Recent Advances in Psoriatic Arthritis from Obscurity to Prominence

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Abstract
Psoriatic arthritis is a fascinating inflammatory arthritis. Till recently it did not generate interest for lack of understanding of its immunopathology, and lack of effective treatment. This has changed. PsA is now one of the hot topics - all due to elucidation of genetic susceptibility associations, immunopathogenesis and availability of effective therapy. In this communication we provide an overview of these aspects of psoriatic arthritis.

Introduction
The association of arthritis with psoriasis was noted by Alibert¹ in the 1850’s.¹ For almost a century arthritis with psoriasis was considered either a co-incidental association or a variant of rheumatoid arthritis (RA). In 1956, Wright² defined psoriatic arthritis (PsA) as a distinct entity based on the features - lack of female predominance, the pattern of joint involvement, absence of rheumatoid factors, and typical radiological features. Later he described the clinical features of psoriatic arthritis. The American College of Rheumatology (ACR) accepted the entity psoriatic arthritis in 1964.³ The Moll and Wright classification criteria for PsA were published in 1973.¹ In 2008 CASPAR criteria (Classification Criteria for Psoriatic Arthritis), were developed to help early diagnosis of PsA.⁴ GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) is currently working on guidelines for research in psoriasis and PsA. In this short review we highlight some of the recent advances in PsA.

Psoriasis affects 2-3% of the population.⁵ PsA develops in approximately 30% of psoriatics. The reported prevalence of PsA varies from 7%- 42%. This variation is at least partly explained by non-uniformity of case diagnosis, the varied clinical features of PsA, and the geographic variation of its manifestations. Possibly the incidence of PsA is increasing. There has recently been a paradigm shift in our approach to and understanding of PsA.

Pathogenesis
It is postulated that in a genetically susceptible individual environmental factors (e.g. trauma, infection) trigger psoriasis and PsA.

PsA is characterized by synovitis, enthesitis, dactylitis and osteitis. A common biomechanical factor is thought to be operative. Two diametrically opposite phenotypes, destructive (erosions, osteolysis) and proliferative (periostitis, bony ankylosis) characterize the disease suggesting involvement of both osteoclasts and osteoblasts in its pathogenesis with local factors (trauma, infection), acting at the entheses and joints, determining the final outcome.

Genetics
GWAS⁶ (Genome Wide Association Studies) suggest psoriasis and PsA to be heritable polygenic disorders with a stronger genetic association with PsA. There is familial clustering and higher concordance amongst monozygotic twins.

The strongest association is with the MHC genes. It is possible that the MHC genes may be in linkage disequilibrium with disease susceptibility genes. The association of HLA B and HLA C is respectively stronger with PsA and psoriasis. Twenty-five percent PsA patients with peripheral arthritis and 60% patients with psoriatic spondylitis carry HLA B27 gene; HLA B38 and HLA B39 show an association with peripheral pattern of PsA. HLA Cw6 is associated with early onset psoriasis but not PsA.

Polymorphism in IL-23R (interleukin 23 receptor), TNF α (tumor necrosis factor α), molecules regulating NFK B (nuclear factor kappa B) expression, IL-12A, IL-12B, IL-17 receptor adapter proteins, KIR (killer immunoglobulin receptor), and mutations in IL-36 receptor antagonist have been implicated

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by GWAS in both psoriasis and PsA. In a study of familial psoriasis mutation in CARD 14 (caspase recruiting domain 14) has been implicated, suggesting similarity in the pathogenesis of psoriasis and Crohn’s disease. But, the extent to which CARD 14 is involved in the pathogenesis of PsA is not clear.

**Environment**

The association of psoriasis and PsA with infection and trauma is well established. Guttate psoriasis has been linked to preceding streptococcal sore throat. Dysbiosis in both the skin and microbial flora of the gut has been implicated. Deep Koebner phenomenon in joints and enthesal sites has been postulated to trigger PsA. The roles of stress and obesity are increasingly recognised, as also of HIV infection. The extent of psoriatic skin involvement, the site of affection (scalp and gluteal regions), and the nail disease are implicated in the development of PsA.

**Histopathology**

The synovium is infiltrated with T cells (CD8, CD4), B cells, and monocytes. The expression of TNF-α, IL1-β, IL-6, and IL-18 is similar to that of RA. Presence of TH17 cells expressing IL-17 have been identified recently. There is increased vascularity, fewer T lymphocytes and greater infiltration of neutrophils than present in rheumatoid synovium. The histopathology resembles that of spondyloarthropathy than of rheumatoid arthritis.

**Skin and Musculoskeletal Inflammation - The Association**

MRI, USG, and scintigraphy studies have revealed subclinical inflammation at entheseseal and other articular sites in patients with psoriasis. The inflammation, however, does not evolve into arthritis in majority of patients. The mechanisms of the link between skin and joint involvement are thought to be:

i. Migration of activated immune cells (T lymphocytes, dendritic cells, or activated monocytes) from skin to joint synovium, promoting inflammation.

ii. Innate immune response to local factors such as trauma, infection or stress evolves into acquired autoimmune response.

iii. Abnormal response of skin and joints to injury – the Koebner phenomenon triggers inflammation.

iv. Gut inflammation initiates an immune response in skin and joints. Multiple mechanisms, such as, molecular mimicry, super-antigen driven inflammatory response, chronic carriage, increased permeability of mucus membranes, and colonization of psoriatic plaques are possibly involved. The presence of subclinical bowel inflammation (present in 30%) patients with PsA and the development of PsA in HLA-B27 expressing rats, only in the presence of intestinal microbes, supports the postulate.

**Cytokines**

Pro-inflammatory cytokines TNFα and IL-17 are major players in skin and joint disease (joint inflammation and erosions). This is supported by evidence from animal models, the association with TNF α gene polymorphisms (TNIP1, TNFAIP3), and analysis of synovial explants. Cartilage destruction is common; TNF-α is an important driver of the damage. It induces marrow oedema, (osteitis) and upregulates OCPs (osteoclast progenitors), leading to bony erosions. Anti-TNF therapy rapidly reduces the levels of MMPs (matrix metalloproteinases) in synovial tissue.

The role of TH17, IL-17 and IL-12/23 is increasingly noted. Compared with RA increased circulating levels of TH17 cells and elevated levels of IL-17 in the synovial fluid have been reported.

**Systemic Disease**

Psoriasis is a systemic disorder. It affects skin, gut (inflammatory bowel disease), eye (anterior and posterior uveitis), vasculature (accelerated atherosclerosis; myocardial infarction, stroke), and endorcrines (metabolic syndrome). Scarpa and colleagues coined the term ‘psoriatic disease’ to denote its systemic nature.

Obesity is considered a risk factor for the development of psoriasis. Obesity is a low grade inflammatory state. Pro-inflammatory cells are present in adipose tissue. Mature adipocytes release chemokine CCL 20 and stimulate the migration of T lymphocytes. Flowcytometry analysis of the subcutaneous adipose tissue in psoriasis has demonstrated the presence of T lymphocytes, innate lymphocytes (NK and NKT cells) and a few B lymphocytes. These express inflammatory markers, release interferon gamma (IFN γ), with systemic inflammatory response.

**Not a Benign Disorder**

Till recently, PsA was looked upon as a benign disorder. Long term studies have revealed that up to 20-30% of PsA patients develop severe erosive disease. There is significant morbidity and mortality. Inflammation causes insulin resistance. Inflammation and insulin resistance are recognised risk factors for the development of subclinical atherosclerosis. They alter the function of endothelial cells leading to structural changes in the arterial wall. Increased carotid intimal thickness has been reported in patients with PsA. Ahlehoff et al. have reported association of psoriasis with increased risk of atrial fibrillation, ischemic stroke and venous thrombo-
embolism. Increased incidence of hyperuricemia (in up to 20%) and gout (hazard ratio: 4.95) has been reported in psoriasis and PsA.

Patients with PsA have a poor quality of life, significant functional impairment, psychosocial disability, and increased mortality. The most common causes of death are cardiovascular, neoplastic (lymphoproliferative cancers, non-melanoma skin cancers) and respiratory.

**Diagnosis**

**Biomarkers**

As of now there are no serological markers to diagnose PsA. This handicap causes diagnostic difficulty especially in arthritis patients without cutaneous manifestations of psoriasis. Many potential markers are under evaluation; none has reached the stage of diagnostic application. Chandran et al reported high-sensitivity CRP, osteoprotegerin, MMP-3, and the ratio of C-propeptide of type II collagen to collagen fragment neoepitopes, Col2–3/4 long mono (C2C) to predict development of PsA in patients with psoriasis. The same authors have reported that serum MMP-3 levels predict response to anti-TNF therapy. A recent trial reported 11 biomarkers (including MMP-3, CRP, VEGF, IL-16 and ICAM-1) measured at baseline to predict response to golimumab.

**Imaging**

With increasing emphasis on early and aggressive therapy diagnosis of early and minimal PsA in patients with psoriasis has assumed importance. Plain x-ray is not sensitive enough to be of use for early diagnosis of PsA. MRI and USG (with Doppler) can identify subclinical disease, predict development of PsA and help to monitor treatment response. USG (with Doppler) detects synovitis, effusion, tenosynovitis, paratendinosis, enthesitis, and erosions in peripheral joints. It can visualize skin and nail changes. Advantages of USG include ease of availability, lack of radiation, and low cost. US can guide intraarticular injections and synovial biopsy. The major disadvantages of USG are observer variability, need for training and narrow acoustic window.

MRI is of help not only in assessing peripheral joints, but also axial (SI joints and spine) changes. MRI T1W images and contrast enhancement, respectively detect erosions and synovitis in peripheral joints. The characteristic MRI (T2 STIR images) finding is osteitis or marrow edema. MRI T2 STIR sequences of spine and sacro-iliac joints additionally show hyper-intensity at the sites of enthesal attachments in the spine (as well as peripheral sites). Chronic changes in the form of sclerosis and fatty infiltration in the spine and sacro-iliac joints appear hyperintense on T1W images. For clinical trials PsA MRI scoring (PsA MRIS) system has been validated by OMERACT (outcome measures in RA clinical trials). Excellent imaging quality and ability to detect very early lesions are the strengths of MRI, while high costs and availability limit its routine use.

**Management**

**Early Screening and Referral**

In most of the patients skin and nail lesions precede articular manifestations. Dermatologists are therefore, best placed to suspect PsA at an early stage and refer the patients to a rheumatologist. Screening tools (self-administered questionnaires) have been developed for this purpose. The currently available screening tools include the PsA Screening and Evaluation (PASE), Toronto PsA Screen (ToPAS), its version (ToPAS2), Psoriatic Epidemiology Screening Tool (PEST), PsA Screening Questionnaire (PASQ), and Early Arthritis for Psoriatic patients (EARP). The screening questionnaires have good and comparable specificity, and sensitivity for the development of cohorts. However, studies suggest that these may not perform as well in the clinic.

**Early Diagnosis and New Classification Criteria**

Until recently the main classification criteria for PsA were those of Moll and Wright. These are not suitable to diagnose early PsA (sensitivity 80-85%). Now CASPAR criteria with high sensitivity and specificity have been developed. Chandran et al have reported good sensitivity of the criteria for the diagnosis of early PsA (<1 year duration).

CASPAR (Classification criteria for PsA): Two points are allotted for current psoriasis, while 1 point each is allotted to personal or family history of psoriasis, psoriatic nail dystrophy on current physical examination, negative RFs (rheumatoid factors), current dactylitis or history of dactylitis, and radiographic evidence of juxta-articular new bone formation. PsA is diagnosed when ≥3 points are assigned in the presence of inflammatory arthritic disease (joint, spine, or enthesal).

**Early, Treat-to-Target (T2T) Treatment**

Early diagnosis and treatment is the present paradigm to treat PsA especially because effective therapy is now available. Smolen J et al in 2010 and Schoels et al in 2014 published the treat-to-target recommendations for spondyloarthritis, including PsA. It was however realised that it was not possible to achieve remission in all patients, especially in those with long-standing disease. The consensus opinion was that ‘low/minimal disease activity’ could be an alternative target in PsA. Criteria for ‘minimal disease activity’ have been endorsed by GRAPPA in 2010. A recent post hoc analysis from the GO-REVEAL trial showed that golimumab-treated patients with psoriatic arthritis...
(PsA) who achieved minimal disease activity (MDA) had better long-term outcomes (less damage) than those who did not receive golimumab.

**Tight Disease Control**

Tight control has been defined as an aggressive management strategy with close monitoring and appropriate adjustments in treatment using a prespecified outcome measure for decision-making.

In the TICOPA (Tight Control of PsA) study in early PsA, 206 patients were randomly assigned to receive either standard care or intensive management. More patients in the tight-control group than in the standard-care group (61.8% vs. 44.6%) achieved an ACR 20 response as well as skin index 75 (PASI 75) at week 48. The study supports the concept of treat to target and tight control of disease.

**Outcome Measures and Composite Indices**

GRAPPA and OMERACT have developed core set of domains to be monitored in clinical trials.\(^3\) Outcome measures for arthritis, spondylitis, skin, dactylitis, enthesitis, quality of life and radiographic changes have been validated.

Composite disease activity indices, DAPSA (disease activity for PsA), CPDAI (composite psoriatic disease activity index), PASDAS (PsA disease activity score) and AMDF (arithmetic mean of desirability function) have been developed for monitoring disease activity.\(^3,5\)

**Treatment Recommendations**

An excellent review on advances in management of PsA was published in 2014.\(^7\) Therapy of PsA has changed dramatically since the introduction of biologic agents. Basically treatment should be tailored to patient’s current manifestations; the treatment of comorbid conditions is equally important. Two sets of international algorithms, the EULAR\(^6\) (European League Against Rheumatism) and GRAPPA\(^5\) have been developed for the management of PsA.

Approved drugs to treat PsA include NSAIDs, glucocorticoids, traditional DMARDs (methotrexate, sulfasalazine, leflunomide, and cyclosporine). Studies evaluating their efficacy are conflicting, with none showing benefit in retarding radiographic damage.\(^7\) All anti-TNF agents have shown equal efficacy for skin and articular manifestations. They slow the radiographic damage and improve quality of life of patients with PsA. Anti-TNF drugs are prescribed only after failure of NSAIDs, intra-articular steroids and traditional DMARDs.

IL-12/23 inhibitor (ustekinumab) and phosphodiesterase 4 inhibitor (apremilast) have been approved by US FDA for the treatment of psoriasis and PsA. Several other drugs are in pipeline.\(^6\) IL-17 inhibitors are in advanced phase of development. IL-17 receptor antagonist, brodalumab, and two biologic agents secukinumab and ixekizumab, that block IL-17A, are being evaluated currently. Secukinumab\(^8\) is approved for psoriasis by US FDA in 2015 and is in advanced phase III trials to treat PsA. Other drugs under investigation to treat PsA are abatacept, rituximab, tocilizumab, and facitinib.

**Conclusion**

PsA has graduated from obscurity to prominence. Realization that it is not a benign disease, unveiling of pathogenic pathways, and development of therapies with specific targets have all contributed to this change. One has not yet reached the point of achieving complete remission and a possible cure. Rheumatologists look forward to these developments with optimism.

**References**


