [IL]-1β and IL-10) in samples from PsA patients than from patients with rheumatoid arthritis suggests that these two disorders may result from a different underlying mechanism.[22] Fibroblasts from the skin and synovia of patients with PsA have increased proliferative activity and the capability to secrete increased amounts of IL-1, IL-6 and platelet-derived growth factors.[23,24] PsA is characterised by severe joint destruction that is manifested in some joints with bone resorption, resulting in the pencil-in-cup change, which leads to clinically flail joints, and in other joints with ankylosis, which leads to clinically fused joints. While the exact mechanisms leading to these outcomes are not clear, T cells, macrophages and their products, cytokines and chemokines are likely to play an important role. T cells, particularly CD8+ cells, are thought to play an important role in the pathogenesis of both the skin and joint manifestations of PsA.[20,25-27] These activated T cells contribute to the enhanced production of cytokines noted both in the synovial fluid and synovial cultures from patients with PsA.[20] These cytokines, including IL-1β, IL-2, IL-10, interferon (IFN)-γ and TNFα, induce proliferation and activation of synovial and epidermal fibroblasts, leading to the fibrosis reported in patients with long-standing PsA.[23,24] The pro-inflammatory cytokines IL-1 and TNFα are not only regulators of the inflammatory response, but also play an important role in bone metabolism; enhancing osteoclastogenesis via upregulation of osteoprotegerin ligand (OPGL),[28] a new member of the TNF receptor family of molecules, expressed by activated T cells.[29,30] A recent study shows that erosive disease in PsA is associated with increased osteoclast precursors in the peripheral circulation.[31] Monocytes also appear to play an important role in the pathogenesis of PsA.[32] Monocytes are responsible for the production of metalloproteinases (MMPs), which are thought to mediate cartilage erosion in inflammatory arthritis. MMPs are regulated by IL-1 and TNFα.[33] MMP-2, MMP-9 and their regulators membrane type (MT)-MMPs and tissue inhibitors of MMPs (TIMPs), as well as MMP-1 and MMP-3, were demonstrated in synovial tissue and lesional and nonlesional skin from patients with PsA.[34,35] In particular, there may be a role for MMP-3, which activates other MMPs.[36] Recently, serum MMP-1 and TIMP-1 levels were found to be increased in patients with polyarticular PsA compared with controls.[37] Many of these molecules may be targets for therapeutic intervention in PsA. Whether the same mechanisms operate in both the peripheral joints and spondylitis remains unclear.

2. Management of PsA

The management of PsA requires attention to both skin and joint manifestations, despite the lack of correlation in onset and severity between the two aspects of the disease.[38] Generally, one attempts to identify treatment modalities that address both skin and joint disease. If the major issue for a patient with

PsA is the skin manifestations, those should be treated primarily, usually by a dermatologist, and the joint manifestations, if mild, can be managed with NSAIDs. However, it should be noted that NSAIDs do not modify the course of the disease, nor do they prevent development or progression of erosions. Thus, if there is already erosive disease, patients should be treated aggressively with disease-modifying antirheumatic drugs (DMARDs). Since ideally patients would be treated before erosive disease is present, and treatment should prevent the development of erosions, it is important for patients with psoriasis and joint complaints to consult a rheumatologist, who should manage their joint disease. To determine whether a patient has erosive disease, radiographs of the appropriate areas must be taken at baseline. Similarly, it is recommended that patients who present with joint disease but have suspected psoriasis consult a dermatologist, who should supervise their skin treatment. Ideally, the dermatologist and rheumatologist would work as a team to supervise all aspects of the patient's disease.

2.1 Assessment of Clinical Response

A major issue in the assessment of drug therapy in PsA has been the lack of standardised validated instruments to assess clinical response. Two methods to assess actively inflamed joints have been used in PsA: the ACR joint count and the Ritchie index.[39] The ACR joint count has been proven reliable in PsA, but it has been suggested that each drug trial should include a training session for participants.[40,41] On the basis of these joint counts, three sets of criteria for response have been devised. The ACR response criteria and the EULAR response criteria have been developed specifically for rheumatoid arthritis, and the Psoriatic Arthritis Response Criteria (PsARC) were developed specifically for PsA.[39] The ACR20 response criteria include tender joint count and swollen joint count, both of which must demonstrate at least a 20% reduction by the end of a trial, and in addition a 20% reduction in at least three of the following five items: patient global assessment, patient pain assessment, physician global assessment (all using a visual analogue scale), patient assessment of disability (such as the Health Assessment Questionnaire [HAQ]), and an acute phase reactant (ESR or C-reactive protein [CRP]). There is concern about the use of inflammatory markers such as ESR or CRP, which may be elevated in only 50% of patients with PsA, as well as with the HAQ scores, which may not be as elevated in patients with PsA.[42] The Disease Activity Index (DAS) is a mathematical formula which is calculated from an assessment of the Ritchie articular index, swollen joint count, ESR, general health status and pain visual analogue scale. Based on the DAS, EULAR response criteria have been identified. While these criteria have not been validated in PsA, they have been used in recent randomised controlled trials in this disease. To date, there are no criteria for the assessment of the spondylitis in PsA.

2.2 Traditional Therapy

Traditional therapy for PsA includes NSAIDs and DMARDs. NSAIDs control pain and may work for mild inflammation in patients with PsA. It should be noted that some NSAIDs have been implicated in worsening the skin lesions in patients with PsA.[43] However, NSAIDs have not been shown to retard progression of joint disease and therefore are considered symptomatic therapy only. When the inflammation persists despite NSAIDs, DMARDs should be used.

Medications that work for both skin and joint manifestations include methotrexate and ciclosporin (cyclosporin). The retinoic acid analogue etretinate and psoralen with UVA light (PUVA) work for the skin and may also control joint manifestations, whereas sulfasalazine and azathioprine may work for both skin and joint manifestations. Aside from methotrexate, which was initially used successfully for the treatment of psoriasis and PsA, and then used in rheumatoid arthritis, the other DMARDs used in PsA were initially used in rheumatoid arthritis and subsequently tried in PsA. These medications were not used specifically because of known indication related to the pathogenesis of the disease. Both because PsA was thought to be mild and rare and because of the fact that there were no classification

Table I. Summary of studies with methotrexate and ciclosporin (cyclosporin) in psoriatic arthritis

Medication/study type	No. of pts	Results	Comments
Methotrexate/RCT[44]	21	Decreased joint count and ESR at 3wk	Intravenous every 10d, 3/21 pts died
Methotrexate/RCT[45]	37	Only physician global assessment demonstrated response	Study underpowered
Methotrexate/retrospective[46]	59	Marked improvement in 37%, modest improvement in 35% at 3y	Uncontrolled study
Methotrexate/retrospective[47]	40	Excellent response in 37%, modest response in 59% at 54mo	Uncontrolled study
Methotrexate/NCC[48]	38	No benefit over control group in joint count or damage progression	Small number of pts
Ciclosporin, sulfasalazine, standard care/3-arm RCT[49]	99	Improvement in pain in ciclosporin-treated pts compared with other 2 arms	No improvement shown with outcome measures chosen
Ciclosporin, methotrexate/ 2-arm RCT[50]	35	Both arms improved, both skin and joint manifestations	More pts withdrew from ciclosporin

ESR = erythrocyte sedimentation rate; **NCC** = nested case control; **pts** = patients; **RCT** = randomised controlled trial.

or diagnostic criteria, there have been few double-blind, randomised controlled trials with these medications in PsA.

2.2.1 Methotrexate

Methotrexate has been used as the standard of practice for the treatment of PsA for some time. It is thought to have a very good efficacy **:** toxicity ratio based on its use in rheumatoid arthritis and has a relatively rapid mode of action. However, there are only two randomised controlled trials of its use in PsA (table I). The initial study, in 1964, included 21 patients and used parenteral methotrexate 1–3mg intravenously every 10 days.[44] The study revealed that the drug reduced the tender and swollen joint count as well as ESR compared with placebo. However, one patient developed bone marrow aplasia, one patient died during an episode of haematemesis and a third patient died of cerebral thrombosis 1 month after study completion.[44] Another randomised controlled trial included 35 patients with PsA, used oral administration of 7.5–15 mg/week and demonstrated very modest results only in physician global assessment.[45] All patients completed the 12-week trial, and the adverse effects were mild and did not necessitate withdrawal. Not only was it a small study that was underpowered to demonstrate effect (they needed twice the number of patients), but the dosage of methotrexate used was much less than the currently used dosages of 15–25 mg/week. Despite the fact that the randomised controlled trials did not show marked efficacy, methotrexate has been used extensively.

A few uncontrolled case series suggest that it is efficacious. In a series of 59 patients treated with oral methotrexate 15 mg/week over 3 years, 37% of the PsA patients showed marked reduction in the signs of inflammation and an additional 35% had modest improvement.[46] Another uncontrolled study of 40 patients given oral methotrexate at an average dose of 11 mg/week for an average of 34 weeks revealed excellent response in 37% of patients and a good response (50% reduction in joint count and no more than four actively inflamed joints remaining) in an additional 58% of patients.[47] However, a nested case-control study of 38 patients revealed that methotrexate at an average dosage of 11 mg/week did not prevent radiological progression over 2 years in patients with PsA treated after an average disease duration of 9 years.[48] Since it has become customary to administer methotrexate parenterally if dosages higher than 17.5–20 mg/week are required, the dose and mode of administration used by most rheumatologists today have not been systematically examined for efficacy in PsA. Despite the lack of randomised controlled trials, methotrexate has been the cornerstone of therapy for PsA in clinical practice.

2.2.2 Ciclosporin (Cyclosporin)

Ciclosporin has been shown to be effective in controlling psoriasis.[51] Although there are no

randomised controlled trials comparing ciclosporin against placebo, there are two published controlled trials comparing ciclosporin with other medications in PsA (table I).

A multicentre Italian controlled trial of 99 patients compared ciclosporin 3–5 mg/kg/day (added to standard therapy), sulfasalazine 2 g/day (added to standard therapy) and standard therapy alone (including NSAIDs and low-dose prednisone).[49] Although their primary outcomes were the ACR response criteria for peripheral joint disease and the Assessment of Ankylosing Spondylitis (ASAS) group response criteria for spondylitis, the study demonstrated significant benefit in pain reduction at 6 months only in the ciclosporin group compared with both the sulfasalazine and standard therapy groups. Individual components of the ACR response criteria also favoured ciclosporin compared with the standard therapy group. However, more patients discontinued ciclosporin because of adverse effects.

Another trial that included 35 patients randomised to either ciclosporin or methotrexate revealed both to be effective at 6 and 12 months in terms of joint tenderness and swelling, Ritchie index, duration of morning stiffness, physician and patient global assessment, and the Psoriasis Area Severity Index (PASI) score.[50] Methotrexate was associated with liver toxicity but more patients were withdrawn from the ciclosporin arm because of toxicity. Thus, while ciclosporin works well for both skin and joint manifestations of PsA, it is rather toxic and is not well tolerated.

2.2.3 Retinoic Acid Derivatives and Psoralen with UVA

Retinoic acid derivatives and PUVA have been reported to be effective in the treatment of severe psoriasis. They were reported in the 1980s to be effective in PsA. One randomised controlled trial comparing 20 patients randomised to etretinate and 20 randomised to ibuprofen revealed that more patients remained in the etretinate group and demonstrated clinical improvement with the drug.[52] The investigators suggested that the skin improvement contributed to patients continuing on the drug. Two small uncontrolled trials were performed and showed a reduction in joint counts and acute phase reactants in patients treated with etretinate.[53,54]

There is one study using PUVA in PsA.[55] This study of 29 patients suggested that aggressive therapy of psoriasis would improve PsA. However, there have been no randomised controlled trials with this therapy. Others have also tried extracorporeal phototherapy as an approach to the treatment of PsA.[56]

2.2.4 Sulfasalazine

Sulfasalazine was initially developed for the treatment of rheumatoid arthritis. Since the 1960s it has been commonly used in Europe. As it also works for inflammatory bowel disease, there was a rationale for using it in the seronegative forms of arthritis. There are five published randomised controlled trials of sulfasalazine in PsA (table II). Although all reported improvement in the sulfasalazine group compared with the placebo group, this was modest at best.

Three small trials were published in the early 1990s. A randomised controlled trial of 30 patients

Table II. Summary of studies with sulfasalazine in psoriatic arthritis

Study type	No. of pts	Results	Comments
RCT[57]	29	Improvement in pt global assessment	Small study, many withdrawals
RCT[58]	30	Improvement in drug-treated pts	40% withdrawal rate
RCT[59]	24	Improvement in pt global assessment	Small study
RCT[60]	117	Improvement in pt global assessment	No other outcome measure improved
RCT[61]	221	Improvement in PsARC (55% drug vs 45% placebo)	Marginal improvement
NCC[62]	36	No difference between drug-treated pts and controls	Only long-term study; shows no disease-modifying effect

NCC = nested case control; **PsARC** = Psoriatic Arthritis Response Criteria; **pt(s)** = patient(s); **RCT** = randomised controlled trial.

revealed improvement in the sulfasalazine-treated group compared with placebo recipients at 24 weeks; however, there was a 40% withdrawal rate in both the drug-treated and placebo groups.[57] A similar observation was noted in a study of 29 patients randomised to either sulfasalazine or placebo for 24 weeks.[58] There was no significant difference in response at 12 weeks and at 24 weeks the response was noted primarily in patient global assessment. Another study of 24 patients randomised to either sulfasalazine 2 g/day or placebo reported improvement in patient and global assessment in the sulfasalazine-treated patients compared with controls.[59]

In a larger study of 117 patients randomised to sulfasalazine 2 g/day or placebo only pain was improved at 6 months in the treatment arm.[60] A multicentre study of 221 patients randomised to receive sulfasalazine 2 g/day versus placebo demonstrated a trend towards improvement and a modest increase of responders among the sulfasalazine group (57.8% vs 44.6% of placebo recipients) at 6 months.[61] The investigators developed a new method to define response in PsA for this trial. The Psoriatic Arthritis Response Criteria (PsARC) were based on four items: tender joint count (reduction by 30%), swollen joint count (reduction by 30%), patient global assessment (reduction by one level) and physician global assessment (reduction by one level). A responder was defined on the basis of improvement in at least two of the four items, one of which had to be a joint measure, and no worsening in any of the four. The high placebo response determined by the PsARC in this trial suggested either that the measure was inappropriate or that the drug was not very effective. None of the individual components of the PsARC reached statistical significance when comparing sulfasalazine-treated patients with placebo recipients.

Although sulfasalazine was reported to be well tolerated in these trials, it did not appear to be a very effective drug.

In a clinic setting, only 20 of 36 patients prescribed sulfasalazine were able to tolerate the drug for more than 3 months. These patients were matched with patients with similar disease duration, activity and severity followed prospectively in the same clinic. There was no difference in the reduction of actively inflamed joints at 6 and 12 months between the two groups. Moreover, there was no difference in the progression of erosive disease in the two groups. Although the trial had a small sample size, it showed that sulfasalazine was not an effective disease-modifying drug in PsA.[62]

2.2.5 Azathioprine

There is only one randomised controlled trial of azathioprine in PsA and it was reported in abstract only.[63] It showed improvement in the azathioprine-treated compared with placebo-treated patients. While several case series suggested that azathioprine is effective in PsA, a nested case-control study failed to show its effectiveness or its ability to prevent disease progression.[64]

2.3 Other Disease-Modifying Antirheumatic Drugs

Other DMARDs used for the management of PsA include antimalarials,[65] gold[66,67] and penicillamine. While dermatologists have been reluctant to use antimalarials for fear of aggravating psoriasis, this has not been demonstrated in large studies. Intramuscular gold is more effective than oral gold for PsA, but because one of the adverse effects is a skin rash that may be confused with psoriasis, it has not been a drug of choice. Moreover, it has a slow mode of action and has not been shown to protect patients from progression of joint damage.[68] Penicillamine use has been limited because of its adverse effects. A meta-analysis of DMARDs used in PsA up to the year 2000 concluded that parenteral methotrexate and sulfasalazine were the only drugs that may have an effect in this disease.[69] On the basis of the published literature to that date, it is clear either that the drugs available were not very effective in PsA or that patients were treated too late in the course of the disease to make a difference.

Table III. Summary of published recent controlled trials in psoriatic arthritis with newer therapies

Medication	Route	Inclusion criteria	No. of pts	Duration (wk)	Primary outcome	Results (%)	
						TRM	placebo
Leflunomide[70]	Oral	RF−; 3 tender, 3 swollen joints	190	24	PsARC	59	29
Etanercept 2[71]	SC	3 tender, 3 swollen joints; typical	60	12	PsARC	87	23
Etanercept 3[72]	SC	features	205	12	ACR20	59	15
Etanercept 3[72]	SC	RF−; 3 tender, 3 swollen joints	205	24	ACR20	50	13
Infliximab[73]	IV	RF−; 5 tender, 5 swollen joints	101	16	ACR20	69	8
Infliximab[74]	IV		88	52	ACR20	70	NA
Infliximab[75]	IV	RF−; 5 tender, 5 swollen joints	200	14	ACR20	58	11
Infliximab[75]	IV		200	24	ACR20	54	14
Adalimumab[76]	SC	3 swollen, 3 tender joints	313	24	ACR20	57	15

ACR20 = 20% reduction in American College of Rheumatology response criteria; **IV** = intravenous; **NA** = not applicable; **PsARC** = Psoriatic Arthritis Response Criteria; **pts** = patients; **RF−** = rheumatoid factor negative; **SC** = subcutaneous; **TRM** = drug treatment.

2.4 Newer Therapies

Over the past 2 decades it has become clear that PsA is a more serious disease and is probably more common than previously thought. Those facts, together with the discovery of new modalities for the treatment of rheumatoid arthritis, have paved the way to newer therapies becoming available for patients with PsA. A major issue that arose as these medications became available was the design of clinical trials in PsA. Since there were no widely accepted criteria for classification or diagnosis, each study depended on its own definition. Thus, in some studies only patients who were seronegative for rheumatoid factor were included, whereas in others seropositive patients were included, as long as they had classic manifestations of PsA, such as dactylitis, distal joint disease or sacroiliitis. This issue may be resolved soon, as there is an international effort to develop widely acceptable criteria for the classification of PsA.

An international effort is under way, through the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), to define domains and instruments to be used in clinical trials in PsA. However, until now investigators have had to use the available measures in order to proceed with therapeutic trials in PsA (table III).[42]

2.4.1 Leflunomide

Leflunomide is considered a DMARD in rheumatoid arthritis.[77] It inhibits *de novo* pyrimidine synthesis and since activated lymphocytes require a large pyrimidine pool, leflunomide preferentially inhibits T-cell activation and proliferation.[78] As outlined in section 1, activated T cells play an important role in both skin and joint manifestations in PsA; thus it makes sense to use this medication in PsA. Several uncontrolled studies suggested its efficacy in PsA.[79-81]

A multicentre, double-blind, controlled trial of leflunomide compared with placebo in PsA was recently completed.[70] The study included 190 patients with at least three tender and three swollen joints and at least 3% body surface involvement with psoriasis. Patients were randomised to either leflunomide (100 mg/day for 3 days followed by 20 mg/day) or placebo. The primary outcome measure was the PsARC, and secondary measures included the ACR20 response (modified for PsA by including the distal joints of the toes), PASI[82] and target area response, and quality of life measured by the HAQ[83] and Dermatology Life Quality Index (DLQI).[84] In 188 patients who actually started the trial, the PsARC was significantly higher among leflunomide- than placebo-treated patients (59% vs 29.7%; $p < 0.0001$). Importantly, superiority of leflunomide was demonstrated for each of the components of the PsARC. The ACR20 response was achieved by a higher number of leflunomide-treated patients than placebo recipients (36% vs 20%; $p = 0.014$). However, it was noted that not all patients had the ACR score calculated because of missing values at baseline. PASI scores also improved more in leflunomide-treated patients than

controls. Both the HAQ and the DLQI improved in leflunomide-treated patients compared with placebo recipients. Leflunomide led to more serious adverse events than did placebo (13% vs 5%). Thus, leflunomide offers an alternative treatment in patients with PsA. Unfortunately, the study design did not include pre- and post-therapy radiographs; therefore, it is not possible to derive information from this study regarding the actual disease modification ability of leflunomide in PsA.

2.4.2 Mycophenolate Mofetil

Mycophenolate mofetil is rapidly converted to mycophenolic acid, a potent and reversible noncompetitive inhibitor of inosine monophosphate dehydrogenase. This enzyme is responsible for the conversion of inosine monophosphate to guanosine monophosphate, which is later converted to deoxyguanosine triphosphate (dGTP). Mycophenolic acid causes a reduction of GTP and dGTP in lymphocytes but not neutrophils.[85] Since lymphocytes play an important role in the pathogenesis of psoriasis and PsA, this drug may have a beneficial effect in both skin and joint manifestations of PsA. While there are no reported randomised controlled trials using mycophenolate mofetil in PsA, there are two reports suggesting that it may be efficacious in PsA, although it is not clear whether it is actually effective in psoriasis.[86,87]

2.4.3 Anti-Tumour Necrosis Factor Agents

TNF plays a pivotal role in both psoriasis and PsA. As outlined in section 1, it is responsible for the inflammatory changes noted in both the skin and joint manifestations and is a factor in the activation of other chemokines and cytokines which may lead to cartilage and bone destruction. Thus, reduction in TNF should lead to marked improvement in both skin and joint manifestations and may prevent joint destruction. Several anti-TNF agents have been developed in the past few years, and some have already been studied in PsA and provide evidence for efficacy in PsA.

Etanercept

Etanercept, a recombinant human soluble TNF receptor (TNFR), is a dimeric fusion protein consisting of the extracellular portion of the human p75 TNFR linked to the Fc portion of a type 1 human IgG1. The primary action of etanercept is to bind and inactivate soluble and cell-bound TNF and lymphotoxin α.[88]

A phase II randomised controlled trial in PsA was carried out in a single centre.[71] Sixty PsA patients were randomised either to etanercept 25mg or placebo subcutaneously twice a week, 30 in each study arm. Within each group half the patients were also receiving methotrexate. The PsARC was used as the primary response criterion and the ACR20 was used as a secondary outcome measure. The PASI score (>75% improvement; PASI75) and target lesion score were also used as secondary outcome measures. At 12 weeks 87% of the etanercept-treated patients responded, compared with 23% of the placebo-treated patients ($p < 0.0001$). All components of PsARC demonstrated significant improvement with etanercept compared with placebo. The ACR20 response was achieved by 73% of etanercept-treated patients compared with 13% of the placebo recipients ($p < 0.0001$). Twenty-six percent of etanercept recipients compared with none of the placebo recipients achieved the skin response. The only significant difference in adverse events between the two groups was injection site reactions, which were more common among the etanercept-treated patients. An open-label, follow-up study revealed improvement in the patients originally treated with placebo, although the magnitude of improvement was not the same as in the group originally treated with etanercept.[89]

A phase III multicentre trial confirmed the results of the phase II trial. Of the 205 patients included, 101 were randomised to etanercept group and 104 to placebo group.[72] The primary outcome measure was the ACR20, which was achieved by 59% of the etanercept-treated patients compared with 15% of those in the placebo arm ($p < 0.001$) at 12 weeks and 50% versus 13% at 24 weeks. The PsARC was used as a secondary outcome measure and also showed a significant difference between etanercept-treated and placebo-treated patients (72% vs 31% at 12 weeks and 70% vs 24% at 6 months). This study

further demonstrated significant responses in quality of life. At 6 months the HAQ improved by 0.6 units in the etanercept-treated patients compared with 0.1 units in those receiving placebo. The improvement was sustained through 72 weeks, with each of the domains of the HAQ showing similar changes (0.5–0.8). Importantly, this etanercept study included radiographic assessments. An evaluation of radiographic progression in the hands that was only based on a modification of the Sharp method to include the distal interphalangeal joints revealed that patients treated with etanercept had less progression of joint damage than those treated with placebo.[72] This was despite the fact that the patients randomised to etanercept had more damage at baseline and would therefore be expected to accrue more damage.[9] While the magnitude of the difference is small, and it remains to be seen whether this change is clinically important, this is the first study to demonstrate lack of progression following treatment in PsA. The safety profile of etanercept in this study was also quite good, showing differences only in injection site reactions.

Infliximab

Infliximab is a chimeric monoclonal antibody that binds specifically to human TNF and is composed of human constant and murine variable regions.[90] Infliximab is administered as an intravenous infusion at 0, 2 and 6 weeks followed by infusions every 8 weeks.

One randomised controlled trial, IMPACT (Infliximab Multinational Psoriatic Arthritis Controlled Trial), demonstrated efficacy of infliximab in PsA.[73,74] The trial included 102 patients with PsA, seronegative for rheumatoid factor, with at least five tender and five swollen joints and either an elevated acute phase reactant (ESR or CRP) or morning stiffness of more than 45 minutes. Patients were randomised to infliximab 5 mg/kg/infusion (51 patients) or placebo (51 patients) for four infusions, followed by an open-label trial of infliximab every 8 weeks to 12 months. Patients were allowed to stay on their baseline DMARD. The primary outcome of the randomised, double-blind portion of the study was the ACR20, which was achieved by 69% of the infliximab-treated patients and only 8% of the placebo-treated patients ($p < 0.0001$) at 16 weeks. Secondary outcome measures included the ACR50 achieved by 49% and ACR70 achieved by 29% of infliximab-treated patients compared with none of the placebo recipients and the PsARC achieved by 76.5% of the infliximab-treated patients and 18% of those receiving placebo ($p < 0.0001$). Skin responses were measured in 21 patients randomised to infliximab and 18 randomised to placebo who had a baseline PASI score >2.5. The average improvement in PASI was 80.7% in the infliximab recipients, compared with worsening by 35% in the placebo recipients. Sixty-seven percent of infliximab-treated patients and none of the placebo recipients achieved a >75% improvement in PASI score. Two of the patients randomised to infliximab discontinued the drug because of infection. The 1-year results of the IMPACT based on 88 patients revealed that among patients initially randomised to infliximab the ACR20, 50 and 70 were 72%, 54% and 35%, respectively, while among patients initially randomised to placebo the ACR20, 50 and 70 responses were achieved by 77%, 49% and 30%, respectively. Skin improvement was maintained among patients initially treated with infliximab and improved significantly among those initially treated with placebo. Seven of the original 102 patients discontinued infliximab because of adverse events including infusion reactions, joint infection, tendon rupture, elevated liver function tests, asthma attack and meningioma. Six patients discontinued because of lack of efficacy. This study clearly demonstrated the efficacy of infliximab in PsA for both joint and skin manifestations. The study further demonstrates that infliximab is effective regardless of DMARD use by the patient prior to its initiation. Assessment of radiographs obtained in these patients before and after therapy is currently under way.

The results of a second multinational trial (IMPACT 2) were presented at the recent meeting of the EULAR.[75] This study revealed an impressive ACR20 response of 58% in the infliximab-treated patients compared with only 11% in the placebo recipients with 63% of the infliximab-treated pa-

tients achieving PASI75 response compared with 2% of placebo-treated patients at 14 weeks. The response was sustained at 24 weeks. Dactylitis and enthesitis improved as well. The drug was well tolerated.

Information derived from clinical experience in patients not responsive to several DMARDs suggests that while the drug may be effective, there are significant adverse effects that must be anticipated as this medication becomes more widely used.[91] One problem with infliximab is the potential for the development of human anti-chimeric antibodies (HACA), which may develop in the course of therapy and may lead to loss of effect, or may develop rapidly in patients treated with the drug who discontinued medication and restart after a period of time.

Onercept

Onercept is a recombinant, unmodified, fully human soluble type I TNF receptor (p55), which acts as an anti-TNF agent.

In a multicentre, double-blind, placebo-controlled study of onercept in PsA, doses of 50 and 100mg were given subcutaneously three times a week for a period of 12 weeks.[92] The study included 126 patients divided between placebo (n = 42), onercept 50mg three times a week (n = 42) and onercept 100mg three times a week (n = 42). At baseline, patients were required to have a PASI of ≥8, a body surface involvement of ≥5%, and at least three actively inflamed joints. The primary articular endpoint was the percentage of patients achieving a PsARC response at the end of the 12-week treatment period. After 12 weeks of treatment at 100mg, 86% (36 of 42) of patients on onercept met the PsARC primary endpoint compared with 45% (19 of 42) taking placebo ($p < 0.001$). The secondary endpoint of ACR20 was achieved by 67% (28 of 42) of onercept-treated patients compared with 31% (13 of 42) taking placebo ($p = 0.001$). Adverse effects for onercept-treated patients were similar to those observed in the placebo group. Injection site reactions were more frequent in the onercept groups. Onercept was generally well tolerated. The most common adverse events (occurring in >5% of patients) in patients receiving onercept were comparable to those observed in the placebo group. Injection site reactions were more frequent in the onercept-treated group. Two serious adverse events (hypokalaemia and angle closure glaucoma) were reported at the 50mg dose. Rate of infections was similar between the placebo and onercept groups. The 100mg dose of onercept was more effective than the 50mg dose. However, the placebo response in this trial was higher than that noted in studies with etanercept. Moreover, the need to have three injections a week makes this molecule less attractive to patients.

The manufacturer of onercept recently announced the discontinuation of two phase III clinical trial programmes following recommendations from two separate, independent data and safety monitoring boards. Investigators had recently reported that two patients in a clinical trial of onercept in the treatment of moderate-to-severe psoriasis, were diagnosed with sepsis, one of whom subsequently died. Although sepsis is a recognised potential risk for patients being treated with anti-TNF therapies, the manufacturer decided that the overall risk/benefit profile did not warrant continuation of the study.[92,93]

Adalimumab

Adalimumab is a humanised anti-TNFα antibody, which has now been approved for the treatment of rheumatoid arthritis.[94] In addition to being fully humanised, thus presumably avoiding the development of HACA, adalimumab has the advantage of being administered subcutaneously at 2-weekly intervals. A preliminary study of adalimumab showing its efficacy in psoriatic arthritis was presented at the EULAR meeting in Berlin.[95] The positive effect of adalimumab on skin psoriasis has also been demonstrated.[96] The results of a phase III multicentre, randomised, double-blind controlled trial of adalimumab in 313 patients with PsA were presented at the ACR meeting in October 2004. Of the 315 patients, 151 were randomised to adalimumab 40mg every other week for 24 weeks and 162 to placebo for the same period. The ACR20 response was the primary outcome and was achieved by 57% of the adalimumab-treated patients

but only 15% of the placebo recipients. ACR50 and 70 responses were achieved by 39% and 23% of adalimumab-treated patients and 6% and 1% of the placebo group, respectively. Sixty-nine patients with >3% body surface area affected by psoriasis were evaluated for the effect of the drug on the skin. PASI50 was achieved by 75%, PASI75 by 59% and PASI90 by 42% of the adalimumab-treated patients, whereas in the placebo group the results were 12%, 1% and 0% for the PASI50, 75 and 90, respectively. The safety profile was similar to that seen in rheumatoid arthritis trials.[76]

2.4.4 T-Cell-Directed Agents

T-cell activation is dependent on two events: one is antigen presentation by antigen-presenting cells through a major histocompatibility complex molecule to the T-cell receptor; the other is receptor ligand binding to form an immunological synapse.[97] Receptor ligand binding provides attachment of the antigen-presenting cell to the T cell, such as the interaction between the cell surface glycoprotein lymphocyte function-associated antigen 1 (LFA-1) and its ligand intercellular adhesion molecule-1 (ICAM-1). LFA-1/ICAM-1 interactions are a prerequisite for full T-cell activation and promote migration of inflammatory cells into the epidermis. This has led to the hypothesis that the LFA-1/ICAM-1 pathway is an attractive target for immunosuppression in diseases of unknown antigen origin such as psoriasis.[98] Other receptor ligand binding leads to T-cell activation, such as the binding of the LFA-3 to the CD2 receptor on T cells. These have provided targets for therapeutic interventions in psoriasis and more recently in PsA.

Efalizumab

LFA-1 consists of an α subunit (CD11a) and a β subunit (CD18), and is expressed on various cell types including lymphocytes. Efalizumab is a humanised monoclonal IgG1 antibody against CD11a. By binding to CD11a and inhibiting LFA-1/ICAM-1 interactions, efalizumab inhibits binding of T cells to vascular endothelial cells, inhibits T-cell trafficking into the dermis and prevents activation of T cells. The net effect is to reduce the release of inflammatory cytokines in the skin, resulting in improvement of psoriasis. Efalizumab has been proven effective in psoriasis.[99,100] Preliminary results from a phase II multicentre, randomised controlled trial of efalizumab in 107 patients were recently reported.[101] After 12 weeks of treatment 28% of the efalizumab-treated patients achieved an ACR20 (primary endpoint) response compared with 19% of the placebo recipients. It was noted that PsA was not worsened by the treatment and the psoriasis improved as seen in previous trials in psoriasis patients.

Alefacept

Alefacept is a fully human fusion protein consisting of the first extracellular domain of LFA-3 fused to the hinge segment and constant regions of IgG1. The LFA-3 portion of alefacept binds to the CD2 receptor on T cells, blocking their natural interaction with LFA-3 on antigen-presenting cells and thereby inhibiting the antigen-dependent activation of T cells. The IgG1 domain interacts with Fc γ receptor type III on accessory cells (e.g. macrophages and natural killer cells) to induce apoptosis. Because CD2 expression is higher on memory T cells than on naive (CD45RA+) T cells, alefacept produces selective apoptosis of the memory T cells.[102,103]

A multicentre, randomised, placebo-controlled trial was carried out in 229 patients with severe psoriasis.[104] Participants were randomly assigned to receive alefacept at a dose of 0.025, 0.075 or 0.150 mg/kg or placebo (normal saline) administered as an intravenous 30-second injection once a week for 12 weeks. A significantly higher number of alefacept-treated patients demonstrated improvement in PASI scores at 12 weeks and the improvement was maintained for a further 12 weeks. The medication was well tolerated. An open-label trial of 11 patients treated with alefacept 7.5mg intravenously once a week for 12 weeks revealed a response in 55% of the patients according to the DAS used for the assessment of rheumatoid arthritis.[102] This measure has not been validated for PsA. Nonetheless, there was a reduction in CD4+ lymphocytes, CD8+ lymphocytes and CD68+ macrophages in the synovial tissue after 12 weeks of treatment. Importantly, patients who demonstrated a DAS response

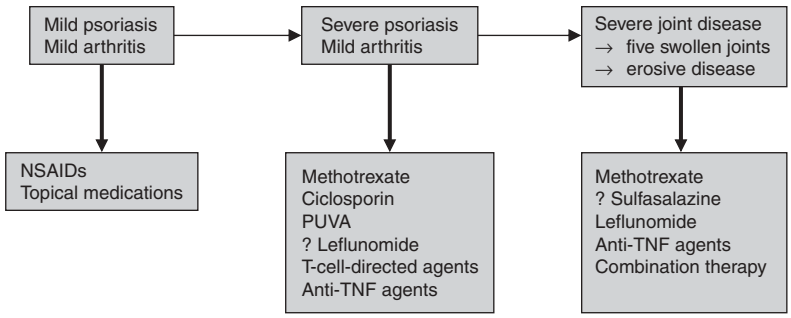

Fig. 1. Approach to the management of psoriatic arthritis based on current evidence. If it becomes clear that anti-tumour necrosis factor (TNF) agents are indeed disease modifiers, they should be used earlier in patients with severe psoriatic arthritis and psoriasis. **PUVA** = psoralen + UVA; **?** indicates consider.

had a higher number of CD45RO+ cells at baseline and demonstrated a significant reduction in those cells following treatment. This agent is currently under investigation in a large multicentre trial in PsA.

2.5 Other Potential New Drugs for PsA

While several other T-cell-directed therapies have been developed, such as CTLA4Ig and anti-CD40 ligand, to date these have not been carried through clinical trials in PsA.

3. How Do We Treat Patients with PsA Today?

Patients with mild arthritis and mild psoriasis should continue to be treated with NSAIDs and topical medications for the skin. Patients whose arthritis is severe, either in terms of the number of joints involved (e.g. more than five swollen joints) require DMARDs (figure 1). At present methotrexate remains the standard of care in most centres, this despite the lack of clear evidence for its efficacy or disease-modifying effect. However, if methotrexate is not tolerated, or if a dose of 25mg parenterally does not lead to a reduction in actively inflamed joint count, another medication should be considered within 3 months. Sulfasalazine up to 4 g/day may be tried for a period of 2–3 months, provided there is no history of allergy to sulfa drugs; it has been used with some success, although as pointed out in section 2.2.4, the evidence for its efficacy from clinical trials is minimal. Leflunomide should also be tried at 20 mg/day. If there is no response within 3 months to these medications an anti-TNF agent should be instituted. Whether anti-TNF agents are more effective than other drugs in early disease has yet to be determined. If indeed these medications are found to prevent progression of damage, they should become the first line of treatment in psoriatic arthritis and should be used early in the course of the disease.

4. Conclusion

PsA is a destructive form of inflammatory arthritis that occurs in about one-third of patients with psoriasis. Traditional medications have not been successful in controlling the disease and preventing joint damage. Understanding the pathogenesis of joint destruction in PsA has led to the use of a number of agents that interfere with the immune response. Recent advances in biological therapies indicate that these may work better than previously available drugs, and may for the first time prevent progression of joint destruction. Further studies are necessary to confirm that these medications are indeed disease modifying. It is also necessary to define guidelines for use of these very expensive medications.

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