

Aman Sharma, Sunil Dogra<sup>1</sup>

## ABSTRACT

Departments of Internal Medicine and <sup>1</sup>Dermatology, Venereology & Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

**Address for correspondence:**  
Dr. Aman Sharma,  
Rheumatology Division,  
Department of Internal  
Medicine, PGIMER,  
Chandigarh, India. E-mail:  
amansharma74@yahoo.com

Psoriatic arthritis (PsA) is a chronic inflammatory disease that can be progressive and may be associated with permanent joint damage and disability. Early identification of PsA will enable these patients with progressive disease to be treated early and aggressively. Due to lack of consistent diagnostic or classification criteria in the past, PsA was considered as uncommon. Overall it affects 6-10% of all psoriasis patients during the course of their disease. Both dermatologists and rheumatologists should be involved in the diagnosis and management of this disorder. Interest in PsA has greatly enhanced over the past several years due to many factors including a better understanding of disease mechanisms, improved investigational tools, better clinical trial design and perhaps most importantly, the availability of newer therapeutic agents. Mild forms of PsA can initially be treated with nonsteroidal antiinflammatory drugs (NSAID). In acute as well as oligo- to polyarticular joint involvement, disease-modifying anti-rheumatic drugs (DMARD) are indicated for PsA. The biologics particularly tumor necrosis factor alpha (TNF- $\alpha$ ) antagonists are gaining increasing significance as second-line therapy. Treatment choice should also take into consideration the extent of skin involvement.

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## INTRODUCTION

The first description of psoriatic arthritis (PsA) was given in the early 19th century but it was identified as a distinct entity by the American Rheumatology Association only in 1964.<sup>[1,2]</sup> The prevalence of arthritis in psoriasis patients has varied widely from 6% to 42%.<sup>[3]</sup> In an Indian study of 530 patients with psoriasis, 48 had arthralgias and 7 had deforming arthritis.<sup>[4]</sup> Five different types of clinical patterns have been described by Moll and Wright.<sup>[5]</sup> These are (a) classical PsA confined to the distal interphalangeal joints (5%), (b) arthritis mutilans (5%), (c) symmetrical polyarthritis resembling rheumatoid arthritis (RA), (d) asymmetrical oligoarthritis (70%) and (e) spondyloarthropathy (15%). In a North Indian study of 20 patients based upon these criteria, four of the five varieties were described and arthritis mutilans was not seen.<sup>[6]</sup> In another study of 116 patients with PsA from south India, symmetrical polyarthritis was the most common subtype seen in almost half of the patients.<sup>[7]</sup> Various other criteria

have also been proposed by Bennett,<sup>[8]</sup> Vasey and Espinoza,<sup>[9]</sup> modified McGonagle criteria,<sup>[10]</sup> modified European spondyloarthropathy criteria<sup>[11]</sup> and Fournie criteria,<sup>[12]</sup> but the classification of psoriatic arthritis (CASPAR) criteria<sup>[13]</sup> is likely to become the standard tool for establishing case definitions for clinical studies. According to the CASPAR criteria, presence of three of the following five features in a patient with inflammatory articular disease (joint, spine or entheses) are required to make a diagnosis of PsA (a) current psoriasis or personal history of psoriasis or family history of psoriasis, (b) psoriatic nail dystrophy including onychomycosis, pitting and hyperkeratosis, (c) a negative test for rheumatoid factor, (d) current or past history of dactylitis and (e) radiological evidence of juxta articular new bone formation.

The predominant clinical manifestations of PsA include peripheral arthritis, axial disease, dactylitis and enthesitis, besides the skin and nail psoriasis.<sup>[14]</sup> Effective drug therapies of PsA are directed towards each of these manifestations. In addition to the drug

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therapy, various non-pharmacological therapeutic interventions like patient education, physical and occupation therapy and interdisciplinary cooperation between the dermatologist, rheumatologist and physical and occupation therapist are very important. Enthesopathy, a major feature of PsA, is often an underdiagnosed entity. Ultrasonography can detect a significantly higher incidence of enthesal abnormalities even in the absence of clinical symptoms of arthropathy.<sup>[15]</sup> The primary focus of various groups studying the role of imaging is on entheses. Magnetic resonance imaging (MRI) and ultrasonography provide evidence of pathological change at the entheses in PsA. The role of newer imaging modalities, such as ultra-short echo time (UTE) MRI, is promising but remains to be fully elucidated.

PsA can produce erosive joint disease and impairment in the quality of life comparable to that produced by RA.<sup>[15,16]</sup> Clinical features that distinguish PsA from RA include distal interphalangeal joint involvement, asymmetrical joint involvement, oligoarticular disease pattern, enthesitis and relative lack of rheumatoid factor positivity.<sup>[17]</sup> Just like in RA, the rapid control of signs and symptoms along with a delay or prevention of radiological joint damage and maintaining good functional capacity is the aim of therapy. It has been shown that early and aggressive control of disease activity in RA leads to good outcome.<sup>[18]</sup> Similar results can be expected from early treatment in patients with moderate to severe PsA. The risk factors for severe disease include polyarticular disease, elevated acute phase reactants, evidence of disability and erosive joint disease, as well as demonstration of lack of response to initial therapeutic agents.<sup>[19]</sup> There is a need for increase in awareness about PsA in patients and dermatologists for an early and accurate diagnosis of PsA. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has developed simple screening tools, which can be used by dermatologists and other clinicians to screen for the presence of PsA in their patient population.<sup>[20]</sup> Ideally, the dermatologist and rheumatologist should work as a team to supervise all aspects of the patient's disease.

The type of therapy employed for PsA depends upon the severity of joint involvement at the time of presentation. Mild joint inflammation may be controlled using nonsteroidal anti-inflammatory drugs (NSAIDs). Severe cases of PsA that present with polyarticular joint involvement or destructive progression require early administration of many

of the traditional disease modifying antirheumatic drugs (DMARDs). Newer biologic agents have shown promise in treating PsA refractory to the traditional drug therapies. Long-term, perhaps lifelong, treatment with the DMARDs is required in patients with active disease.

## TRADITIONAL THERAPY

Traditional treatment of PsA includes NSAIDs and traditional DMARDs. NSAIDs may produce some symptomatic relief but do not have any effect on the progression of joint disease and some of the NSAIDs can worsen the skin disease.<sup>[21]</sup> The choice of NSAIDs depends upon the efficacy, safety, convenience and cost. COX inhibitors should be avoided in patients with risk factors for coronary artery disease. Routine co-prescription of antacids is not required unless there are risk factors for NSAID-induced gastrointestinal (GI) events like age more than 65 years, history of peptic ulcer disease or bleeding from the GI tract, concomitant use of corticosteroids (CS). Traditional DMARD therapies have not been studied very extensively. The data are derived from small, poorly controlled trials which did not use any validated outcome measures.<sup>[22]</sup>

### Corticosteroids

Low dose CS therapy has been shown to slow the radiological progression in RA but such studies have not been done in PsA.<sup>[23]</sup> Intraarticular CS can be given in oligoarticular disease or polyarticular disease with one or two active joints. CS should be used very judiciously because of the risk of flare up of pustular psoriasis on stopping them.

### Sulphasalazine

Sulfasalazine (SSZ) is used to treat inflammatory bowel disease and RA. The exact mechanism of action of sulfasalazine is unknown, though it is thought to function as an anti-inflammatory agent. The efficacy of SSZ in PsA has been evaluated in a number of studies. In a large placebo-controlled study of 221 patients with active disease, there was a significant improvement in the PsA response criteria (PsARC) but there was no significant improvement in the secondary outcome measures and lab parameters. These included enthesitis, dactylitis and spondylitis.<sup>[24]</sup> The PsARC took into account the number of swollen and tender joints and patients' and physicians' global assessment. No useful conclusion could be drawn from other studies comprising of small number of patients. There

have been high drop-out rates and the most commonly reported side effects are rash and GI intolerance. The benefit of SSZ is usually confined to peripheral disease with no significant effect on axial disease. It is usually started at a low dose of 500 mg twice a day and the dose is increased weekly by 500 mg. The usual adult dose is 2–3 g/day.

### **Methotrexate**

The first randomized controlled trial (RCT) showing the efficacy of methotrexate (MTX) in PsA was published in 1964.<sup>[25]</sup> The other RCT published was not powered and used only low dose MTX. Few uncontrolled case series have demonstrated its efficacy in PsA.<sup>[26,27]</sup>

MTX is generally given as a single weekly dose. It is usually started at a low dose of 7.5 mg/week and is gradually increased to 20 and 25 mg/week. In a Cochrane review published in 1999 on the efficacy of SSZ, auranofin, etretinate, fumaric acid, intramuscular gold, azathioprine and MTX in PsA, it was concluded that parenteral high dose MTX and SSZ are the only two agents with well-demonstrated efficacy in PsA.<sup>[28]</sup>

All dosing schedules are adjusted according to the individual patient to achieve maximum disease control and to minimize the side effects. Folic acid should be supplemented to decrease the MTX toxicity. The usual dose of folic acid is 1–5 mg/day except on the day of administering MTX.<sup>[29]</sup>

Minor toxicities of MTX include nausea, anorexia, stomatitis, and fatigue. The major toxicities are myelosuppression, hepatotoxicity, and pulmonary fibrosis. MTX is teratogenic and should be stopped by both male and female patients, 3 months prior to conception. The risk factors for hepatotoxicity are history of or current greater than moderate alcohol consumption, persistent abnormal liver chemistry study findings, history of liver disease including chronic hepatitis B or C, family history of inheritable liver disease, diabetes mellitus, obesity, history of significant exposure to hepatotoxic drugs and hyperlipidemia.<sup>[30]</sup> MTX toxicity in psoriatic disease has been the focus of discussion and debate. In a study aimed to assess the prevalence of hepatic fibrosis in both psoriasis and PsA patients on long-term MTX therapy, a prospective study of 54 patients showed that despite other risk factors for NASH (Non alcoholic steatohepatitis), monitoring for hepatic fibrosis using serial liver function and American

college of rheumatology (ACR) guidelines tests alone as in RA appeared safe in psoriasis and PsA. Liver biopsy should be considered to assess the liver if liver function tests (LFT) are persistently elevated.<sup>[31]</sup>

In an Indian study of 33 patients of PsA treated with MTX, 39.5% had complete remission, 54.5% had partial remission and 6% had no response according to the American rheumatism association (ARA) criteria. The mean dose of MTX was 7.8 mg/week.<sup>[32]</sup> No significant side effects requiring discontinuation of therapy was seen.

### **Cyclosporine A**

It acts by inhibiting the first phase of T-cell activation. It has been shown to be very effective for skin involvement by the disease but its role in the treatment of PsA has not been evaluated extensively barring a few open label studies.<sup>[33]</sup> The initial daily dose of cyclosporine A (CSA) is 2.5–3 mg/kg in divided doses.<sup>[29]</sup> The main side effects of cyclosporine are nephrotoxicity and hypertension. There is an increased risk of developing cutaneous squamous cell carcinomas especially in patients with more than 200 psoralen with ultraviolet A (PUVA) treatments.<sup>[34]</sup> Combination therapy with MTX in patients with disease refractory to MTX monotherapy was shown to produce improvement in psoriasis area and severity score (PASI) and synovial ultrasound score.<sup>[35]</sup> It can also cause side effects like hypertrichosis, headache, pseudotumor cerebri and gingival hypertrophy.

### **Leflunomide**

Leflunomide is a pyrimidine antagonist. Its efficacy in PsA was studied in 188 patients. At a dose of 20 mg/day, the PsARC response was achieved in 59% of leflunomide-treated patients compared with 29.7% of placebo-treated patients.<sup>[36]</sup> The usual adult dose is 100 mg/day for 3 days, followed by 20 mg/day.

The main side effects are GI irritation (diarrhea, nausea, dyspepsia), but also include elevated liver enzymes, leukopenia, drug eruption, headache, increased risk of infections.<sup>[37]</sup> It is a highly teratogenic drug and is contraindicated in pregnancy and women of childbearing potential not using reliable contraceptive methods. Women should not become pregnant for 2 years after the cessation of therapy or should undergo a rapid wash-out procedure with cholestyramine. Men wishing to father a child should discontinue leflunomide and should also undergo the wash-out procedure.

Retinoic acid derivatives and PUVA are effective in severe skin disease. In a study of PUVA in 27 patients with PsA, published in 1979, it was shown that aggressive therapy can improve PsA in a subgroup of patients with nonspondylitic disease.<sup>[38]</sup>

The other DMARDs used in the management of PsA include mycophenolate mofetil,<sup>[39]</sup> azathioprine,<sup>[40]</sup> antimalarials,<sup>[41]</sup> gold,<sup>[42,43]</sup> and penicillamine. There is concern regarding the flare up of psoriasis with antimalarials but it has not been demonstrated in large studies. The dosing schedule, side effects and the monitoring required during use of these drugs are given in Table 1.

## BIOLOGIC THERAPIES

The biologics currently approved for the treatment of PsA are antitumor necrosis factor-alpha (anti-TNF- $\alpha$ ) compounds, etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira). Etanercept and infliximab are available in India. Recent trials with the T-cell modulating agents, alefacept and efalizumab, have been completed. A pilot study with abatacept in PsA is also being completed.

### Etanercept

It is a recombinant human soluble TNF- $\alpha$  receptor antagonists given in a dose of 50 mg/week as 25 mg twice a week. In the placebo-controlled etanercept trial in PsA, ACR 20 response was achieved by 59% in the etanercept group versus 15% in the placebo group.<sup>[44]</sup> A recent study compared the effect of etanercept given 50 mg twice weekly for 12 weeks, followed by 50 mg weekly, with that of a dosage of 50 mg weekly in 752 patients. A composite joint score, the PsARC, showed similar improvement in both the groups.<sup>[45]</sup>

### Infliximab

It is a chimeric monoclonal anti-TNF- $\alpha$  antibody approved for the treatment of PsA. A phase 3 study of infliximab in 200 PsA patients (IMPACT II) showed significant benefit.<sup>[46]</sup> Dactylitis and enthesitis decreased significantly and there was an inhibition of radiological disease progression at 24 weeks in the infliximab group.<sup>[47]</sup> Infliximab is given at a dose of 3 mg/kg as an infusion over 2 hours on 0, 2, and 6 weeks, and then every 2 months.

### Adalimumab

This is a fully human anti-TNF- $\alpha$  monoclonal antibody administered subcutaneously, 40 mg, every other week or weekly. New anti-TNF- $\alpha$  agents being developed for use in PsA are certolizumab pegol and golimumab.

### Other biologic agents

Alefacept is a fully human fusion protein that blocks the interaction between leukocyte function-associated antigen (LFA)-3 on the antigen-presenting cell and CD2 on the T cell, or by attracting natural killer lymphocytes to interact with CD2 cell to yield apoptosis of the particular T cell clones.<sup>[48]</sup> A phase 2 controlled trial of alefacept in PsA showed that 54% of patients in alefacept and MTX combination group had an ACR 20 response as compared to 23% in the MTX alone group.<sup>[49]</sup>

Efalizumab is a humanized monoclonal antibody to the CD11 subunit of LFA-1 on T cells. Abatacept (CTLA4-Ig) is a recombinant human fusion protein that binds to the CD80/86 receptor on an antigen presenting cell, blocking the second signal activation of the CD28 receptor on the T cell. Ustekinumab, an IL12/23 inhibitor, has also shown efficacy in a preliminary study in PsA.<sup>[50]</sup>

**Table 1: Dosing schedule, monitoring and side effects of disease modifying drugs**

Drug	Dose	Monitoring	Side effects/comments
MTX	7.5–25 mg/week	CBC, LFT at baseline and every 4 weeks initially for 3 months, then every 8 weeks	Nausea, fatigue, mouth ulcers, elevated LFTs
SSZ	2–3 g/day	CBC every 2–4 weeks, LFT 6 weekly for 3 months and then every 3 months	Azoospermia
Leflunomide	100 mg/day for 3 days, then 10–20 mg/day	CBC after 2 weeks and then after every 8 weeks	Should not be used in young females of child bearing age
Hydroxychloroquine	200–400 mg/day	Eye examination every 12 months	
Cyclosporine A	2.5–3 mg/kg/day	Serum creatinine and BP every fortnightly till dose is stable and then monthly; CBC and LFT monthly till dose is stable and then every 3 months, serum lipids every 6 months	BP should be normal before starting; in the case of rise in creatinine by 30%, BP, hyperkalemia or significant rise in lipids, withhold the drug

CBC: Complete blood counts, LFT: Liver function tests, BP: Blood pressure, MTX: methotrexate, SSZ: sulfasalazine

Anakinra, an IL 1 inhibitor, has not shown significant effect.<sup>[51]</sup> B cell depletion therapy with Rituximab is being evaluated in PsA. If approved for use in PsA, it would have the advantage of no risk of tuberculosis (TB) in endemic countries. Tocilizumab, a monoclonal antibody to IL6, has also shown benefit in PsA.<sup>[52]</sup>

The mechanism of action, dosing schedule and major risks with the biologic therapies are given in Table 2.

### Investigations before starting tumor necrosis factor alpha inhibitors

Indian rheumatology association guidelines for the management of RA in adults recommend hemogram, biochemistry to include liver and renal function tests, hepatitis B and C serology, routine urine microscopy, chest X-ray and Mantoux test before starting TNF- $\alpha$  inhibitors. It is recommended that all the patients must be screened for active/latent TB. The issue of prophylaxis for TB is controversial and it has been suggested that all patients with positive Mantoux test, past history of TB or abnormal Chest X-Ray suggestive of TB should receive prophylactic anti-TB therapy. All the patients commenced on anti-TNF- $\alpha$  therapies need to be closely monitored for TB. This needs to be continued for 6 months after discontinuing infliximab treatment due to the prolonged elimination phase of infliximab. Patients on anti-TNF- $\alpha$  therapy who develop symptoms suggestive of TB should receive full anti-TB chemotherapy, and discontinue anti-TNF- $\alpha$  therapy.<sup>[53]</sup> The following observations have also been made regarding the use of anti-TNF- $\alpha$  therapy in RA:<sup>[53]</sup>

1. There is no evidence to suggest that one type of anti-TNF- $\alpha$  therapy is more efficacious than the others.
2. Infliximab can be useful when etanercept has failed and vice versa. There is also evidence for adalimumab substitution.  
MTX has to be co-administered with infliximab. Although it is not necessary to co-prescribe MTX with etanercept, in patients with inadequate response to etanercept, the addition of MTX is a

useful option and vice versa.

3. Treatment with TNF- $\alpha$  inhibitors may be withheld for 2–4 weeks prior to major surgery and restarted post operatively.
4. If live vaccines are required, they should ideally be given 4 weeks prior to commencing treatment or 6 months after the last infusion of infliximab (or potentially earlier if risks from not vaccinating are high) or 2–3 weeks after the last dose of etanercept.

There is very limited reported experience of using anti-TNF- $\alpha$  agents in RA from India.<sup>[54]</sup> The reported risk of TB in a small study of 14 patients of spondyloarthropathy treated with anti-TNF- $\alpha$  agents in India was 21%.<sup>[55]</sup>

Special precautions have to be taken while using the DMARDs and biologic therapy in the presence of renal failure, liver disease, cardiovascular disease, history of demyelinating disease, pregnancy and lactation.

### SURGERY

Synovectomy may be considered in a patient with refractory arthritis involving a single joint. Joint replacement can be considered in patients with severe involvement of hip or knee joints.

### CONCLUSION

In conclusion, broad management of PsA is similar to RA. SSZ should be preferred in patients with mild disease. MTX should be the drug of choice in patients with moderate to severe disease. Cyclosporine should be used in refractory disease. TNF blockers should also be considered in patients with refractory disease.

Finally, patient education, early diagnosis, institution of early appropriate therapy, physiotherapy and rehabilitation therapy backed by surgical intervention for permanently damaged joints are the cornerstones for satisfactory treatment outcomes.

**Table 2: Mechanism of action, dosing schedule and major risks with the biologic therapies**

Agent	Action	Dose	Route	Risks/significant side effect
Infliximab (Remicade)	Anti-TNF- $\alpha$	5 mg/kg at 0, 2, 8 weeks and then 8 weekly	Intravenous	Infections especially TB
Etanercept (Enbrel)	Anti-TNF- $\alpha$	25 mg biweekly or 50 mg weekly	Subcutaneous	Infections especially TB
Adalimumab (Humira)	Anti-TNF- $\alpha$	40 mg once every 2 weeks	Subcutaneous	Infections especially TB
Rituximab (Mabthera)	Anti-CD 20, B cell depletion	1000 mg at 0, 2 weeks; can be repeated after 6 months	Intravenous	Infusion reactions

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