

How to Manage and Treat a Psoriatic Arthritis Patient Population to Improve Outcomes

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Summary

Psoriatic arthritis is a disabling condition that increases morbidity and mortality. Newer agents that target tumor necrosis factor (TNF) alpha have been shown to improve all domains of the psoriatic arthritis, and are the treatment of choice. There are more agents targeting different aspects of the pathophysiology of this disease on the horizon.

Key Points

- Psoriatic arthritis can result in significant bone deformities and disability.
- Traditional systemic DMARDs have not been proven to retard disease progression or effectively treat bone issues.
- Anti-TNF agents have been proven effective for the comprehensive management of psoriatic arthritis, including the ability to inhibit progressive structural damage of peripheral joints.
- New therapeutic targets are being explored for the treatment of anti-TNF non-responders.

PSORIATIC ARTHRITIS IS AN AUTOIMMUNE disease with known human leukocyte antigen (HLA)-associated risk factors. Psoriatic arthritis affects the ligaments, tendons, fascia, and joints, and occasionally develops in the absence of detectable psoriasis.¹ Psoriasis occurs in 1 to 2 percent of the population. Psoriatic arthritis occurs in approximately 30 percent of patients with psoriasis. The prevalence of psoriatic arthritis is 0.3 percent and it occurs equally among men and women.¹

Psoriatic arthritis and rheumatoid arthritis (RA) are similar but have some differences. With psoriatic arthritis, the small joints at the ends of the fingers and the nails tend to be affected. Symptoms of joint inflammation in psoriatic arthritis include distal interphalangeal (DIP) synovitis, proximal interphalangeal (PIP) synovitis, asymmetric oligoarthritis, and actylitis (inflammation of the entire finger). Nail involvement is seen in 80 percent of psoriatic patients. Enthesitis is a characteristic finding of psoriatic arthritis that is not seen in RA. Enthesitis is an inflammation of the entheses, the location where a bone has an insertion to a tendon or a ligament. Unlike RA, the spine can be involved in this disease.

Patients also usually have psoriatic plaques.

Patients with psoriatic arthritis may have significant morbidity, disability, and early mortality. New evidence suggests that psoriatic arthritis may be as disabling and destructive as RA when the appropriate comparisons are made; thus, treatment should be aggressive in those individuals with progressive joint disease.¹

Historically, psoriatic arthritis was classified using the Moll and Wright criteria developed in mid-1970s.² This classification divided patients into subgroups - oligoarticular asymmetric (<5 involved joints), polyarticular, DIP predominant, spondylitis predominant, and arthritis mutilans. More recently, a more quantified classification has been developed and tested. This Classification Criteria for the Diagnosis of Psoriatic Arthritis (CASPAR) is shown in Exhibit 1.³

The pathophysiology of this disease also is different from RA. There is less inflammatory cell infiltration into affected joints. There is increased vascularity in the affected synovium and bone involvement. This disease extends beyond the synovium of the joint to involve bone, cartilage, and tendons, unlike

Exhibit 1: Diagnostic criteria for psoriatic arthritis (CASPAR)

| Established inflammatory musculoskeletal disease (joint, spine, or enthesal) With three or more of the following: | | |
|--|----------------|---|
| 1. Psoriasis | Current* | Psoriatic skin or scalp disease as judged by a qualified health professional |
| | History | A history of psoriasis that may be obtained from patient, or qualified health professional |
| | Family history | A history of psoriasis in a first- or second-degree relative according to patient report |
| 2. Nail changes | | Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination |
| 3. A negative test for RF | | By any method except latex but preferably ELISA or nephlemetry, according to the local laboratory reference range |
| 4. Dactylitis | Current | Swelling of an entire digit |
| | History | A history of dactylitis recorded by a qualified health professional |
| 5. Radiological evidence of juxta-articular new bone formation | | Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain X-rays of hand or foot |

*Current psoriasis awarded two points
Criteria yield specificity 98.7 percent, sensitivity 91.4 percent

RF, rheumatoid factor
Reference: 3

RA, which is typically contained within the synovium. Unique enthesial and subendosteal inflammatory infiltrate also are found in the affected joints.^{4,5} Although immunopathophysiologic distinctions exist between RA and psoriatic arthritis, a key common feature is the important role of the pro-inflammatory cytokine tumor necrosis factor (TNF) alpha in the initiation and sustenance of articular and systemic inflammation.

The same cells that are implicated in skin involvement also are involved in joint manifestations of the disease. In patients with psoriasis, unidentified antigens continuously activate T cells. Activated T cells migrate into the skin and induce macrophages to produce TNF-alpha and other cytokines. TNF-alpha stimulates keratinocyte proliferation and inhibits keratinocyte apoptosis.⁶

Patients with psoriatic arthritis can develop significant bone erosions – leading to arthritis mutilans. The osteoclasts, which breakdown bone, are activated in this disease.⁷ Some medications that are under study target the activated osteoclasts. One example is denosumab. TNF-alpha inhibitors also decrease osteoclast precursors, which helps decrease bone inflammation.

Exhibit 2 is a compilation of the various available

treatment approaches for psoriatic arthritis.⁸ In milder cases, benefit can be achieved with the simpler therapies. Moderate or worse disease will require systemic therapy. There have been very few controlled trials evaluating the traditional oral disease modifying agents (sulfasalazine, methotrexate, cyclosporine, gold, azathioprine, and leflunomide) in psoriatic arthritis. The data from these limited trials indicate modest benefit from these agents. The most commonly used agent of these is methotrexate. There are a lot of issues with methotrexate use. Patients with psoriasis are more likely than patients with RA to have histologic liver toxicity secondary to methotrexate (7.7 percent versus 2.7 percent, P = 0.003).¹⁰ For full effect through all the domains of this disease, only the TNF-alpha inhibitors (etanercept [Enbrel[®]], adalimumab [Humira[®]], infliximab [Remicade[®]]) are effective.

In order to determine which patients would benefit the most from a biologic agent, predictors of a more aggressive disease course should be examined. Exhibit 3 lists some presenting and ongoing elements that may indicate a patient is likely to have an aggressive course.⁹ Without adequate therapy, more than 50 percent of patients with an aggressive course will develop deforming arthritis. Their mortality is

Exhibit 2: Psoriatic Arthritis Treatment

| | Peripheral arthritis | Skin and nail disease | Axial disease* | Dactylitis | Enthesitis |
|----------------------------------|----------------------|-----------------------|----------------|------------|------------|
| NSAIDs | X | | X | X | |
| Intra-articular steroids | X | | | | |
| Topicals | | X | | | |
| Physiotherapy | | | X | | |
| Psoralen UVA/UVB | | X | | | |
| DMARDS (anti-TNF antagonists) | X | X | | | |
| Biologics (anti-TNF antagonists) | X | X | X | | X |

*Based on data from ankylosing spondylitis trials (used as surrogate for PsA spondylitis)
 NSAID, nonsteroidal anti-inflammatory, MTX, methotrexate, CsA, cyclosporine; SSZ, sulfasalazine; Lef, leflunomide; PsA, psoriatic arthritis

Reference: 9

Exhibit 3: Who Will Progress Aggressively?

PRESENTING ELEMENTS TO CONSIDER:

- Lack of response to NSAIDs
- Number of joints involved
- Erosions on X-ray
- Elevated ESR or CRP
- Disability

OBSERVATION OVER TIME

- Inadequate response to serial therapy trials
- Progression of erosions on X-ray

NSAID, nonsteroidal anti-inflammatory; ESR, erythrocyte sedimentation rate; CRP, C reactive protein

increased relative to the general population, primarily from cardiovascular disease secondary to inflammation-induced atherosclerosis.

All the TNF- α inhibitors produce similar clinical response rates in psoriatic arthritis. Treatment with TNF- α inhibitors has not only resulted in substantial improvement in the signs and symptoms of arthritis, but also has improved functional status and quality of life in patients with psoriatic arthritis.¹¹⁻¹³ Improvements in associated inflammatory features, such as enthesitis in psoriatic arthritis, also have been observed. Exhibit 4 shows an example of the nail response to etanercept. A similar dramatic improvement is seen in number and severity of psoriasis plaques. More importantly, in psoriatic arthritis

there is radiologic evidence for slowing disease progression with treatment in bones (Exhibit 5).

The ability of TNF- α inhibitors to restore patients to normal function and prevent progressive damage is important. Investment in medications has benefits in reducing disability, preventing hospitalizations, and possibly reducing mortality.

Although it now appears that TNF- α inhibition benefits most patients with psoriatic arthritis, we cannot yet determine a priori which patients will not adequately respond or why, and we cannot rationally predict a preferable target.⁶ Patients who have an inadequate response to one TNF- α inhibitor can be switched to another for a trial.

Serious infections can occur when patients are treated with TNF- α inhibitors. There also may be a slight increase in risk for lymphomas.¹⁴

There are some unanswered questions in the treatment of psoriatic arthritis with TNF- α inhibitors. One is the question whether there would be a better effect by combining anti-TNF agents with methotrexate. This is true in RA but no study has been done in psoriatic arthritis. Another issue is the effect of anti-TNF agents on psoriatic arthritis comorbidities. The typical reduction in heart attack and stroke rates is about 50 percent in RA patients treated with TNF- α agents, presumably as a result of reduction in inflammation induced atherogenesis. A reduction in overall mortality of RA also

Exhibit 4:

Example of Nail Response with Etanercept Therapy: Baseline



Example of Nail Response with Etanercept Therapy: 20 Weeks



Courtesy of Ivor Caro

has been shown. There also is improvement in osteoporosis and depression in RA patients. There are no large registry databases of psoriatic arthritis patients, so these data are not yet available for TNF-alpha inhibitor treated psoriatic arthritis patients.

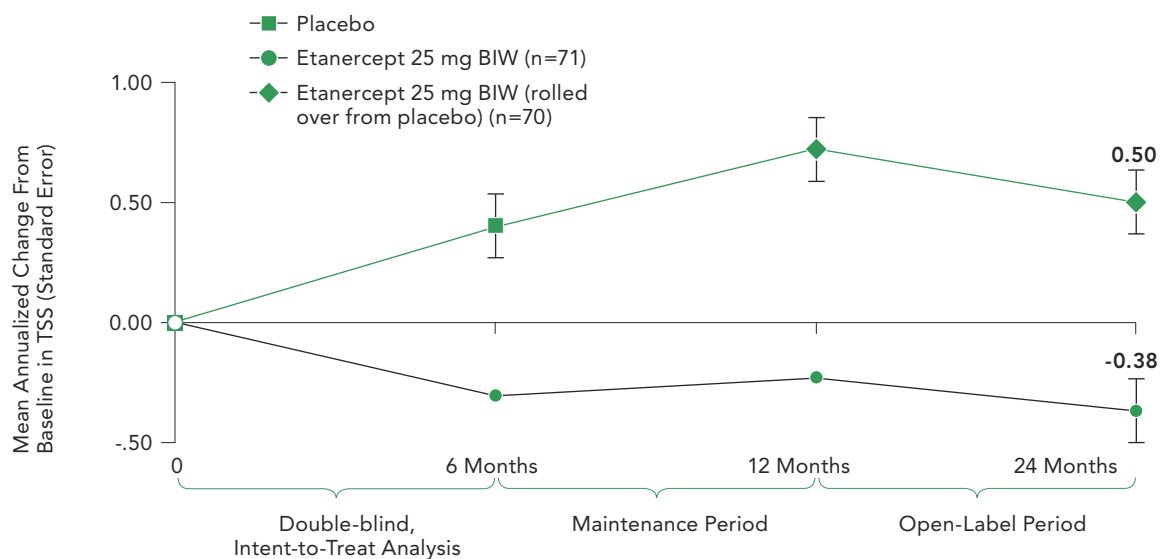
Another TNF-alpha inhibitor, golimumab, is likely to be FDA approved in the near future for psoriatic arthritis. This agent is given once a month and has similar clinical and radiographic efficacy to the other TNF-alpha inhibitors.

There are emerging therapies for anti-TNF incomplete responders or those intolerant of anti-TNFs. A number of other cytokine targets are being studied. These include interleukins 6, 12/23, and 15. Co-stim-

ulatory blockade leading to diminishment of T cell activity by blocking a signal of T cell activation also is being studied. Agents under study include alefacept (Amevive®) and abatacept (Orencia®). These agents are showing modest efficacy in psoriatic arthritis.

An oral agent, which is a janus kinase (JAK) 3 inhibitor, also is under study for many different autoimmune diseases including psoriatic arthritis. Specific inhibition of JAK3 would block cytokine signaling by IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. Preliminary data, which have only been presented at scientific meetings but has not yet been published, are showing positive results. Hopefully, an oral agent like this will be less expensive than the parenteral biologics.

Exhibit 5: Etanercept in Psoriatic Arthritis: Mean Change From Baseline in Sharp Score at 2 Years



Reference: 11

Denosumab, a monoclonal antibody that binds RANKL, which is necessary for osteoclast development, is an agent under study for osteoporosis and RA. It has been shown to inhibit structural damage in RA patients and likely will be studied for psoriatic arthritis.

Conclusion

Psoriatic arthritis represents a disease of joint, enthesial, and skin inflammatory processes unique in genetic, immunopathologic, and clinical presentation. Outcome measures are being improved and validated to accurately assess the key domains of disease activity, function, and quality of life in trials of new therapies and clinical registries. Traditional systemic DMARDs are indicated for more active disease signs and symptoms, but have not been proven to retard disease progression or effectively treat the spine. Biologics, particularly anti-TNF agents, have been proven effective for the comprehensive (joints, enthesium, spine, skin, function, and QOL) management of psoriatic arthritis, including the ability to inhibit progressive structural damage of peripheral joints. New therapeutic targets are being explored for the treatment of anti-TNF incomplete responders. *JMCM*

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