Review Article

Psoriatic Arthritis A Systematic Review

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Abstract: Psoriatic arthritis is an inflammatory disorder of unknown etiology generally with negative rheumatoid factor and associated with patients having psoriasis. The prevalence of uncomplicated psoriasis is between 1-3% in the general population. Arthritis is found in increased frequency in psoriatic patients and its incidence is estimated to be 5-7%. In severe psoriasis, arthritis can occur in up to 30-40% of the patients and can go on to develop usually within 6- 10 years of cutaneous onset of disease. Dermatologist are in a better position to detect psoriatic arthritis earlier once the skin lesions are found through regular screening and proper follow-up. The clinical course of peripheral and axial psoriatic arthritis is usually less severe than rheumatoid arthritis and Ankylosing spondylitis, respectively. There are five recognized presentations of psoriatic arthritis Asymmetric arthritis, Symmetric arthritis, Arthritis mutilans, Ankylosing spondylitis, Special form. Here we review the literature to identify the clinical types and genetic factors most highly associated with development of psoriatic arthritis, with the goal of assisting dermatologists in risk-stratifying their psoriasis patients. Local corticosteroid injections and non-steroidal anti-inflammatory drugs are recommended in milder forms. Sulphasalazine and methotrexate are effective in peripheral psoriatic arthritis. Recent studies have provided evidence on the efficacy of anti-tumor necrosis factor-α drugs to control symptoms and to slow or arrest radiological disease progression.

Keywords: psoriatic arthritis, joint damage, genetic factors, clinical factors, methotrexate

INTRODUCTION

The recognition of psoriatic arthropathy (PsA) as a separate entity is a relatively recent occurrence. However, Jean Louis Alibert, a French physician, described an association between psoriasis and arthritis in 1818[1] and Earnest Bazin and Charles Bourdillon conducted further studies on this condition.[2] In 1973, Moll and Wright identified and related clinical aspects which affected both the joints and the skin, defining PsA as an inflammatory arthritis, generally with a negative rheumatoid factor and associated with psoriasis.[2] The true prevalence of psoriasis and PsA is not known with certainty, partly because of the elusive nature of the psoriatic skin lesion. The prevalence of uncomplicated psoriasis is between 1-3% in the general population. Arthritis is found in increased frequency in psoriatic patients and its incidence is estimated to be 5-7%. In severe psoriasis, arthritis can occur in up to 30-40% of the patients [3, 4].

EPIDEMIOLOGY

Psoriatic arthritis has a prevalence of 0.1%, about half that of rheumatoid arthritis. Somewhere between 5 and 30% of psoriasis patients have arthritis. The disease can start at any age but usually appears in individuals between the ages of 35 and 45 years, about 10 years later than psoriasis. In monozygotic twins, there is 30-40% concordance. [5].

HERITABILITY OF PSORIASIS AND PSORIATIC ARTHRITIS

Family and twin studies have clearly demonstrated that psoriasis has a strong genetic basis. Two large-scale epidemiological studies revealed a substantially higher incidence of psoriasis in relatives of patients with psoriasis compared to the general population. The recurrence risk for affected siblings (λ_s) was estimated to be between 4 and 10. Twin studies reveal a concordance rate for monozygotic twins to be between 62 and 70% compared to 21-23% for dizygotic twins. A polygenic or a multifactorial pattern is the most likely mode of inheritance. The recurrence risk

ratio for PsA is substantially higher than that for psoriasis. In the first study published in 1973, the prevalence of PsA among first-degree relatives of probands with PsA was found to be 5.5% compared to the calculated prevalence in the UK population of 0.1%. The recurrence risk ratio for first-degree relatives (λ_1) was 55, according to Risch's method. In more recent studies, the λ_1 for PsA was 30.4 and that for psoriasis was 7.6. Strong heritability was also demonstrated in a recent study from Iceland. The only twin study in PsA to date confirmed that genes are important for psoriasis but did not have the power to detect a genetic effect in PsA. Thus, both psoriasis and PsA have a strong genetic component, and studies to unravel the genes underlying susceptibility are worthwhile [6].

ETIOLOGY AND PATHOGENESIS

The source of connection between the skin and the joints in psoriasis remain elusive. The most clearly associated genes are at 6p and 16q. HLA - B27 is more common; 20% of patients carry this allele and the percentage is significantly higher in those with involvement of the axial skeleton. There is a cellular immune response, with activated CD8+ T cells playing a central role. There may be an auto antigen involved, likely one that is expressed on the synovia since the initial changes are a hyperplastic swelling and proliferation of the synovia coupled with bony changes (psoriatic arthropathy). There are numerous macrophages in the affected tissue; these release TNF alpha and other mediators as well as free radicals. There is also evidence of angiogenesis. As a result, there is remodeling of bone and cartilage (typical radiological signs of bone formation and destruction simultaneously). In addition to the bones and cartilage, the tendons and ligaments are often affected (enthesopathy) [5].

Clinical findings:

Almost all patients (67-90%) with psoriatic arthritis have nail changes. It is most unusual to see an affected finger with swelling and destruction but without psoriatic nail lesions. About 60% of patients already have signs of psoriasis; in perhaps 20% the two appear simultaneously while another 20% present with joint pain and have no confirmatory skin findings. A number of types of psoriatic arthritis can be identified, incorporating clinical, serologic and radiologic parameters. Common features include digital involvement, sacroiliac disease, and pain in areas of tendon insertions. In addition the rheumatoid factor should be negative. Striking differences in the clinical patterns of psoriasis occur [5].

There are five recognized presentations of psoriatic arthritis [7]. Asymmetric arthritis. The most common pattern is an asymmetric arthritis involving one or more joints of the fingers and toes. Usually one or more proximal interphalyngeal (PIP), distal interphalyngeal (DIP), Meta tarsophalangeal, or metacarpophalangeal joints are involved. During the acute phase, the joint is red, warm, and painful. Continued inflammation promotes soft tissue swelling on either side of the joint ("sausage finger") and restricts mobility.

Symmetric arthritis:

A symmetric polyarthritis resembling rheumatoid arthritis occurs, but the rheumatoid factor is negative. The small joints of the hands and feet, wrists, ankles, knees, and elbows may be involved.

Distal inter phalangeal joint disease:

Perhaps the most characteristic presentation of arthritis with psoriasis is the involvement of the DIP joints of the hands and feet with associated psoriatic nail disease. The disease is chronic but mild, is not disabling, and is responsible for approximately 5% of cases of psoriatic arthritis.

Arthritis mutilans:

The most severe form of psoriatic arthritis involves osteolysis of any of the small bones of the hands and feet. Gross deformity and subluxation are attributed to this condition. Severe osteolysis leads to digital telescoping, producing the "opera glass" deformity. This deformity may be seen in rheumatoid arthritis.

Ankylosing spondylitis:

This condition occurs as an isolated phenomenon or in association with peripheral joint disease. The association of HLA-B27 and spondylitis is well known.

Special form:

There are many even more unusual variants of psoriatic arthritis with considerable overlap between the entities. SAPHO syndrome (synovitis, acne conglobata, palmoplantar pustulosis, hyperostosis and osteitis). These patients have sterno clavicular joint disease and usually either severe acne or palmoplantar pustulosis. Chronic recurrent multi-focal osteomyelitis (CRMO): Association of palmoplantar pustulosis, multi focal non infectious osteomyelitis, and often, inflammatory bowel disease.

Pustur Arthrosteitis:

This rare disorder was first identified in Asians. Patients typically have palmoplantar pustular psoriasis associated with inflammation of the sterno clavicular joints or the other joints of the sternum. The sternal region is tender and the swollen joints show erosions on radiological examination. Occasionally, an osteomyelitis develops. Alkaline phosphatase levels

maybe elevated along with the ESR and neutrophil count.

Psoriatic onycho pachydermo periosteitis (POPP):

POPP describes patients with nail onycholysis, painful soft tissue swelling of the digits, and periosteal inflammation and thickening of bone (ivory fingers) without joint involvement [5].

Diagnosis of PsA

The presence of inflammatory arthritis in a patient with past or current psoriasis is the basis of diagnosis of PsA. However, in about 10% to 20% of patients, there is no history of obvious skin involvement by psoriasis. In these patients, one should search diligently for psoriasis at hidden sites such as the natal cleft, behind the ear, in the umbilicus, and on the scalp, and for nail changes like nail pitting, onycholysis and total nail dystrophy.

Various diagnostic criteria have been proposed for PsA including the widely used Moll and Wright criteria. This criteria necessitates the presence of:

1. Psoriasis vulgaris
2. A negative serology for rheumatoid arthritis (RA)
3. Clinical features suggestive of inflammatory arthritis in one or more of the following patterns:
   a. Distal interphalyngeal joint disease
   b. Asymmetric, oligoarticular (< 5 joints involved)
   c. Symmetric, polyarticular "rheumatoid arthritis-like",
   d. Mainly spondylitic (axial involvement)
   e. Destructive arthritis (arthritis mutilans)
4. Several other diagnostic criteria have been proposed, including those by Bennett, Vasey and Espinoza, McGonagle (Modified criteria), Fournie and the European Spondyloarthropathy Study Group (Modified criteria). The classification criteria for psoriatic arthritis (CASPAR) have been recently described. The CASPAR group has also developed a simpler classification of PsA, into axial or peripheral disease [8].

DIFFERENTIAL DIAGNOSIS

PsA needs to be distinguished from other common forms of arthritis, viz. rheumatoid arthritis, osteoarthritis, connective tissue disease, infective, and gouty arthritis. Oligoarticular disease, asymmetry, distal interphalangeal joint involvement, enthesitis, and negative serology are typical of PsA. Those with rheumatoid arthritis may have, in addition, rheumatoid nodules and extra-articular signs without enthesitis and

central axial involvement. Osteoarthritis mainly involves the knee and hip joints, occurring with "wear and tear" of the joints. Lupus arthritis, occurring in patients of systemic lupus erythematosus, affects the wrists, hands, and knees. Anti-nuclear antibody (ANA) and dsDNA may be positive. An acutely swollen, painful joint swelling may be seen in infective/septic arthritis or gouty arthritis. Culture of the joint fluid will reveal the causative organism. A negative culture should alert to the possibility of gouty arthritis. Elevated serum uric acid level helps to confirm the diagnosis. Gouty arthritis is usually monoarticular, commonly involving meta tarsophalangeal joint. A radiograph of the affected joint shows lytic areas with sclerotic margins described as "rat bite" lesions [8].

INVESTIGATIONS

The following hematologic, serologic, and imaging studies, although not specifically diagnostic, can be supportive.

1. The erythrocyte sedimentation rate and C-reactive protein may be raised, but this is not specific.
2. Rheumatoid factor test should be performed. Although, a negative serology can rule out rheumatoid arthritis, about 25% of PsA patients of the rheumatoid type may have a positive or equivocal test result.
3. HLA-B27, though not specific, is strongly supportive of axial disease.
4. X-rays of the hands and feet may be needed. Early changes may be limited to peri-articular soft tissue swelling and joint erosions similar to rheumatoid arthritis. Sites of entheseal attachments may show periostitis and new bone formation. Advanced cases, especially of the mutilating variety, may show widespread joint destruction, with "penciling" or narrowing of the heads of the metacarpals and metatarsals. Destruction of the central portion of the articular surface gives the "pencil-in-cup" appearance. With the destruction of the interphalangeal joints, especially the distal ones, bony ankylosis can occur.
5. The sacroiliac changes in PsA are similar to those in ankylosing spondylitis, but with the ossification of the paravertebral tissues in the thoracic and lumbar area occurring more laterally.
6. Ultrasound and MRI are more effective for the detection of enthesitis.
7. Lipid profile, HbA1C, liver function tests (LFT), body mass index (BMI) for evaluating co-morbidities [8].

MANAGEMENT

Ideally, the dermatologist and rheumatologist or orthopaedician 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 [9].

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. NSAIDs are still widely used for PsA treatment and may even be the only therapy for patients with very mild disease. In addition, they are often considered "milder" or "less toxic" therapy than DMARDs. NSAIDs can be associated with important adverse effects. The choice of NSAIDs depends upon the efficacy, safety, convenience and cost. These include renal toxicity, gastrointestinal toxicity and risk for cardiovascular events. Therefore, the lowest effective doses and the shortest duration of NSAIDs should be used [11].

Corticosteroids: Low dose CS therapy has been shown to slow the radiological progression in RA but such studies have not been done in PsA. 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.

DMARDS
Methotrexate (MTX)

Methotrexate (MTX) has a long history of use in PsA, despite a relative paucity of data establishing its efficacy specifically in this condition. Nevertheless, extrapolated from treatment algorithms in RA, it has been recommended that patients who have active disease despite previous NSAID therapy should receive DMARDs. However, DMARDs including MTX are clearly ineffective for treating axial disease and there is little evidence supporting their role treating other manifestations such as enthesitis. There are no head-to-head comparisons among DMARDs, but MTX is often recommended as the first-choice DMARD in PsA, either as monotherapy or in combination .Although the data are limited, there is a suggestion that weekly doses

of MTX above 15 mg might have greater clinical efficacy for PsA treatment than lower doses [13].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. 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. Minor toxicities of MTX include nausea, anorexia, stomatitis, and fatigue. The major toxicities are myelosuppression, hepato toxicity, and pulmonary fibrosis. MTX is teratogenic and should be stopped by both male and female patients, 3 months prior to conception.

Sulphasalazine (SSZ):

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. 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.

Cyclosporine:

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. The initial daily dose of cyclosporine A (CSA) is 2.5-3 mg/kg in divided doses. 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. 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. It can also cause side effects like hypertrichosis, headache, pseudo tumor cerebri and gingival hypertrophy.

Leflunomide:

Leflunomide is a pyrimidine antagonist. 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. 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. The other DMARDs used in the management of PsA include mycophenolate mofetil, azathioprine, antimalarials, gold and penicillamine. There is concern regarding the flare up of psoriasis with antimalarials but it has not been demonstrated in large studies [9].

Table 1: Dmards Frequently Used In Psoriatic Arthritis[10]

DRUG	METHOD OF USE	AVERAGE ADULT DOSAGE
Hydroxychloroquine	Oral	200-400 mg/day
Gold sodium thiomalate	i.m	25-50 mg every 2 week
Auranofin	Oral	3-6 mg/day
Sulfasalazine	Oral	500 mg t.i.d initially(max 4g/day)
Methotrexate	Oral or parenteral	10-25 mg/weekly

Biologics Therapies

The biologics currently approved for the treatment of PsA are anti-tumor necrosis factor-alpha (anti-TNF-α) compounds, etanercept (Enbrel), infliximab (Remicade), and adalimumab. 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-α 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. 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.

Infliximab:

It is a chimeric monoclonal anti-TNF-α antibody approved for the treatment of PsA. A phase 3 study of infliximab in 200 PsA patients (IMPACT II) showed significant benefit. Dactylitis and enthesitis decreased significantly and there was an inhibition of radiological disease progression at 24 weeks in the infliximab group. 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-α monoclonal antibody administered subcutaneously, 40 mg, every other week or weekly. New anti-TNF-α 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. 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.

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.

Anakinra, an IL 1 inhibitor, has not shown significant effect. 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.

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-α 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-α 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-α therapy who develop symptoms suggestive of TB should receive full anti-TB chemotherapy, and discontinue anti-TNF-α therapy. The following observations have also been made regarding the use of anti-TNF-α therapy in RA:
1. There is no evidence to suggest that one type of anti-TNF-α 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-α 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-α agents in RA from India. The reported risk of TB in a small study of 14 patients of spondyloarthropathy treated with anti-TNF-α agents in India was 21%. Special precautions have to be taken while using the DMARDs and biologic therapy in the presence of renal failure, liver disease, and cardiovascular disease, history of demyelinating disease, pregnancy and lactation [9].

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 [9].

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