

Psoriatic Arthritis: A Review

Introduction

Psoriatic arthritis (PsA) is a chronic, autoimmune, systemic inflammatory arthropathy characterized by the association of inflammatory arthritis and psoriasis.¹ This is a disease which usually follows an insidious onset and a progressive course. Nail abnormalities of variable degree may be present. While most patients have mild to moderate and manageable arthritis some exhibit progressive, erosive or even disabling disease.

Arthritis may manifest as axial or peripheral joint inflammation. Peripheral arthritis usually presents as an asymmetric oligoarthropathy, a symmetric distal interphalangeal joint arthritis, or a rheumatoid-like metacarpophalangeal and proximal interphalangeal joints arthritis. Inflammatory sausage-like digit swelling (dactylitis) is a common feature of PsA and when axial involvement is present (approximately 20% of cases), it typically manifests as spinal stiffness, pain and/or limited range of motion affecting the lower spinal areas and unilateral sacroiliitis. Enthesitis (inflammation of an enthesal structure) commonly affects one or both heels, greater trochanter or anterior iliac crests. Arthritis may precede, follow or present concurrently with psoriasis. Reports on prevalence of PsA in psoriatic patients has varied from 6% in a study conducted in Olmstead County by the Mayo Clinic, to 30% in a Danish survey.^{2,3}

Examination of all skin areas (including scalp, retroauricular, sacral, umbilical) may provide valuable diagnostic information when assessing a patient with inflammatory arthritis. Ocular disease (red and/or painful eye involvement) may be seen as frequently as 30% of cases.

There is increasing interest in PsA due to developing new insight into the pathobiology of the disease, underscoring its important differences with rheumatoid

arthritis (RA). New translational approaches are surging and the development of collaborative groups are providing a fresh look at traditional and novel therapies by designing clinical trials and registries with the goal of providing validation of reliable outcome measures. International research consortia such as GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) have been created as a result of common interest in the clinical characterization and disease classification of PsA, with the purpose of creating updated assessment and clinical therapeutic response criteria.⁴

Classification of Psoriatic Arthritis

Psoriatic arthritis is an inflammatory arthritis associated with psoriasis, which is usually negative for rheumatoid factor (RF).⁵ As such, in 1964 the American Rheumatism Association recognized psoriatic arthritis as a distinct type of arthritis, more prevalent in patients with psoriasis than in negative controls.⁶ When RF is factored into studies of prevalence, the association of this arthritis with psoriasis is greatest amongst RF negative patients.^{7,8} In 1973, Moll and Wright proposed the first classification criteria based on a cohort of patients from personal experience in their clinic in Leeds, England.⁹ (Table 1) Subsequently, a consortia of multiple rheumatology experts presented a newly validated classification criteria (CASPAR criteria)* for PsA, with data from multiple and different patient groups yielding better sensitivity (91.4%) and specificity (98.7%) to the classification of this subtype of seronegative arthritis.¹⁰ (Table 2) In addition to its noteworthy diagnostic specificity, further studies using the CASPAR criteria have set a higher mark for sensitivity (99.1%) when it is applied to diagnosing patients with early PsA.¹¹

*CASPAR: Classification Criteria for the Study of Psoriatic Arthritis.

Table 1.⁹ Moll and Wright Classification*Psoriasis in addition to:*

- Axial or peripheral inflammatory arthritis
- Negative rheumatoid factor (not always)

Five clinical subsets:

- Oligoarticular
- Arthritis mutilans
- Distal interphalangeal joint predominant
- Spine predominant
- Polyarticular

Table 2.¹⁰ CASPAR Diagnostic Criteria*Inflammatory musculoskeletal disease activity (joint, spine, enthesal with three or more of the following):*

- Current psoriasis (determined by a qualified health professional (QHP)) such as a dermatologist, and or history of psoriasis by patient or QHP or history of psoriasis in a first or second degree relative)
- Characteristic psoriatic nail changes
- Negative RF serology
- Dactylitis (current or recorded by a QHP, rheumatologist)
- Radiographic findings: juxta-articular new bone formation

Pathophysiology and Unique Characteristics of Psoriatic Arthritis

Psoriatic arthritis and RA share common denominators, such as the presence of high levels of the synovial fluid and tissue pro-inflammatory cytokines tumor necrosis factor-alpha (TNF- α) and interleukin one (IL-1).¹² Despite this and other common features, we are reminded that PsA is a unique disease entity with an original synovial-enthesal histopathologic signature. (Table 3) Research into the pathophysiology of PsA and its connection to psoriasis is at an early, yet promising stage.

Table 3.^{13,14} Comparison between RA and PsA Pathobiology

PsA	RA
Lesser degree of cellular infiltrate	Higher cellular infiltrate
Increased vascularity	Comparatively lesser vascularity (characteristic pannus formation) ^b
Prominent neutrophil (PMN) infiltration	Comparatively lesser PMN infiltration
Increased number of CD 163+ ^a subsynovial monocytes	Lesser number of CD 163+ subsynovial monocytes
Increased number of lymphocytes	Lesser number of lymphocytes
<i>Some key clinical differences:</i>	
More likelihood of digit ray-like ^c involvement	Joint ray-like distribution not a characteristic feature
More likelihood of dactylitis ^d	Dactylitis is less likely
Presence of enthesitis ^e	Enthesitis not a characteristic clinical feature
<i>Some key radiographic differences:¹⁵</i>	
Maintenance of normal mineralization	Erosions and periarticular demineralization are common
Bony proliferation	Bony proliferation is not a characteristic
Periostitis and spinal bridging osteophytes present	Periostitis and/or bridging osteophytes not a feature

^a Mature monocyte marker¹³^b Membrane of granulation tissue composed of mesenchyme and bone marrow-derived cells seen in rheumatoid arthritis^c Inflammation of all joints in one digit while potentially sparing other digits^d Dactylitis or sausage digit is the inflammation of an entire finger or toe in a fusiform fashion^e Inflammation of an enthesitis, the location where a bone has an insertion to a tendon or a ligament

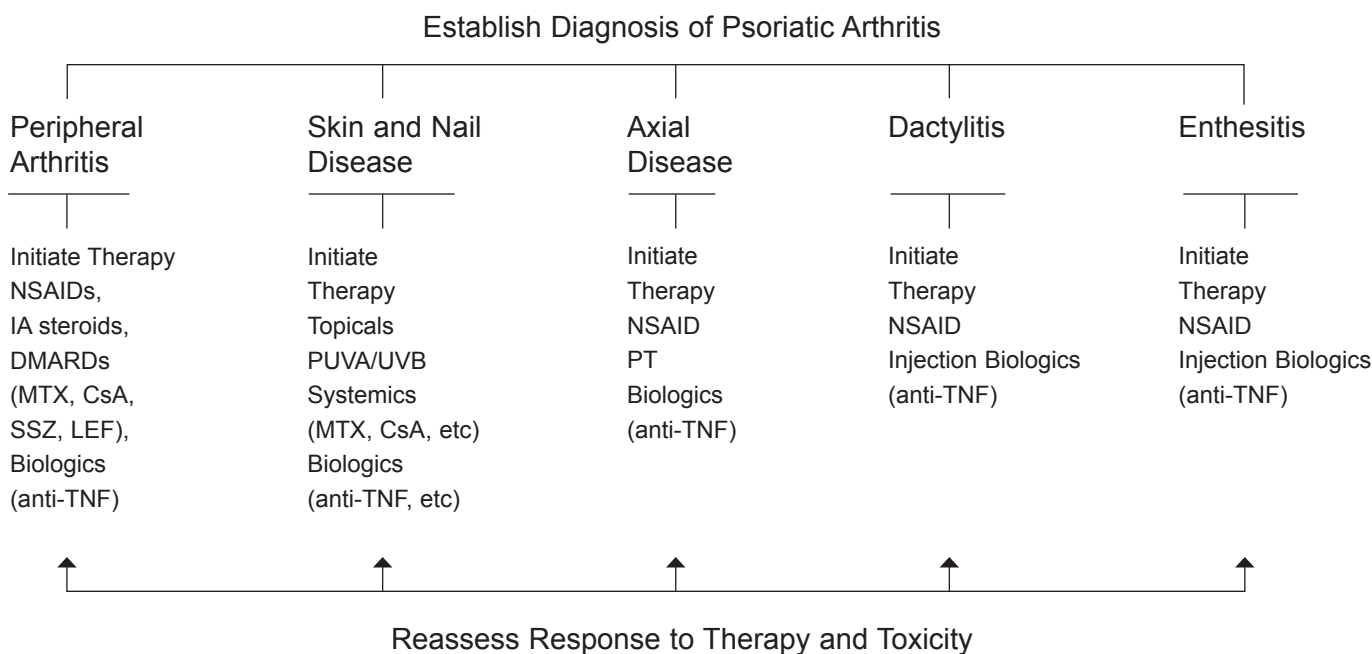
Assessment and Management

Understanding that PsA is a systemic inflammatory disease, complex, and characterized by variable involvement of different musculoskeletal structures, members of GRAPPA came together and developed a set of comprehensive recommendations for the treatment of its various clinical manifestations, based on evidence obtained from systematic review of the available literature and consensus opinion.^{1,4,16,17}

Because PsA is a complex disease with various cardinal disease domains, each individual therapeutic plan should be directed towards targeting the most severe manifestation at the time of evaluation.^{1,4} (Figure 1)

Figure 1.

GRAPPA PsA Treatment Guidelines



NSAIDs: non-steroidal anti-inflammatory drugs; IA: intra-articular; MTX: methotrexate; CsA: cyclosporine-A; SSZ: sulfasalazine; LEF: leflunomide; PT: physical therapy; PUVA: psoralen plus ultraviolet light A; UVB: ultraviolet light B; TNF: tumor necrosis factor. Reprinted with permission.⁴

Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute the initial therapeutic approach in patients with PsA. They are effective in treating axial and peripheral arthritis, as well as enthesitis and dactylitis. The presence of comorbid conditions (such as chronic kidney disease or the presence of peptic ulcer disease) are common limitations to their use.¹

If contraindications exist, or if insufficient therapeutic response is confirmed, disease-modifying anti-rheumatic drugs (DMARDs) are an appropriate choice for the treatment of moderate to severe PsA.

Although there is limited data regarding the efficacy of methotrexate (MTX) in peripheral synovitis, this drug is commonly used in practice based on good results from direct clinical experience. The reference study for the use of MTX in PsA is an essentially

negative randomized-controlled study, performed in 1984. Albeit, the dose used was small and the number of patients studied and duration of follow-up were equally limited.¹⁸

Toxicity monitoring is important, since studies have confirmed a relative excess of hepatotoxicity with cumulative doses of MTX in PsA patients relative to RA. Higher liver biopsy scores were observed in the PsA group.¹⁹ Other DMARD used in clinical practice include leflunomide, sulfasalazine and, occasionally, cyclosporine.²⁰ Of the existing studies, none has substantially demonstrated significant efficacy of DMARDs in the treatment of inflammatory axial disease.^{20,21}

Although there are no validated trials proving the efficacy of systemic steroids for polyarticular

involvement, these are sometimes used in clinical practice to control disease for short periods of time. Systemic steroids are relatively contraindicated since they appear to increase the likelihood of exacerbation of psoriasis when tapered.^{1,22}

Although there are no randomized controlled studies, expert opinion supports the utility of local steroid injections in patients with oligoarticular arthritis, enthesitis or bursitis.^{1,23,24} Despite some anecdotal reports of exacerbation of psoriasis in patients treated with hydroxychloroquine, data from a small Canadian study conducted in 1994 suggests that chloroquine, a similar compound, may in fact not exacerbate psoriasis. A prospective, randomized double-blind, controlled trial with antimalarials would be warranted to further answer this particular question.²⁵

Axial Disease in Psoriatic Arthritis

There is insufficient data on the management of sacroiliitis in PsA, and any available data has been historically extrapolated from studies in ankylosing spondylitis (AS).¹ This is likely to change soon since emphasis is now made on studying the therapeutic response of patients with PsA and axial involvement independently.

Tumor necrosis factor-alpha blocking agents are considered the best available option when NSAIDs and physical therapy are insufficient to control axial symptoms.^{1,4,21}

TNF Blocking Agents in Psoriatic Arthritis

Clinical trials support the use of TNF- α blocking agents (etanercept, adalimumab, infliximab). As a group, they are relatively safe and effective in all disease domains, improving disease control. Long-term data is now available and supports the effectiveness of TNF- α blockers in sustaining prolonged radiographic, skin and joint control.^{26,27,28} Functional measures and quality-of-life, all of which are patient-based reports, improved with TNF- α blocking agents.²⁹

Developing Therapies

New and promising therapies are emerging. Such is the case for a novel anti-TNF agent, golimumab, a human monoclonal antibody which can be administered subcutaneously once every four weeks. An initial study suggested improvement in all disease domains in patients treated with this drug and a more recent study published this year showed encouraging results with improvement of active PsA and associated skin and nail psoriasis after

24 weeks of therapy.^{30,31} Anakinra, an IL-1 blocking agent has not been proven to be effective in PsA.³² Abatacept is an immunoglobulin (CTLA4-Ig), which blocks a main costimulatory signal between antigen presenting cells (APC) and T cells by binding the CD80/86 receptor on the APC and, therefore, blocking interaction with the CD28 receptor on the T cell. Abatacept stands the trial of time as an effective drug in patients with RA and ongoing studies are evaluating its efficacy and safety in PsA.³³ Ustekinumab, a human interleukin (IL)-12/23 monoclonal antibody, has shown modest effects in studies with PsA.³⁴ Other agents such as alefacept (blocks the interaction between LFA-3 on the APC and CD2 T cell receptor) have shown modest efficacy in psoriasis and PsA.³⁵ Efalizumab, a drug used for psoriasis, has been voluntarily withdrawn from the market due to increasing cases of progressive multifocal leukoencephalopathy (PML).³⁶ Other potential therapies geared towards blocking cytokine networks are now in the pipeline.

Current and future bench-to-bedside applications are increasingly opening the gamut of therapeutic options.

Conclusion

Better understanding of the pathobiology and clinical characteristics of psoriatic arthritis has led to the optimization of therapeutic approaches. While new treatments with a positive impact on quality of life, disability, and disease control are increasing, their long-term safety needs further evaluation.

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