Psoriatic Arthritis Update

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Abstract
Psoriatic arthritis is an inflammatory arthritis occurring in up to 30% of patients with psoriasis. Its clear distinction from rheumatoid arthritis has been described clinically, genetically, and immunohistologically. Updated classification criteria have been recently derived from a large international study. Key pathophysiologic cellular processes are being elucidated, increasing our understanding of potential targets of therapy. Therapies that target cells, such as activated T cells, and proinflammatory cytokines, such as tumor necrosis factor alpha (TNFα), are rational to pursue. Outcome measures have been “borrowed” from rheumatoid arthritis and psoriasis studies. A variety of domains are assessed including joints, skin, enthesium, dactylitis, spine, function, quality of life, and imaging assessment of disease activity and damage. The performance qualities of outcome measures in these various domains is being evaluated by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), and improved measures are being developed and validated specifically for psoriatic arthritis. Traditional therapies for psoriatic arthritis have included nonsteroidal anti-inflammatory agents, oral immunomodulatory drugs, topical creams, and light therapy. These therapies have been helpful in controlling both musculoskeletal and dermatologic aspects of the disease, but they may not be fully effective in all disease domains, may eventually show diminished benefit, and may produce treatment-limiting toxicities. In the past several years, use of biologic agents has generally yielded greater benefit across more domains, yielding significant and enduring benefits for clinical manifestations, function, and quality of life, and especially with the anti-TNF agents, inhibition of structural damage. Adverse effects with these agents can be significant but are usually manageable. Cost is also significant, but cost-effectiveness analysis is demonstrating reasonable trade-off between cost and benefit.

Psoriatic arthritis (PsA) is an inflammatory arthritis that occurs in individuals with psoriasis. PsA is classified as a subtype of spondyloarthropathy based on common HLA associations and characteristic inflammatory clinical and immunopathologic features. PsA often results in significant functional impairment and reduced quality of life. Focus on more aggressive treatment of patients with progressive disease, both with traditional disease-modifying drugs and emerging biologics, has improved the outlook for patients with PsA with respect to control of symptoms in both the joints and skin, inhibition of progressive joint destruction, and improvement of function and quality of life.

Classification and Epidemiology
Historically, the Moll and Wright criteria have been used for the classification of PsA. According to these criteria PsA can be classified when a patient with psoriasis has an inflammatory form of arthritis, negative rheumatoid factor, and one of five distinct clinical subsets: 1) oligoarticular (<5 tender and swollen joints) asymmetric arthritis, 2) polyarticular arthritis, 3) distal interphalangeal (DIP) joint predominant, 4) spondylitis predominant, and 5) arthritis mutilans. Although several classification criteria for PsA have been proposed since the initial Moll and Wright criteria, the Classification of Psoriatic Arthritis study group (CASPAR), has developed a new classification schema based on extensive analysis of over 500 patients with PsA and 500 patients with another type of inflammatory arthritis serving as controls (Table 1).
Psoriasis is known to affect approximately 2% to 3% of the general population, and the prevalence of PsA in psoriasis patients is between 6% and 39%.9,10 Telephone surveys recently conducted in Europe and in the United States, respectively, suggest a prevalence of 30%11 and 11%.12 This latter range is partly related to the lesser severity of psoriasis in the US population studied, which may be correlated with difference in PsA prevalence.12 It is also possible that the condition remains generally underdiagnosed, related to lack of awareness by both the patient and physician.13

Genetic Epidemiology

The relative risk for PsA among first-degree relatives indicates a strong genetic association.14 PsA is associated with human leukocyte antigen (HLA) class I alleles. Linkage with the short arm of chromosome 6 has been shown, demonstrating associations with HLA-B13, B-17, B-27, B-38, B-39, HLA-Cw6, and HLA-DRB1*07.15,16

Immunopathogenesis of PsA

Synovial biopsy studies have documented the similarity of immunohistology of various spondyloarthropathy (SpA) subsets, including PsA and ankylosing spondylitis (AS). Synovial biopsy studies have also documented the distinction of these from rheumatoid arthritis (RA). In PsA angiogenesis is prominent in both the synovium and psoriatic skin lesions, induced by angiogenic growth factors such as vascular endothelial growth factor (VEGF), transforming growth factor β (TGFβ), and angiopoietins.17 Some distinguishing features of the spondyloarthropathies include decreased quantity of cellular infiltrate despite increased vascularization, infiltration with polymorphonuclear cells and CD163+ macrophages, and upregulation of Toll-like receptors 2 and 4.1,17,19

Evidence now exists documenting the central role of TNF-α in both PsA and psoriasis.17,20 High levels of TNF-α are found in psoriatic skin lesions and in the synovial fluid, serum, and synovial tissue of patients with PsA. Therapy with TNF-α inhibitors provides substantial benefit, which provides evidence for the central role of TNF-α in the inflammation of PsA and psoriasis. TNF-α is produced by macrophages, keratinocytes, mast cells, monocytes, dendritic cells, and activated T-cells. It upregulates nuclear transcription factors, including NFkB, resulting in enhanced expression of many molecules central to the inflammatory response, including other cytokines (eg, IL-1, IL-6) and chemokines. In the joints, TNF-α mediates other biologic processes that can result in cartilage and bone damage, including expression of metalloproteinases by fibroblasts and chondrocytes, maturation and activation of osteoclasts from monocyctic stem cells, and angiogenesis. In both the joints and the skin, TNF-α induces the expression of endothelial, keratinocyte, and dendritic cell surface adhesion molecules that attract immune cells to sites of inflammation. In addition to stimulating proinflammatory cells and cytokines in the skin, a key role played by TNF-α is promotion of keratinocyte hyperproliferation and survival, an important contributor to the psoriatic lesion.17,20,21

Other key cytokines that can be upregulated in PsA, and thus have potential as targets for therapy, include IL-1, IL-6, IL-12, IL-15, and IL-18.22 T-cell activity in general is significantly upregulated; thus inhibition of T-cell activation via blockade of “second signal” pathways is also a promising therapeutic approach.22

Recently, a Viennese group has developed an animal model for psoriasis and PsA. Inducible epidermal deletion of the gene JunB and its functional companion c-Jun in adult mice led to the histologic and immunohistochemical hallmarks of psoriasis and arthritis. In humans, JunB is a component of the activator protein 1 (AP-1) transcription factor, localized in the psoriasis susceptibility region PSORS6, and this gene has diminished expression in human psoriatic skin lesions. This group further showed that development of arthritis, but not psoriasis, required the presence of T and B cells as well as signaling through tumor necrosis receptor 1 (TNFR1). Their conclusion was that deletion, or at least diminishment,
of JunB/AP-1 in keratinocytes induces chemokine/cytokine expression, which in turn recruits PMNs and macrophages to the epidermis, leading to both skin and joint lesions.\textsuperscript{23}

**Outcome Measures**

PsA outcome measures have generally been adapted from similar measures used in assessment of RA and psoriasis (Table 2). These have been used in clinical trials and clinical registries of PsA patients. These measures have been shown to effectively assess peripheral joint and skin symptoms and signs, function, quality of life, fatigue, and structural damage determined by x-ray, as well as to distinguish treatment from placebo. Approaches to assessment of enthesitis, dactylitis, and spine involvement are still in development. A consortium of international investigators, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), both rheumatologists and dermatologists, are involved in developing, refining, and validating these measures in PsA.\textsuperscript{24-27} Detailed reviews are provided elsewhere.\textsuperscript{28-31}

Adaptation of RA methodologies to assess change of radiographs in PsA has been done in a number of recent clinical trials,\textsuperscript{30} suggesting that such approaches are appropriate in PsA despite its differences from RA. Several studies have documented the effectiveness of ultrasound\textsuperscript{32-37} and magnetic resonance imaging\textsuperscript{38-39} in detecting inflammation in the joints and enthesium of SpA patients, as well as the extent of structural damage. As these tools become more refined, they also will enhance our ability to assess the effectiveness of new therapies on the progression of joint damage in PsA.

Psoriatic arthritis has been the subject of focus of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group over the past several years. Consensus has been achieved on a core set of clinical domains to be assessed in clinical trials, and preliminary agreement on outcome measures to assess many of these domains has been achieved.\textsuperscript{40} The GRAPPA group is addressing areas where outcome measures are still in development.

**PsA Therapy**

A challenge of PsA therapy is addressing the multiple clinical domains involved in the disease: arthritis, enthesitis, dactylitis, spine disease, skin, and the significant impairment of function and quality of life that may occur. In patients with milder disease, nonsteroidal anti-inflammatory drugs (NSAIDs) may be adequate for arthritis and topical ointments (eg, corticosteroid or vitamin D), or forms of light therapy may be adequate for skin disease. However, moderate to severe manifestations in these domains often require systemic therapy. Drugs such as sulfasalazine or methotrexate may substantially help the arthritis, but not always the skin manifestations, and agents such as cyclosporine may help the skin but not adequately help the joints, and none of these traditional disease-modifying therapies may help the spine. Thus, advances in targeted therapy with the newer biologic agents, especially the TNF antagonists, have been welcome as they appear to address all domains with significant effectiveness. Comprehensive reviews of therapy of PsA have been recently published.\textsuperscript{41-44}

**Update on Traditional Systemic Therapies of PsA**

The agent leflunomide, a pyrimidine antagonist approved for RA at a dose of 20 mg per day, was assessed in 188 PsA patients. Psoriatic arthritis response criteria (PsARC), the primary endpoint, was met by 59% of leflunomide-treated patients compared with 29.7% of placebo treated patients ($P<.0001$). ACR20 response was achieved by 36.3% and 20%, respectively ($P=.0138$), and Psoriasis Area and Severity Index (PASI) 75 response achieved by 36.3% and 20%, respectively ($P=.0138$), and Psoriasis Area and Severity Index (PASI) 75 response by 17.4% and 7.8%, respectively ($P=.048$).\textsuperscript{45} As with methotrexate (MTX), liver function test abnormalities may be noted and need to be monitored.

Seventy-two patients with incomplete response to MTX were randomized to placebo or addition of cyclosporine.\textsuperscript{46} At 48 weeks, significant improvements in tender and swollen joint count, C-reactive protein, PASI, and synovial ultrasound score occurred in the combination group, but statistical differentiation between the combination and MTX alone group occurred just in PASI and ultrasound score.

**Update on Biologic Agents for PsA**

Biologic agents currently approved for treatment of PsA, based on controlled phase 2 and 3 trials and the safety database from these trials and the RA database, include the anti-TNF-α compounds, etanercept (Enbrel),\textsuperscript{47} infliximab (Remicade),\textsuperscript{48} and adalimumab (Humira).\textsuperscript{49} Controlled

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**Table 2: Psoriatic Arthritis Outcome Measures**\textsuperscript{28}

<table>
<thead>
<tr>
<th>Arthritis response</th>
<th>ACR Response Criteria (including DIP and CMC joints)</th>
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<tbody>
<tr>
<td>Psoriatic Arthritis Response Criteria (PsARC)</td>
<td>Disease Activity Score (DAS)</td>
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<tr>
<td>Radiographic assessment</td>
<td>Modified Sharp</td>
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<td></td>
<td>Modified van der Heijde/Sharp</td>
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<tr>
<td>Skin response</td>
<td>Psoriasis Area and Severity Index (PASI)</td>
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<tr>
<td></td>
<td>Dermatologist Static Global</td>
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<td></td>
<td>Physician Global Assessment (PGA) of Psoriasis</td>
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<tr>
<td>QOL/function improvement</td>
<td>Short-Form 36 Health Survey (SF-36\textsuperscript{48})</td>
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<td></td>
<td>Health Assessment Questionnaire (HAQ) Disability Index</td>
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<td></td>
<td>Dermatology Life Quality Index (DLQI)</td>
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<td>Functional Assessment of Chronic Illness Therapy (FACIT)</td>
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phase 2 trials have been completed with the costimulatory blockade agents alefacept and efalizumab. Pilot trials with other biologics in development have been completed. Several agents either approved or in development for RA and psoriasis will likely be assessed in PsA.

**TNF-α Inhibitors**

The anti-TNF-α agents approved for use in PsA and psoriasis include etanercept, infliximab, and adalimumab.

In the placebo-controlled portion of the phase 3 etanercept trial (N=205), utilizing 25 mg administered subcutaneously twice a week, ACR20 response was achieved by 59% of etanercept-treated patients versus 15% in the placebo group (42% and 41% on background MTX, respectively) *(P<.0001)*. Skin response as measured by the PASI score, which was considered evaluable (BSA ≥3%) in 66 of the etanercept and 62 of the placebo patients, showed a 75% improvement in 23% and 3%, respectively, at 24 weeks *(P=.001)*. A change of 0.51 units of the Health Assessment Questionnaire (HAQ), a measure of physical function, was noted in the etanercept group, a difference that was both statistically significant and clinically meaningful.*51* Improvement in quality of life as assessed by Short-Form 36-Item general health survey (SF-36) was also demonstrated in the treatment group. Inhibition of progression of joint space narrowing and erosions was shown, with 1 unit of modified total Sharp score (mTSS) progression in the placebo group and none (-0.03 units) in the etanercept group *(P=.001)*. A total of 169 patients participated in open-label follow-up use of etanercept between 1 and 2 years. At the end of this period, 64% and 63% of the original etanercept-treated and placebo-treated patients, respectively, demonstrated an ACR20 response, and 38% of all patients achieved a PASI 75 response by 12 weeks, indicating an enduring clinical response in joints and skin. The mTSS, evaluable in 141 patients at 2 years, showed a change of -0.38 and -0.22 units in the original etanercept and placebo groups, respectively, indicating continued inhibition of structural damage.*52* The drug was well tolerated, and no new safety issues emerged apart from those seen in clinical trial and general clinical experience with etanercept.

A phase 3 study of infliximab in 200 PsA patients (IMPACT II) showed significant benefit.*53* Baseline demographic and disease activity characteristics were similar to those of the etanercept phase 3 trial. At week 14, 58% of infliximab patients and 11% of placebo patients achieved an ACR20 response *(P<.001).* Presence of dactylitis decreased in the infliximab group (41% to 18%), compared with the placebo group (40% to 30%) *(P=.025).* Likewise, incidence of enthesitis, assessed by palpation of the Achilles tendon and plantar fascia insertions, decreased in the infliximab group (42% to 22%) compared with the placebo group (35% to 34%) *(P=.016).* At 24 weeks, PASI 75 was achieved by 64% of the treatment group and 2% of the placebo group *(P=.001).* The median PASI response was 87% in ACR20 responders and 74% in ACR20 nonresponders, suggesting that infliximab may be effective in treating skin symptoms, even when joints do not improve significantly.*54* Utilizing the van der Heijde-Sharp scoring method (hands and feet), modified for PsA, infliximab-treated patients showed inhibition of radiographic disease progression at 24 weeks, although PsA-specific radiographic features, including pencil-in-cup deformities and gross osteolysis, did not differ between the treatment groups, as has been observed in other anti-TNF-α trials, presumably due to the more fixed nature of these changes.*54* HAQ score improved for 59% of infliximab patients, compared with 19% of placebo patients, while both the physical and mental components of SF-36 scores improved for patients receiving infliximab. Improvement was sustained at 1 year.*55*

Adalimumab, a fully human anti-TNF-α monoclonal antibody administered subcutaneously at 40 mg every other week or weekly, was studied in a large (N=313) phase 3 study, the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT).*56* At 12 weeks, 58% of patients receiving adalimumab 40 mg every other week achieved ACR20 response compared with 14% of patients receiving placebo *(P<.001).* This response rate did not differ between patients taking adalimumab in combination with MTX (50% of patients) and those taking adalimumab alone, similar to observations made in the etanercept and infliximab trials. Mean improvement in enthesitis and dactylitis was greater for patients receiving adalimumab, but this result did not achieve statistical significance. PASI 75 was achieved by 59% in the adalimumab-treated group and 1% in the placebo group *(P<.001)* in those evaluable for PASI (n=138). Radiographic progression of disease was significantly inhibited by adalimumab, as evaluated by x-rays of hands and feet, using a modified Sharp score.*56* Mean change in TSS was -0.2 for patients receiving adalimumab and 1.0 for patients receiving placebo *(P<.001).* Mean change in HAQ was -0.4 for adalimumab patients and -0.1 for placebo patients *(P<.001).* Mean change in the physical component of the SF-36 was 9.3 for the treatment group and 1.4 for the placebo group *(P<.001).*

Spine disease was not assessed in these trials, due to variability of expression of this domain in this patient group. However, significant efficacy of anti-TNF treatment of axial symptoms and signs has been demonstrated in a closely related disease, ankylosing spondylitis.*57* Extrapolation of this experience to PsA seems reasonable.

In summary, the anti-TNFα medications have shown the greatest efficacy of any treatment to date in the various clinical aspects of PsA. Their efficacy in joint disease activity, inhibition of structural damage, function, and quality of life are similar. There may be some differentiation in efficacy in the skin and enthesis, but all have excellent effects in these domains. These agents tend to be well tolerated, and patients generally acclimate to their parenteral administration, especially when they experience significant efficacy.
Safety concerns are present, such as risk for infection, but no new concerns have arisen in the PsA population compared to the more extensively studied RA patient experience. Recent studies have also demonstrated the cost-effectiveness of anti–TNF-α therapy in PsA.61-63

New anti–TNF-α agents are being developed for use in PsA, including cimzia and golimumab, each with advantages of infrequent subcutaneous administration. Experience in management of RA suggests that when a clinician switches from one of these agents to another, if the first has not had or has lost efficacy or caused side effects, that a substantial percentage of patients will respond to another medication in this class.64,65 Anecdotally, a similar experience has been noted in the management of PsA patients.

**Other Biologic Agents**

Alefacept is a fully human fusion protein that blocks interaction between LFA-3 on the antigen-presenting cell and CD2 on the T cell, or by attracting natural killer lymphocytes to interact with CD2 to yield apoptosis of particular T cell clones.66 It is approved for treatment of psoriasis66,67 and is administered weekly as a 15-mg intramuscular injection in an alternating 12-weeks-on/12-weeks-off regimen in order to allow return of depleted CD4 cells in the off period. A phase 2 controlled trial of alefacept in PsA (N=185) showed that 54% of patients given a combination of alefacept and MTX had an ACR20 response as compared to 23% in the MTX alone group (P<.001) at week 24. PASI 75 results were 28% and 24%, respectively.67

Efalizumab is a humanized monoclonal antibody to the CD11 subunit of LFA-1 on T cells. Its binding to T cells interferes with T-cell coupling with ICAM-1 on antigen-presenting and endothelial cells. It interferes with activation of T lymphocytes and migration of cells to the site of inflammation. It is administered subcutaneously once per week and is approved for use in psoriasis.68 In a 12-week trial of efalizumab in patients with PsA, 28% of patients achieved an ACR20 response versus 19% in the placebo group (P=.2717). Since this response was not statistically significant, efalizumab is not recommended for treatment of arthritis.69

Abatacept (CTLA4-Ig) is a recombinant human fusion protein that binds to the CD80/86 receptor on an antigen-presenting cell, thereby blocking the second-signal activation of the CD28 receptor on the T cell. It is administered intravenously once per month and has been approved for use in RA.70 A phase 2 trial for use in psoriasis has been conducted.71 It is anticipated that this drug will be evaluated in PsA.

**Conclusion**

Numerous studies have increased our understanding of the basic pathophysiology of PsA, providing support for the clinical effects of targeted therapy—for example, inhibition of TNF-α. The consequent emerging treatments for PsA have demonstrated significant benefit for clinical signs and symptoms in the joints, enthesis, and skin, inhibition of joint damage as assessed by radiographic progression, and improved quality of life and functional status. Agents that block the cell–cell interactions required to activate T cells are effective in the skin and may benefit the joints as well. Observation of the effectiveness of these agents has helped elucidate the pathogenesis of PsA and psoriasis, which, in turn, may lead to more novel and effective interventions.

Development of targeted therapies has also increased interest in the accurate diagnosis and classification of PsA, which would facilitate the institution of appropriate therapy in a timely fashion. Significant efforts are underway to further develop and validate outcome measures that accurately assess the effect of therapies and determine the natural history of these diseases. This effort, along with the development of evidence-based treatment guidelines and general educational initiatives, is being led by international research consortia such GRAPPA and other groups.

The benefits of biologic agents must be weighed against their cost: patient improvement and inhibition of disease progression on one hand versus allocating limited resources on the other. Comprehensive health economic analyses are being developed to aid our ability to see the full impact of these more effective treatments on patient function, productivity, and quality of life in the context of society as a whole.

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