Current Treatment for Psoriatic Arthritis and Other Spondyloarthritides

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Psoriatic arthritis (PsA) is a chronic and progressive form of inflammatory arthritis. It occurs in individuals with psoriasis, which affects approximately 2% to 3% of the general population. The reported range of prevalence of PsA in psoriasis patients is 6% to 39%, and recent large telephone surveys in Europe and in the United States suggest ranges of 30% and 11%, respectively. This wide range is related to differing methods of ascertainment and heterogeneity of the populations studied. There currently is no predictive marker to indicate in which psoriasis patients arthritis will develop. Nearly one half of patients have a family history of PsA, although the concordance of PsA in identical twins is only 30% to 40%. About 25% of PsA patients have spinal involvement. The condition often is classified as one of the subtypes of spondyloarthropathy, given shared HLA associations among those with spinal involvement, and characteristic inflammatory clinical and immunopathologic features. PsA generally is considered an autoimmune disease, albeit with unknown antigenic determinants.

Disease Features

The key clinical feature of the most common form of psoriasis, plaque psoriasis, is thickened, erythematous, hyperkeratotic skin lesions. These scaly patches usually occur over extensor surfaces, such as the elbows or knees, and may coalesce to cover large parts of the body. Other psoriasis variants, such as guttate, pustular, and erythrodermic, are less common. Psoriasis usually develops before joint involvement, typically by many years. Whereas the severity of the psoriasis is not predictive of the severity of PsA, recent studies suggest that there may be a correlation between psoriasis severity and the occurrence of PsA. Joint involvement often is asymmetric, with frequent inflammation of the distal interphalangeal (DIP), as well as other joints. Other characteristic features include enthesitis, dactylitis, and spine inflammation, particularly in the sacroiliac joints. Enthesitis involves inflammation at sites where tendons, ligaments, and joint capsule fibers insert into bone—for example, at the insertions of the Achilles tendon and plantar fascia—as well as at ligaments around the rib cage and pelvis. Dactylitis, swelling of a whole digit, includes both synovitis of the joints and enthesis of tendon and ligament attachments in the digit. Other features may include episodic iritis and frequent nail psoriasis, evidenced by pitting or gross onycholysis. Distinct from RA, serum test results for rheumatoid factor (RF) usually are negative. Elevations in levels of the acute phase reactants, such as the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), are variable. Radiographic features that help distinguish PsA from RA include both lytic changes—such as the pencil-in-cup change, which reflects gross bone and cartilage lysis—as well as evidence of new bone formation, such as complete ankylosis of joints and juxta-articular osteitis. A significant proportion of patients experience functional impairment.

Immunopathology

Because nearly all of the newest treatments for PsA involve biologic agents that target underlying immunologic pathways of this condition, it is useful to briefly review its immunopathology. T cells are known to play a strong role in psoriasis and in PsA. A number of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), also serve important roles in the disease. TNF-α has gained much recent attention, as agents that block its activity have become available. TNF-α is produced by macrophages, keratinocytes, mast cells, monocytes, dendritic cells, and activated T cells. It up-regulates nuclear transcription factors, including nuclear factor κB (NFκB), resulting in enhanced expression of many molecules central to the inflammatory response, including other cytokines (eg, IL-1, IL-6) and chemokines (eg, IL-8). TNF-α also induces the expression of endothelial, keratinocyte, and dendritic cell surface adhesion receptors that are involved in the trafficking of leukocytes to inflammatory lesions, such as intercellular adhesion molecule (ICAM)-1 and E-selectin (CD62E). TNF-α also mediates numerous other biologic processes that can result in joint and bone damage, such as expression of metalloproteinases by fibroblasts, maturation of activated osteoclasts from monocyctic stem cells, and angiogenesis. A comprehensive discussion of the immunohistochemical features of PsA is given elsewhere.
Classification of PsA

New classification criteria for PsA have been developed by an international working group (CASPAR) to improve the sensitivity and specificity of the classification of this disorder. Although a number of classification criteria for PsA have been proposed since the initial Moll & Wright criteria, it is the latter criteria that primarily have been used. By this criteria set, PsA is classified as inflammatory arthritis in a patient with psoriasis and (usually) negative RF presenting with one of the following five clinical subsets: (1) oligoarticular (< 5 tender and swollen joints) asymmetric arthritis, (2) polyarticular arthritis, (3) predominant DIP joints, (4) spondylitis predominant, and (5) arthritis mutilans.

Outcome Measures in PsA

For the most part, outcome measures for PsA have been adapted from similar measures used in assessment of RA and psoriasis. These are used both in clinical treatment trials, as well as in longitudinal studies of the natural history of PsA. Although these measures can effectively assess peripheral joint and skin inflammation, function, and quality of life, they have yet to be fully refined and validated in PsA and do not adequately assess domains such as enthesis, spine inflammation, dactylitis, and fatigue. A brief synopsis of these scales is given in Table 1. Most have not been specifically validated in PsA, although their performance characteristics in clinical trials have been good. These measures have been reviewed in detail.

Several studies have documented the effectiveness of ultrasound and magnetic resonance imaging (MRI) in detecting inflammation in the joints and entheses of patients with spondyloarthritis, as well as the extent of structural damage. As these tools become more refined, they will enhance our ability to assess the effectiveness of new therapies on the progression of joint damage in PsA.

Treatment

Treatment of PsA depends on the severity of the condition and the features involved. The approach to treatment uses similar principles as RA treatment, on the one hand, and psoriasis treatment on the other. One challenge in determining which medications are the most useful for an individual patient is that some medications may preferentially impact psoriasis symptoms, but not joint problems, and vice versa (Fig. 1). Another challenge is matching the potency of the medication to the severity of the disease as well as the likelihood of future progressive damage.

If the skin lesions of psoriasis are mild, topical creams such as vitamin D or steroid cream or various forms of light therapy may be used. Traditional nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, corticosteroids, or traditional disease-modifying anti-rheumatic drugs (DMARDs) can help mild to moderate, and occasionally severe, arthritis manifestations.

For moderate to severely affected patients who do not respond adequately to traditional DMARDs, biologic agents, such as the anti-TNF-α medications, have contributed greatly to our ability to improve joint and skin disease, to inhibit progression of structural damage to the joints, and to improve patients’ functional ability and quality of life.

Physical therapy also is an important component of treatment that helps to maintain or improve joint mobility, muscle strength, and range of motion. Occupational therapists focus on procedures and devices to aid hand and wrist function. Orthopedic procedures, including joint modification or replacement, can help with more severely damaged joints.

Traditional Medications: NSAIDs, COX-2 Inhibitors, Corticosteroids and DMARDs

NSAIDs are used to treat mild cases of PsA that involve fewer joints and little or no disability and that demonstrate no evidence of progressive structural damage. These medications help reduce inflammation and relieve pain, and thus restore joint mobility. However, gastrointestinal side effects render these medications intolerable for some patients. Selective COX-2 inhibitors, such as celecoxib, and relatively selective COX-2 inhibitors, such as meloxicam, may be associated with less gastrointestinal toxicity than other NSAIDs.

Corticosteroids must be used cautiously in patients with PsA because withdrawal may trigger a flare of psoriasis. The DMARDs traditionally used in PsA are methotrexate (MTX) and sulfasalazine, although cyclosporine, azathioprine, and antimalarial drugs also are used.

Methotrexate

Most of the published data for MTX pertain to its safety and efficacy in treating RA. In the few controlled trials involving the
use of MTX in PsA, there has been only marginal benefit shown in the joints or skin.\textsuperscript{35, 36} However, more satisfactory results have been obtained in clinical practice when higher doses of MTX are used compared with those used in older clinical trials. In a 26-year retrospective study of long-term, low-dose MTX therapy in 157 patients with severe psoriasis, 76% of patients had a good response to MTX. However, 61% experienced side effects, including liver function abnormalities, bone marrow suppression, and gastric complaints, and 20% discontinued treatment.\textsuperscript{37} In a 12-week, prospective, double-blind trial, Willkens and colleagues\textsuperscript{35} found that PsA patients receiving either 7.5 mg or 15 mg of MTX per week experienced a greater decrease in psoriasis skin surface area than patients receiving placebo. Patients receiving MTX also rated better on the physician’s global assessment in joint activity than patients receiving placebo. There was, however, no difference between MTX and placebo in terms of joint pain, tenderness, and swelling or duration of morning stiffness. Although patients with PsA receiving MTX showed a great decrease in skin surface area involvement, there was no difference in terms of lesion induration or scaling. In a retrospective open-label study designed to examine the disease-modifying effects of MTX, there were no differences in radiographic progression between patients treated with MTX (n = 38) and matched controls.\textsuperscript{38}

**MTX Versus Cyclosporine**

In a prospective, randomized study of 35 patients treated for 1 year, Spadaro and colleagues concluded that MTX was as effective as cyclosporine in treating PsA.\textsuperscript{39} Cyclosporine dosages of 3 to 5 mg/kg per day and MTX at 7.5 to 15 mg per week were associated with several clinical improvements, such as fewer painful or swollen joints, decreased Ritchie index score, shorter duration of morning stiffness, improvement in Psoriasis Area and Severity Index (PASI), improved grip strength, and improved patient and physician global assessments. The ESR improved to a greater extent with MTX than with cyclosporine, but MTX was associated with elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes. Fewer patients given MTX withdrew from the study, despite issues with hepatotoxicity.\textsuperscript{39} The most significant adverse effect of prolonged, intensive use of either MTX or leflunomide, another DMARD, is the potential for liver toxicity. This seems to occur more frequently in patients with psoriasis than among those with RA.\textsuperscript{40} A number of reasons have been speculated, including a proclivity toward obesity in psoriasis patients, increasing their risk for hepatic steatosis (fatty liver) as a concomitant problem.

**Leflunomide**

Leflunomide, a recently approved synthetic DMARD for RA, also has been shown to be effective in treating PsA. In a randomized clinical trial (n = 190), leflunomide was found to be statistically superior to placebo in reducing the symptoms of PsA, with Psoriatic Arthritis Response Criteria (PsARC) of 59% for the treatment group and 29.7% for the placebo group.\textsuperscript{41} The drug achieved clinically significant but modest results in modified ACR 20 and PASI measurements. Adverse effects for leflunomide include diarrhea and elevations in ALT.

**Cyclosporine**

In a double-blind trial comparing cyclosporine with placebo in patients with PsA, 80% of patients in the highest-dosage group of cyclosporine (7.5 mg/kg) exhibited clearing or near-clearing of psoriasis.\textsuperscript{32} A recent meta-analysis of three major randomized studies of patients with severe psoriasis concluded that cyclosporine is highly effective and well tolerated in the short term for management of skin disease.\textsuperscript{43} Cyclosporine Versus Sulfasalazine

In the absence of placebo-controlled trials, cyclosporine appears to be at least as effective as sulfasalazine in treating PsA, and it may be more effective than sulfasalazine in providing pain relief. For example, a 24-week, open-label study of 99 patients who had PsA compared cyclosporine with sulfasalazine and with symptomatic therapy (eg, analgesics, NSAIDs). Patients receiving cyclosporine experienced significantly greater improvement in pain after 6 months than did patients in the other two groups (p < .05). Treatment with cyclosporine also was associated with a reduction in CRP.\textsuperscript{44}

**Sulfasalazine**

Sulfasalazine has been used in more published PsA trials than most conventional therapies. In 221 patients with PsA whose disease was resistant to NSAIDs, Clegg and colleagues\textsuperscript{45} administered either 2 g/day of sulfasalazine or placebo for 36 weeks. Patients’ response to therapy was calculated according to PsARC,\textsuperscript{24, 25, 45} Although individual elements of the response criteria did not show a significant benefit for sulfasalazine, the distinction of the treatment and placebo groups did achieve statistical significance when using the composite criteria (58% vs. 45%, p = .05). When these patients were included in a larger retrospective re-analysis of data from various studies on treatment of spondyloarthritides (n = 619), sulfasalazine was found to be more effective than placebo in overall response to therapy, but its effectiveness was limited to peripheral articular symptoms, not axial manifestations.\textsuperscript{16} In a 6-month trial with 351 patients who had spondyloarthritis, high-dose (3 g/day) sulfasalazine was superior to placebo only in patients’ overall assessment. However, when the subgroup of PsA patients was analyzed, Dougados and colleagues found significant benefits from sulfasalazine in the patients’ and physician’s global assessments, overall pain, joint pain and swelling, and duration of morning stiffness.\textsuperscript{46} Other studies have shown marginal benefits of sulfasalazine compared with placebo in PsA.\textsuperscript{47-50}

**Other DMARDs**

Etretinate, a retinoid medication traditionally used for psoriasis, has been shown to have some marginal benefit for patients with PsA.\textsuperscript{51} In a study of 82 patients with PsA, intramuscular gold provided more relief of overall pain and improvement in the Ritchie Index than did oral gold, but it was not statistically superior to placebo.\textsuperscript{52}

The use of antimalarial medications is controversial because psoriasis flares have been associated anecdotally with use of these drugs.\textsuperscript{53} A 1999 review of 18 English-language publications revealed that up to 18% of patients who had psoriasis developed an exacerbation of their disease following antimalarial therapy.\textsuperscript{54} However, with this caution in mind, antimalarial medications can be used for mild PsA.\textsuperscript{52}

**New DMARDs: Biologic Agents**

Biologic agents are designed to target specific immunologic mechanisms operative in a variety of inflammatory diseases. Rheumatologists are using these drugs increasingly to treat RA (see Volume 1/Issue 1 in this series). Dermatologists are using these agents to treat moderate to severe psoriasis. Both specialists are using these agents to treat PsA that has not responded adequately to NSAID or DMARD therapy alone (Fig. 2). Biologic agents differ in their mechanisms of action but share an ability to interrupt specific parts of the cascade of immunologic cell activation involved in rheumatic diseases. In PsA, these agents, particularly those targeting the proinflammatory cytokine TNF-α, have produced dramatic improvements in arthritis, enthesis, and psoriatic skin lesions.\textsuperscript{25-50}
**Current anti–TNF-α agents include etanercept (Enbrel, Immunex Corporation, Thousand Oaks, CA), infliximab (Remicade, Centocor, Inc., Malvern, PA), and adalimumab (Humira, Abbott Laboratories, Chicago, IL).** The precise mechanism of action responsible for the efficacy of these agents has not been fully delineated. Some of the observed histologic and immunohistochimical effects of TNF inhibition include reductions of: synovial lining layer thickness, vascularity, endothelial expression of avb3 and vascular cell adhesion molecule (VCAM)-1, sublayer expression of ICAM-1 and E-selectin, T-cell and macrophage infiltration, vascular endothelial growth factor (VEGF) expression, synovial Fk-1 expression and reduction in the numbers of osteoclast precursors, as well as in osteoclast differentiation. Several studies have shown correlative findings in skin biopsies. Studies of patients with RA show that a substantial number of those who have inadequate efficacy with one anti–TNF-α medication may switch to another and attain at least an ACR 20 response. Although interesting, this has not been formally studied in patients with PsA.

**Etanercept**

Etanercept is a soluble receptor TNF-α antagonist currently approved for the treatment of RA, JA, PsA, AS, and psoriasis. Dosage is typically 25 mg given subcutaneously twice a week or 50 mg given once a week, although when a higher dose is used in skin psoriasis. The approval of etanercept in PsA was based on two placebo-controlled trials. In a single-center trial, 60 patients with PsA, about half of whom (47%) were receiving concomitant stable MTX were randomized to etanercept or placebo. On average, patients had nearly a 20-year history of psoriasis and a 15-year history of inflammatory arthritis. In the 3-month placebo-controlled phase of the study, 87% of patients receiving etanercept and 23% of patients receiving placebo improved according to the composite outcome measure PsARC. In addition, 73% of patients receiving etanercept and 13% of patients receiving placebo improved according to the composite ACR 20 response criteria, a standard for assessing treatment response in rheumatoid arthritis (p = .015). Skin lesions also improved. The concomitant use of MTX did not affect the results, suggesting that etanercept can be effective as monotherapy or in combination with a traditional DMARD.

In a larger, multicenter study of similar design, 205 patients with PsA received etanercept or placebo. Concomitant MTX was used by 42% of patients.57 Fifty-nine percent of etanercept patients and 15% of placebo patients achieved an ACR 20 response. PsARC response was observed in 72% and 31%, respectively. The treatment group showed significant changes in all individual measures of the composite criteria. Skin responses were good at 6 months; the etanercept group achieved 47% PASI 50 and 23% PASI 75, respectively, and the placebo group achieved 18% PASI 50 and 3% PASI 75 (p ≤ .001). Also, there were significant improvements in measures of quality of life (Short Form Health Survey general questionnaire [SF-36], Dermatology Life Quality Index [DLQI]) and function (Health Assessment Questionnaire [HAQ]). Inhibition of disease progression, as documented radiographically, also was shown, the first demonstration of such an effect in PsA. Thus, after 48 weeks, there was no worsening of Total Sharp Score (TSS) in the active treatment group, a significant benefit compared with placebo, where worsening was observed. As in the previous trial, background treatment with MTX did not affect outcome.

**Infliximab**

Infliximab, a chimeric monoclonal antibody, is currently approved for RA, Crohn’s disease, PsA, AS, and ulcerative colitis. It typically is administered as an intravenous infusion every 8 weeks. There have been two major placebo-controlled trials using this drug at a dose of 5 mg/kg intravenously in PsA: the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT, n = 104) and a phase III study, IMPACT II (n = 200). In both studies, background DMARD use was allowed but not required. In IMPACT II, MTX was the only DMARD allowed. In both studies, about half of enrolled patients received treatment with concomitant MTX, and this did not have an impact on efficacy.

IMPACT showed an ACR 20 response in 69% of patients receiving infliximab and 8% of patients receiving placebo at 16 weeks and a PsARC response in 78% and 18%, respectively. Patients with a good or moderate European League Against Rheumatism (EULAR) response were 85% and 23%, respectively. Enthesitis and dactylitis improved significantly. Thirty-nine patients had a baseline PASI of 2.5. Of these, 67% had at least a PASI 75 response compared with 0.05% in the placebo group (all p values ≤ .001). In an open-label, 1-year follow up of this group, patients originally taking placebo quickly achieved similar results with equivalent efficacy. Radiographic data of hands and feet (including the DIP joints of the hand) were analyzed according to the modified van der Heijde-Sharp method. These showed no disease progression in both groups over 50 weeks. Because of the short duration of placebo treatment (14 weeks), no difference in the treatment groups could be shown over 1 year. However, the calculated annual progression rate was reduced, indicating that even delayed treatment with infliximab after 14 weeks inhibited radiographic progression of PsA.

Results from IMPACT II showed ACR 20 response in 58% of patients receiving infliximab and 11% of patients receiving placebo, PsARC in 77% and 27%, and PsA 75 and 65% and 2%, respectively (all p values = .001). Median PASI improvement was 87% in ACR 20 responders and 74% in ACR 20 non-responders, suggesting that skin response could be achieved even when joint response was not demonstrated. Radiographic data showed significantly less disease progression in patients receiving infliximab at week 24 than in patients receiving placebo. When PsA-specific radiographic features—including pencil-in-cup deformities and gross osteolysis—were examined, there was no difference between the treatment groups, a result found in radiographic results of the other anti–TNF-α agents as well.

**Adalimumab**

Adalimumab is a human anti–TNF-α monoclonal antibody. It is administered subcutaneously, 40 mg every other week. It currently is approved for use in RA and PsA. It was first shown...
effective for PsA in an open trial of 15 patients.\textsuperscript{72} In a larger placebo-controlled trial (n = 313) in PsA, in which 50% of patients were on background MTX, 58% of the treatment group and 14% of the placebo group showed ACR 20 response at 3 months, the primary endpoint (p < .001). Initial response in skin was rapid (as early as 2 weeks) and significant. As in the studies of the other TNF inhibitors, concomitant use of MTX did not have an effect on efficacy. At 6 months, PASI 50/75/90 responses were 75%, 59%, and 42% in the adalimumab group and 12%, 1%, and 0% in the placebo group, respectively (all p values < .001).\textsuperscript{60} Radiographic progression of disease was significantly inhibited by adalimumab.\textsuperscript{60}

A number of other anti–TNF-\(\alpha\) agents are in various phases of development for PsA, including a human monoclonal antibody for subcutaneous administration (golimumab), a PEGylated Fab fragment of a monoclonal antibody (certolizumab pegol [CDP870]), and even oral agents that have TNF-\(\alpha\)-inhibiting capability.

### Safety of Anti–TNF-\(\alpha\) Agents

An in-depth review of safety issues regarding anti–TNF-\(\alpha\) agents was provided in Volume 1/Number 1 of this Updates series. No significant new safety issues have developed in PsA trials, other than those reported in RA trials (such as administration reactions and infection). However, the experience to date with TNF-\(\alpha\) inhibitors in PsA is relatively small. Of note, there has been no observed increase in frequency of Koebner phenomenon or cellulitis in patients with PsA.

### Other Biologic Agents

Several agents being developed for use in RA or psoriasis eventually will be assessed for use in PsA and other spondyloarthritides (see Fig. 2). The common feature of these agents is their ability to target different key cells and cytokines of the immune response and inflammatory processes. Agents currently being tested for efficacy in PsA include drugs that inhibit T cells by blocking the “second signal” of T-cell activation. The “first” signal is provided by the cognate interaction of antigen appropriately presented in the context of major histocompatibility complex molecules on the surface of antigen-presenting cells, with specific T-cell receptors on the surface of T cells. There are several pairs of receptor/counter-receptors capable of providing stimulatory “second” signals. Several of these are the targets of immunomodulatory therapies for autoimmune diseases and are characterized below.

#### Alefacept

Alefacept is a human fusion protein that blocks the interaction between leukocyte function associated antigen-3 (LFA-3) on antigen-presenting cells and CD2 on T cells. It is given as a weekly (15 mg) intramuscular injection and currently is approved for use in psoriasis.\textsuperscript{73, 74} Treatment leads to a depletion of T cells, preferentially memory T cells, via interactions through the molecule’s Fc piece. The drug is given as a regimen of 12 weeks on and 12 weeks off, partly to allow recovery of CD4 counts, which must be monitored during therapy. Despite the transient depletion of CD4 cells, there has been no increase risk of infection in psoriasis trials.\textsuperscript{73, 74} In a small (n = 11) open-label trial of this compound in PsA, more than half of patients showed ACR 20 responses. Synovial biopsies showed a decrease in CD4, CD8, and CD68 (macrophage) cells in the synovial lining.\textsuperscript{75}

A recent randomized clinical trial (n = 185) to evaluate the efficacy and safety of alefacept in combination with MTX for patients with PsA\textsuperscript{76} found that this combination provided significant clinical improvement in PsA. Patients given a 12-week course of alefacept and MTX had significantly greater response rates in both PsA (ACR 20) and psoriasis (PASI 50) than patients given placebo plus MTX. There was incremental improvement in ACR 20 response during the treatment-free phase, indicating that response to alefacept continues even when the drug is not being administered.\textsuperscript{77}

#### Efalizumab

Efalizumab is a humanized antibody to the CD11 subunit of LFA-1 that inhibits the interaction of LFA-1 with its counter-receptors, including ICAM-1. It can interfere with the activation of T lymphocytes, as well as migration of cells from the circulation to sites of inflammation. Demonstrated efficacy in psoriasis has led to its approval for this condition.\textsuperscript{78} In a 12-week trial of patients with PsA, in which efalizumab was administered subcutaneously once a week, 28% of patients achieved an ACR 20 response versus 19% in the placebo group (p = .2717).\textsuperscript{79}

#### Abatacept

Abatacept, previously known as CTLA4-Ig, is a recombinant human fusion protein comprising the extracellular domain of human CTLA4 along with the Fc piece of a human immunoglobulin G (IgG1) molecule. CTLA4 is a naturally occurring inhibitor molecule that binds to CD80 and CD86 on antigen-presenting cells, thereby inhibiting the ability of CD28 to bind to these molecules and provide an activating signal. Recently approved for use in RA, abatacept is administered intravenously once per month.\textsuperscript{80} A Phase II trial for psoriasis has been conducted.\textsuperscript{81} It is anticipated that further assessment of this drug will be conducted for PsA and for psoriasis.

### Other Potential Treatments

A number of other agents are being tested or potentially could be tested in PsA, including a number of cytokine inhibitors. A pilot trial of an IL-15 inhibitor in PsA has shown efficacy.\textsuperscript{82} A trial currently is underway to assess the efficacy and safety of an IL-1 antagonist, anakinra, in PsA (Fitzgerald O, personal communication, 2005). A humanized antibody to the \(\alpha\)-subunit (CD25) of the IL-2 receptor that blocks IL-2 binding to the T-cell receptor has been tried in psoriasis, albeit with some loss of efficacy noted over time.\textsuperscript{83, 84} A monoclonal antibody to the IL-6 receptor (MRA) is in phase III development for the treatment of RA; benefit has been shown in phase II, and this antibody will likely be tested in PsA.\textsuperscript{85} Several inhibitors of IL-12 are undergoing active evaluation in psoriasis, with good early success (Leonardi C, personal communication, 2005); these are likely to be assessed in PsA as well. Similarly, it is anticipated that inhibitors of IL-18 will be studied.

Conversely, some cytokines may have anti-inflammatory effects, and thus, their administration may be therapeutic. A recombinant IL-10 agent has been studied in psoriasis, with demonstration of preliminary benefit.\textsuperscript{86} However, a controlled study with human IL-10 in patients with PsA showed benefit in the skin but not in joints.\textsuperscript{87} Similarly, a recombinant human IL-11 has been used to treat psoriasis, with preliminary benefit noted clinically and histologically.\textsuperscript{88}

huOKT3\(\gamma\), a monoclonal antibody to CD3 and a component of the T-cell receptor complex, has demonstrated some benefit in PsA, although issues such as transient T-cell depletion and mild cytokine release symptoms have been noted.\textsuperscript{89}

Pioglitazone is a ligand for peroxisome proliferator-activated receptor (PPAR) that is administered orally. It originally was developed to treat diabetes but has been considered as a potential therapy for inflammatory autoimmune disease, such as PsA, due to observations that it led to a marked inhibition of angiogenesis and down-regulation of proinflammatory cytokines.\textsuperscript{90} In an uncontrolled trial of pioglitazone treatment, 60% of patients met the
PsARc criteria and 50% achieved an ACR 20 response after 12 weeks. This agent may be beneficial for treating PsA, but its efficacy must be evaluated in a well-controlled study.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is the most prevalent of the spondyloarthritides. Among the spondyloarthritides, AS and PsA have the most severe disease course. The pathophysiologic features of AS are similar to those of PsA and, indeed, at a cellular and immunohistochemical level, appear to be identical. Progression of inflammation in AS produces radiographic damage in the spine and in peripheral joints, leading to pain, loss of function, and loss of mobility for patients. Many patients with AS also show gut lesions similar to those seen in Crohn’s disease. Disability and consequent absence from work is increased threefold for patients with AS. Thus, the condition results in substantial costs for the patient and society.

Treatment

Treatment for AS traditionally has included medications, such as NSAIDs, that largely relieve symptoms, although they may also modify the disease. Recent trials demonstrated the efficacy of celecoxib and etoricoxib (not approved or marketed) in AS. Traditional synthetic DMARDs have not proved effective for spinal aspects of AS, the predominant clinical issue for these patients. Physical therapy traditionally has played an important role in treatment and has shown effective for patients with AS.

As with PsA and RA, the most significant advance in pharmacologic treatment for AS has been the development of biologic agents that may modify progression of the disease. In RA and PsA, the three currently available anti-TNFα agents used in clinical trials in AS include etanercept, infliximab, and adalimumab. Of these, etanercept and infliximab have gained approval thus far. In contrast to RA, clinical studies in AS have not included MTX in combination with biologic agents because the efficacy of MTX in AS is doubtful. A comprehensive discussion of biologic agents in AS is given by Braun et al.

TNF Inhibitors in AS

Etanercept has demonstrated efficacy in AS. An initial randomized, double-blind, placebo-controlled study of etanercept (25 mg administered biweekly subcutaneously for 4 months) demonstrated significant improvement in disease activity over baseline values, as measured by assessment of spinal pain, morning stiffness, enthesitis, ESR, CRP, chest expansion, functioning, and quality of life. Improvement was rapid and sustained. There was no significant difference in rates of adverse events between the etanercept and placebo groups. A larger, multicenter, double-blind, placebo-controlled study confirmed these results in patients with moderate to severe AS. Patients treated with etanercept achieved significant improvement in clinical features, with a greater percentage achieving ASAS (Assessment in Ankylosing Spondylitis) 20 by week 12 compared with patients receiving placebo. Improvement was significant within 2 weeks and was sustained through 2 years of treatment.

Several randomized clinical trials have documented the efficacy of infliximab in AS. A key outcome has been the regression of spinal inflammation, as documented by MRI studies.

In a recent international, multicenter randomized clinical trial, 61.2% of patients receiving infliximab achieved ASAS 20 compared with 19.2% of patients receiving placebo. In the same study, 22.4% of patients taking infliximab achieved ASAS criteria for partial remission, compared with 1.3% of patients taking placebo. Long-term results with infliximab indicate continuous improvement over 3 years, including reduction of NSAID dosage in 70% of patients. All patients were withdrawn from treatment after 3 years to assess the nature of the subsequent disease course. Two thirds of these patients relapsed within the first 6 months, with a mean relapse time of 3 months. When infliximab was re-instituted, efficacy as originally noted was re-achieved. A recent study comparing the effectiveness of etanercept and infliximab in RA compared with AS found that patients with AS experienced health-related quality-of-life improvement that was comparable to, and sometimes greater than, that observed in patients with RA.

Preliminary data from the only current study of adalimumab in AS show significant improvement in pain and function.

ASAS/EULAR Recommendations

The Assessment in Ankylosing Spondylitis (ASAS) international working groups and the European League Against Rheumatism (EULAR) recently released recommendations for the management of AS. These were developed using evidence-based recommendations from a multidisciplinary development committee, as well as a systematic literature search. The group developed 10 key recommendations (Table 2) to assist clinicians in assessing both clinical and observational data, thus enabling them to select the most effective treatment for specific patients. The recommendations specify that optimal treatment of AS includes both pharmacologic and nonpharmacologic therapies. The group also emphasizes these are recommendations, not guidelines, and that the recommendations will be modified as new clinical and patient evidence is elucidated.

TABLE 2. ASAS/EULAR Recommendations for the Treatment of Ankylosing Spondylitis

1. Treatment of AS should be tailored according to: current manifestations of the disease; level of current symptoms, clinical findings and prognostic indicators; general clinical status; and wishes and expectations of the patient.
2. Disease monitoring of patients with AS should include: patient history (eg, questionnaires), clinical parameters, laboratory presentation, as well as the ASAS core set. The frequency of monitoring should be decided on an individual basis, depending on symptoms, severity, and drug treatment.
3. Optimal management of AS requires a combination of nonpharmacological and pharmacological treatments.
4. Nonpharmacological treatment of AS should include patient education and regular exercise. Individual and group physical therapy should be considered. Patient associations and self-help groups may be useful.
5. NSAIDs are recommended as first-line drug treatment for patients with AS with pain and stiffness. In those with increased gastrointestinal (G) risk, nonselective NSAIDs plus a gastroprotective agent, or a selective COX-2 inhibitor could be used.
6. Analgesics, such as acetaminophen and opioids, might be considered for pain control in patients in whom NSAIDs are insufficient, contraindicated, and/or poorly tolerated.
7. Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered. The use of systemic corticosteroids for axial disease is not supported by evidence.
8. There is no evidence for the efficacy of DMARDs, including sulfasalazine and methotrexate, for the treatment of axial disease. Sulfasalazine may be considered in patients with peripheral arthritis.
9. Anti-TNF treatment should be given to patients with persistently high disease activity, despite conventional treatments according to the ASAS recommendations. There is no evidence to support the obligatory use of DMARDs before, or concomitant with, anti-TNF treatment in patients with axial disease.
10. Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal surgery—for example, corrective osteotomy and stabilization procedures—may be value in selected patients.

AS = ankylosing spondylitis; ASAS = Assessment in Ankylosing Spondylitis; COX-2 = cyclooxygenase-2; DMARD = disease-modifying anti-rheumatic drug; EULAR = European League Against Rheumatism; NSAID = nonsteroidal anti-inflammatory drug; TNF = tumor necrosis factor.
TREATMENT OF OTHER SPONDYLOARTHRITIDES

Other forms of spondyloarthritis, including reactive arthritis, undifferentiated spondyloarthritis, and inflammatory bowel disease–associated spondyloarthritis, affect relatively smaller populations and are clinically heterogeneous. Thus, there are fewer studies documenting effective treatments.

Reactive arthritis (previously known as Reiter syndrome) is a term used to describe arthritis that can include spondyloarthritis and that, in some cases, is triggered by infectious agents. This includes those infecting the urogenital or gastrointestinal tract, such as Campylobacter, Salmonella, Versinia, and Chlamydia. Poststreptococcal reactive arthritis appears to be a heterogeneous condition, with a group that resembles rheumatic fever and a group with spondyloarthropathy traits. There are numerous theories regarding a link between infectious triggers and resultant prolonged activation of the immunologic and inflammatory cascades, even when the infectious agent is no longer present. Mechanisms suggested to be potentially relevant to the etiology and pathogenesis of reactive arthritis include molecular mimicry, arthritogenic peptides, and genetic factors.

Undifferentiated spondyloarthritis includes conditions that have spondyloarthritides features but do not fit into any other defined spondyloarthritis subgroup. Spondyloarthritis associated with inflammatory bowel disease may be associated with peripheral joints, including a pauciarticular, asymmetrical, transitory form, along with enthesopathy. It is observed in 10% to 20% of patients with inflammatory bowel disease–associated arthritis and frequently coincides with a flare-up of intestinal disease.

Demonstration of the benefit of treatments for these other subtypes of spondyloarthritis has been limited. As in PsA, physical therapy may play an important role. NSAIDs relieve pain and inflammation and have been proved effective in a recent trial. Sulfasalazine may be used to treat patients with gut disease or peripheral arthritis in early and active stages of these other subtypes of spondyloarthritis.

Use of Biologic Agents in Other Spondyloarthritides

Preliminary studies suggest that infliximab and etanercept are effective in treating arthritis associated with inflammatory bowel disease, TNF-α inhibition with infliximab and adalimumab, but not etanercept (at the doses studied), have proved effective in Crohn’s disease and in ulcerative colitis, which can be associated with AS. Rapid, substantial, and sustained improvement in symptoms has been reported following treatment with infliximab, suggesting an essential role for TNF-α in spondyloarthropathy, similar to that observed in Crohn’s disease.

Biologic Agents for Juvenile-Onset Spondyloarthritis

Although the experience with anti-TNF-α agents is limited in children and adolescents with juvenile-onset spondyloarthritis, current results suggest that infliximab and etanercept are at least as effective as in children as in adults. Most patients are able to stop taking NSAIIDs and other medications. In a recent study, administration of 0.2 to 0.8 mg/kg of etanercept subcutaneously twice weekly in eight patients with juvenile-onset AS produced a prolonged reduction in the number of active joints, morning stiffness, and ESR. The mean age of the group was 15.9 years (range, 12–25 years), and the mean follow-up of these patients was 15.4 months. All patients tolerated etanercept without side effects. In unpublished observations, Burgos-Vargas has treated six patients with juvenile-onset spondyloarthritides with 5 mg/kg of infliximab at weeks 0, 2, 6, and then every 2 months for nearly 1 year. There were significant reductions in peripheral and axial signs of disease after the first and second infusion of the drug, including a decrease in the number of peripheral joints with active arthritis and tender entheses. A decrease in CRP values, in pain as evaluated by visual analog scale (VAS), and in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores also was observed. Long-term follow up is required to determine safety and efficacy

Table 3. ASAS/EULAR Guidelines for Use of Biologic Agents to Treat Ankylosing Spondylitis and US Modifications of These Guidelines

<table>
<thead>
<tr>
<th>ASAS</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Modified New York Criteria</td>
</tr>
<tr>
<td>Disease Activity</td>
<td>BASDAI Score of &gt; 4 cm (scale 0–10) and Physician Global Assessment by “expert” opinion (yes/no)</td>
</tr>
<tr>
<td>Previous Treatment</td>
<td>Failure by lack of response or intolerability to &gt; 2 NSAIDs for 3 months for all clinical 3 presentations: axial, peripheral arthritis, and enthesitis</td>
</tr>
<tr>
<td>Dosing</td>
<td>Etanercept 25 mg SQ twice a week, Infliximab 5 mg/kg IV q 6–8 weeks</td>
</tr>
<tr>
<td>Responder Criteria</td>
<td>Infliximab 5 mg/kg IV q 6–8 weeks</td>
</tr>
<tr>
<td>Time of Evaluation</td>
<td>Between 6–12 weeks</td>
</tr>
<tr>
<td>TB Precaution</td>
<td>Use country-specific guidelines</td>
</tr>
</tbody>
</table>


ASAS = Assessment in Ankylosing Spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; DMARD = disease-modifying anti-rheumatic drug; EULAR = European League Against Rheumatism; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; SQ = subcutaneously; TB = tuberculosis.

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<td>BASDAI Score of &gt; 4 cm (scale 0–10) and Physician Global Assessment of 2 or greater on Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe)</td>
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<tr>
<td>Responder Criteria</td>
<td>Improvement in BASDAI by at least 2 units and Physician Global of &gt; 1</td>
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<tr>
<td>Time of Evaluation</td>
<td>Between 6–8 weeks</td>
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<tr>
<td>TB Precaution</td>
<td>TB screening and treatment per the American Thoracic Association recommendations</td>
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of these medications in children, and whether anti-TNF-α agents can halt the progressive destruction characteristic of juvenile-onset spondyloarthritides.

Cost-Effectiveness Analysis

There is an emerging focus on the economic implications of these biologic therapies, whose acquisition costs exceed those of older anti-rheumatic therapies. Appropriate pharmacoeconomic assessment must take into consideration the costs of the therapies themselves, but also the costs of the disease, in terms of work disability and the interference with the ability to perform activities of daily living. Highly effective therapies may be shown to be cost-effective if they are able to avoid the costs of rheumatic diseases. Several recent studies have demonstrated the potential cost-effectiveness of anti-TNF-α agents in PsA.139,140 Similar studies have been accomplished for AS.141,142

CONCLUSION

As emerging treatments for PsA, AS, and other spondyloarthritides show significant benefit for clinical signs and symptoms, quality of life, functional status, and the inhibition of joint damage as assessed by radiographic progression, there has been increasing interest in accurate diagnosis and classification of these diseases. This would facilitate the institution of appropriate therapy in a timely fashion. Additionally, numerous studies have increased our understanding of the basic pathophysiology of the diseases, providing support for the clinical effects of targeted therapy, for example, inhibition of TNF-α. There are fewer studies documenting these benefits with traditional DMARDS, whose effectiveness does not seem, as great as TNF-α inhibitors. In AS, recent trials suggest that DMARDS are not effective in the spine. Targeted therapies that inhibit proinflammatory cytokines, such as the TNF-α inhibitors, have proved highly effective in managing joint and enthesial disease. 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.

Significant efforts are underway to 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 as the ASAS international working group and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).

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

REFERENCES


