Supplement-Psoriasis

Diagnosis and management of psoriatic arthritis

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ABSTRACT

Psoriatic arthritis (PsA) is a multi-faceted disease marked by varying combinations of peripheral arthritis, dactylitis, spondylitis, and enthesitis. Rarely, recurrent uveitis occurs. Skin involvement may or may not exist. However, patients with nail psoriasis have a higher probability of developing PsA. Untreated patients have significant morbidity and mortality. Timely diagnosis and aggressive treatment of the disease can lead to lower morbidity. Drug therapy of PsA includes symptomatic therapy and therapy with disease-modifying anti-rheumatic drugs. Biologics are the only agents that address all the pathological changes, of this chronic condition.

Key words: Biologics, dactylitis, enthesitis, psoriatic arthritis, spondylitis

INTRODUCTION

Over the last decade, significant strides have been made in our understanding of psoriatic arthritis (PsA). There is recognition that PsA is a multi-faceted disease, often with differing pathologies at different sites.[1] Patients often have varying combinations of peripheral arthritis, spondylitis, dactylitis, and enthesitis. In a proportion of patients, the presence of extra-articular manifestations like recurrent uveitis also influences therapeutic decisions.[2,3] Untreated patients with PsA have significant morbidity and probably early mortality.[2,3] Increased cardiovascular mortality due to inflammation-mediated premature atherogenesis has also been described.[4] Hence, there is a need to diagnose, stage, and treat this disease aggressively.

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[5-8] 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 interphalangeal joint disease
   b. Asymmetric, oligoarticular (< 5 joints involved)
   c. Symmetric, polyarticular "rheumatoid arthritis-like",
   d. Mainly spondylitic (axial involvement)
   e. Destructive arthritis (arthritis mutilans)

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.[9]

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The group for research and assessment of psoriasis and psoriatic arthritis (GRAPPA) has selected three simple screening tools, which can be used by clinicians to screen for PsA.[10] These are still undergoing validation in population studies.

1. Toronto Psoriatic Arthritis Screening Tool (ToPAS)
2. Psoriasis Epidemiology Project (PEST)
3. Psoriatic Arthritis Screening and Evaluation tool (PASE)

Sensitivity and specificity of the various criteria

The sensitivity of most of the above criteria has been compared. The criteria by Vasey and Espinzoa, McGonagle and the CASPAR criteria exhibited a sensitivity of almost 96%. The specificity of the various criteria was anywhere between 93% and 99%. One would choose a more sensitive criteria when conducting community based studies especially of early PsA and specific criteria when doing drug trials.

As dermatologists, concentrating on psoriasis of the skin and nail, we may be missing many cases of early arthritis. Dactylitis, a uniform sausage-like swelling of the fingers and toes, and enthesitis, which is pain and inflammation at the point of tendon insertion, may be early signs of arthritis in these patients. Furthermore, nail involvement is postulated to be due to a Koebner's phenomenon secondary to enthesitis of the distal phalanx, and may be predictive for the development of PsA.[11] Recently, Soscia *et al*. have studied nails with magnetic resonance imaging (MRI), and concluded that MRI can detect nail changes in patients of psoriasis even when there is no clinical evidence in any nail.[12]

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 [Figure 1], 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 metatarsophalangeal joint. A radiograph of the affected joint shows lytic areas with sclerotic margins described as "rat bite" lesions.

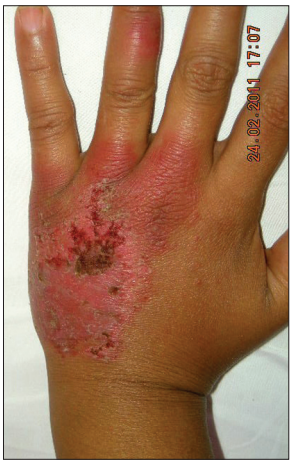

Figure 1: Distal interphalengeal joint (DIP) of the ring finger showing erythema and swelling suggestive of arthritis. Plaque of psoriasis also seen on the dorsum of the hand. DIP involvement is never seen in RA

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.[13]
3. HLA-B27, though not specific, is strongly supportive of axial disease.
4. X-rays of the hands and feet may be needed [Figure 2]. 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.

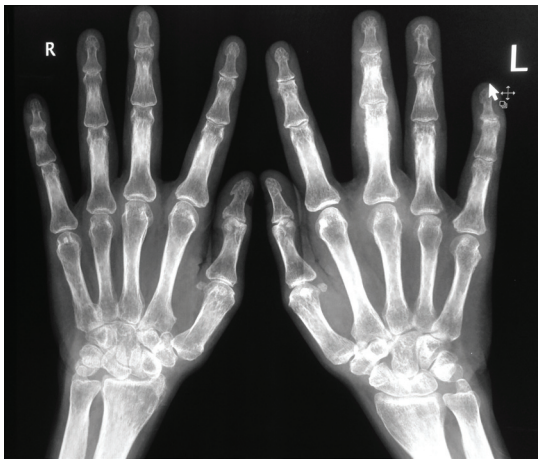

Figure 2: Radiograph of both hands showing fluffy periosteitis in the proximal phalanges of all fingers bilaterally. A soft tissue swelling is seen around the middle finger of the left hand suggestive of "sausage digit"

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.[14]
6. Ultrasound and MRI are more effective for the detection of enthesitis.[15]
7. Lipid profile, HbA1C, liver function tests (LFT), body mass index (BMI) for evaluating co-morbidities.

MANAGEMENT OF PSA

Treatment needs to be holistic and includes drug therapy and management of co-morbidities such as obesity, deranged lipid profile, abnormal liver functions, and underlying diabetes mellitus. A BMI> 25 kg/m^2 increases the risk of PsA.[16] Such patients need encouragement for dietary changes and life-style modifications. It has been estimated that up to 50% of untreated patients may develop persistent inflammation leading to joint damage culminating into disability and deformation, severely limiting physical activity. However, there is paucity of data about reduction of PsA incidence rates if it is treated early and aggressively.

Assessment of PsA should begin with assessment of the following five domains: skin disease, peripheral arthritis, axial disease, enthesitis, and dactylitis. Various measures of assessment are available for each of these domains [Table 1]. Based on these domains a disease severity grid has been devised [Table 2]. Once a patient's data has been entered in the grid, therapeutic decisions can be made.

Table 1: Measures of assessment of various domains

Domains	Modes of assessment
Peripheral arthritis	68/66 tender swollen joint count, ACR, DAS and PsARC
Spondylitis	BASDAI, BASFI, BASMI
Enthesitis	Leeds index, Berlin, 4-point, Mander and MASES
Dactylitis	Acute/chronic, Leeds enthesitis index, present/absent
Skin	Global assessment, PASI

ACR: American college of rheumatology, DAS: Disease activity score, PsARC: Psoriatic arthritis response criteria, BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, BASMI: Bath ankylosing spondylitis metrology index, MASES: Maastricht ankylosing spondylitis enthesitis score, PASI: Psoriasis area severity index

Table 2: Staging of psoriatic arthritis

Parameter	Mild	Moderate	Severe
Peripheral arthritis	<5 joints No damage on X-ray No LOF QoL minimal impact Pt. evaluation mild	>5 joints (S or T) Damage on X-ray NIR to mild Rx Mod LOF Mod impact on QoL Pt. evaluation moderate	>5 joints (S or T) Severe damage on X-ray NIR to mild–moderate Rx Severe LOF Severe impact on QoL Pt. evaluation severe
Skin disease	BSA<5%, PASI<5, asymptomatic*	Non-response to topicals, DLQI, PASI<10	BSA>10, DLQI>10 PASI>10
Spinal disease	Mild pain No loss of function	Loss of function or BASDAI>4	Failure of response
Enthesitis	1-2 sites	>2 sites or loss of function	Loss of function or>2 sites and failure of response
Dactylitis	Pain absent to mild Normal function	Erosive disease or functional loss	Failure of response

NR: Not responding, LOF: Loss of function, QoL: Quality of life, BSA: Body surface area, PASI: Psoriasis area severity index, DLQI: Dermatology life quality index, BASDAI: Bath ankylosing spondylitis disease activity index

Various organizations have laid out treatment guidelines for PsA depending on the disease severity, derived from prevalent data. Prominent among these include GRAPPA,[10] European League against Rheumatism (EULAR),[17] and the American Academy of Dermatology (AAD).[18]

DRUG THERAPY OF PSA

Drug therapy in PsA has been extrapolated from drugs used to manage RA. These include those giving symptomatic relief and those with disease-modifying anti-rheumatic drugs (DMARDs) effect.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDs are used to reduce symptoms in acute episodes of PsA. The choice of the drug depends on efficacy, adverse effects and co-morbidities. Long acting agents like celecoxib[19] and nimesulide,[20] in a dose of 200-400 mg once daily, help to control symptoms and also to reduce morning stiffness.

CORTICOSTEROIDS

Systemic corticosteroids are usually avoided in PsA for the fear of precipitating of pustular psoriasis when they are withdrawn suddenly.[21] However, when low dose systemic steroids (≤ 7.5 mg/day of prednisolone)[22] are combined with other DMARDs, good control of symptoms can be achieved. Intra-articular corticosteroid injections are reserved for mono/oligoarthritis and maybe used as an adjuvant in patients with well-controlled polyarthritis experiencing single joint flares. Intra-articular injections are also helpful in patients experiencing dactylitis and enthesitis.

DMARDS

Methotrexate (MTX), cyclosporine, and leflunomide (LEF) are often used as the first-line DMARDs in PsA because of their ability to control both, the arthritis, and the cutaneous manifestations of psoriasis.

METHOTREXATE

MTX has long been the mainstay drug for starting therapy in PsA. However, surprisingly, a literature search revealed only a few randomized controlled trials (RCTs) demonstrating efficacy of MTX in PsA.[23-25] In a recently concluded RCT to demonstrate the efficacy of MTX for treatment of synovitis for PsA, no improvement was noted in symptoms of synovitis and the publication questioned the role of MTX as a DMARD.[26] Another study suggested co-administration of a biologic (infliximab) for better patient outcome.[27] MTX acts via inhibition of DNA synthesis in the folate pathway, preferentially within lymphoid cells. It increases adenosine (anti-inflammatory) concentration and decreases s-adenyl methionione (pro-inflammatory) production. It is recommended to administer folic acid (1-5 mg/day) everyday, while on MTX therapy to minimize its toxicity. Early signs of MTX intolerance include oral aphthosis, stomatitis, cutaneous ulceration and increased gastrointestinal adverse events. Hepatotoxicity is the dreaded side-effect and has been the topic for much debate. It was generally felt that patients with PsA are more prone to MTX hepatotoxicity than those with RA. However, it has been recently understood that it is not the psoriasis but the presence of pre-existing risk factors like a history of chronic viral hepatitis, consumption of excessive alcohol, hepatotoxic drugs or an inherited liver disease, which could predispose to hepatotoxicity.[28] Even so, it is safe to administer MTX by monitoring the patients with serial LFTs and tests as per the American College of Rheumatology (ACR) guidelines. A liver biopsy should only be considered if LFTs are persistently elevated.[29] MTX is teratogenic (Category X) and should be stopped in women at least 3 months before conception.

CYCLOSPORINE A

Cyclosporine A (CyA) combines with cyclophilin and forms a complex, which inhibits the intracellular enzyme, calcineurin. This reduces IL-2 (a potent pro-inflammatory mediator) production by CD4-T cells. It also reduces other pro-inflammatory cytokines such as Granulocyte-macrophage colony stimulating factor (GM-CSF), Tumor necrosis factor-alfa (TNF-α), Interleukin (IL)-1, IL-3, IL-4, IL-5, IL-6, IL-8 by inhibiting their transcription. This effectively results in decreased T-cell and keratinocyte proliferation. CyA has been used in doses ranging from 3-6 mg/kg/day with variable outcome. Although, it shows excellent results in reducing peripheral joint disease, its role in controlling axial disease is dismal.[30] Potential, irreversible nephrotoxicity is the dreaded complication of CyA. With regular blood pressure monitoring and renal function tests, the toxicity can be kept in check. Development of hypertrichosis may be a cosmetic concern in women. Abrupt discontinuation of CyA may result in a flare of psoriasis.

LEFLUNOMIDE

Kaltwasser *et al.*,[31] randomized 190 patients of PsA and psoriasis into 2 groups. One group of 95 patients received 100 mg LEF, daily for 3 days and then 20 mg daily up to 24 weeks. The second group (91 patients) received placebo. At the end of 24 weeks, 58.9% versus 29.7% were responders. The LEF group had higher GI symptoms and abnormal LFTs as compared to the placebo group. LEF is a teratogenic drug and is contraindicated in women of childbearing potential.

Women should undergo a rapid wash-out procedure with cholestyramine or should not become pregnant for 2 years after the cessation of therapy. It is advisable that men wishing to father a child should discontinue LEF and should also undergo the wash-out procedure.

SULFASALAZINE (SSZ)

Large RCT for SSZ in PsA are few. In a study by Clegg Do, *et al*. of 264 patients comparing the efficacy of SSZ vs placebo in treating ankylosing spondylitis revealed a trend favoring SSZ treatment ($P = 0.13$). The authors concluded that SSZ at a dosage of 2,000 mg/day was well-tolerated and may be more effective than placebo in the treatment of patients with PsA.[32] Most of the other studies are small, precluding meaningful conclusions.

The other DMARDs used in the management of PsA include mycophenolate mofetil,[33] azathioprine,[34] antimalarials, gold,[35,36] and penicillamine.

It is important to note that DMARDs in PsA have their limitations. Although, some of them can control psoriasis and the peripheral arthritis, they have not been shown to be of value in the other facets of PsA [Table 3].

BIOLOGIC THERAPY IN PSA

Over the last decade, targeted therapy with biologic agents has revolutionized the treatment of PsA since they are the only agents that can address all the pathological changes seen in PsA. They not only control the psoriasis but also control synovitis, enthesitis, and non-infectious inflammatory osteitis seen in PsA [Table 3]. As a general consensus, biologic agents are reserved for resistant disease [Table 4]. However, they may be considered as first line for the treatment of enthesitis/dactylitis and those with predominantly axial disease.[17]

Biologics target very specific components within the inflammatory pathway of psoriatic disease process. Most widely used and studied are those which block TNF-α, a potent pro-inflammatory cytokine. These include etarnercept,[37] infliximab[38,39] and adalimumab[40] all of which have received FDA approval for treatment of PsA. Newer ones like certolizumab pegol,[41] and golimumab[42] have shown similar beneficial effects, but adequate trials are still lacking. On starting therapy, functional capacity of the joints improves dramatically. Concurrent administration of MTX improves drug survival, especially in patients receiving infliximab.[43] Patients who develop reduced/no response to their first anti-TNF-α drug can be switched over to another anti-TNF-α drug and this shows good improvement.[44]

Efalizumab, a humanized monoclonal antibody, which was in the market, has been withdrawn because of it's complication of causing progressive multifocal leukoencephalopathy.[45]

Ustekinumab is a newer humanized monoclonal antibody, which selectively binds to the p40 subunit of IL-12 and IL-23, and inhibits their binding to

Table 3: Efficacy of drugs in psoriatic arthritis

Drugs	Psoriasis	Nail disease	Peripheral arthritis	Spondylitis	Enthesitis	Dactylitis	Extra-articular features (uveitis)
NSAIDs	−	−	+	+	−	−	−
MTX	+	+	+	−	−	−	±
CyA, LEF	+	+	+	−	−	−	±
Other DMARDs	−	−	+	−	−	−	−
Biologic agents	+	+	+	+	+	+	+

MTX: Methotrexate, CyA: Cyclosporine A, DMARDs: Disease-modifying anti-rheumatic drugs NSAIDs: Non-steroidal anti-inflammatory drugs, LEF: Leflunomide

Table 4: Indications for biologic agents in psoriatic arthritis

Psoriasis	Nail	Peripheral arthritis	Spondylitis	Enthesitis	Dactylitis	Extra-articular features (uveitis)
Extensive Ps not responding to Phototherapy, retinoids, MTX and CyA	NR to local and traditional systemic retinoids, MTX and CyA	NR to NSAIDs, intra-articular injections and traditional DMARDs	NR to NSAIDs	NR to NSAIDs and local cortisone injections	NR to NSAIDs and local cortisone injections	NR to local therapy, systemic steroids and other immunosuppressants

NR: not responding, MTX: Methotrexate, CyA:Cyclosporine A, DMARDs: Disease-modifying anti-rheumatic drugs

the receptor IL-12Rβ1. IL-23 plays a key role in the Th17 mediated inflammatory pathway while IL-12 is a key cytokine in the Th1 inflammatory pathway. So ustekinumab can potentially inhibit both inflammatory pathways. Early clinical studies have shown to improve dactylitis and enthesitis in PsA.[46]

Alefacept inhibits LFA-3/CD2 interaction by blocking the CD2 receptor on the T lymphocytes which then prevents T-cell activation. It is important to monitor CD4 T-cell levels while on treatment with Alefacept.[47]

Tocilizumab binds to IL-6 receptor and thus inhibits the inflammatory events by IL-6. It has been approved for the treatment of rheumatoid arthritis and is currently being tried for PsA[48]

Abatacept prevents T-cell activation by inhibiting co-stimulatory signals responsible for inflammation in PsA. Hence, its use in early disease and in biologicaly naïve patients has garnered much interest.

The Danish Society of Gastroenterology has laid out detailed guidelines for investigations prior to initiating anti-TNF-α treatment.[49] Recommended tests to be done at baseline include complete hemogram, urine routine/microscopy, chest radiograph, Mantoux test, viral serology and liver and renal function tests. The issue of prophylaxis for tuberculosis is controversial and it has been suggested that all patients with a positive Mantoux test, past history of tuberculosis or abnormal chest X-ray suggestive of tuberculosis should receive prophylactic anti-tuberculosis therapy before starting the biologic therapy. All patients on anti-TNF-α therapy who develop tuberculosis should discontinue therapy and receive anti-tuberculosis chemotherapy. In the case of infliximab, monitoring needs to be continued for 6 months after discontinuing treatment due to the prolonged elimination phase of infliximab. Cautious use of DMARDs and biologics is recommended in pregnant and lactating mothers, and in patients with pre-existing liver, kidney, cardiac and neurologic dysfunction.

CONCLUSIONS

Untreated PsA leads to significant morbidity and mortality. The GRAPPA has identified screening tools, which dermatologists can use to diagnose PsA early, an important step towards proper treatment. The treatment protocol can be individualized once the disease extent and severity have been staged. Biologic agents have been impressive in the management of severe PsA. However, patient selection and screening for latent tuberculosis are both important. Combined management by the dermatologist and rheumatologist is required for better patient care.

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