Psoriatic arthritis (PsA), a chronic, inflammatory disease that causes pain, stiffness, and swelling in and around the joints, generally develops between the ages of 30 and 50 years, but it can affect people of all ages, including children. In the United States, the overall prevalence of PsA is estimated to range from 101 to 250 cases per 100,000 people; however, the prevalence of PsA has historically been challenging to determine, because of its misdiagnosis and the lack of widely accepted diagnostic criteria. PsA is sometimes misdiagnosed as rheumatoid arthritis, gout, or osteoarthritis.

Both PsA and psoriasis are chronic autoimmune diseases. Of the estimated 7.5 million patients (approximately 2.2% of the US population) who have psoriasis, 10% to 30% will also develop PsA. Although the exact cause of PsA is unknown, research suggests that it develops from a combination of genetic (ie, heredity) and environmental factors. In addition, immune system conditions, infection, and physical trauma may play a role in the development of PsA. PsA may also be triggered by a streptococcal throat infection.

PsA also has a substantial impact on the patient’s psychological and psychosocial functioning and daily living activities. The visible nature of skin involvement may also lead to embarrassment, self-consciousness, and, in some cases, depression. Moreover, PsA may be associated with an increased risk for osteoporosis and cardiovascular disease, as well as an increased risk for other inflammatory conditions, including uveitis and iritis. Patients with PsA have a slightly increased risk for high blood pressure, high cholesterol, obesity, or diabetes. Anemia and fatigue are also common in patients with PsA.

Based on a 2010 review of 49 studies, PsA accounts for nearly $1.9 billion in direct annual healthcare costs. Hospitalizations are the key driver of the direct costs, accounting for approximately 60% of the total direct costs. Indirect costs, including disability and lost productivity, account for 52% to 72% of the total costs. Furthermore, worsening physical function and disease activity are associated with increases in both direct and indirect costs.

The early diagnosis and treatment of PsA are essential to relieving pain and inflammation and to helping prevent progressive joint involvement and damage. The therapeutic goals for patients with PsA are to alleviate symptoms, including pain and skin symptoms; to protect the joints; and to maintain mobility. Treatment decisions are based on disease severity, the number of joints involved, and associated skin symptoms.

Treatments for PsA may include a combination of nonpharmacologic and pharmacologic options. Nonpharmacologic approaches include exercise, heat and cold therapy, water therapy, the use of splints, joint protection and energy conservation, and surgery (when severely damaged joints need replacement). Pharmacologic treatments include nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs). Corticosteroid injections may be useful in patients with PsA and swollen joints. DMARDs are generally used in patients with erosive disease or in patients who fail to respond to NSAIDs. DMARDs that are effective in treating PsA include methotrexate, sulfasalazine (Azulfidine), cyclosporine, and leflunomide (Arava). In addition to reducing the signs and symptoms of PsA, the biologic DMARDs also slow the progression of joint damage. The biologic DMARDs include the following tumor necrosis factor (TNF)-α inhibitors: adalimumab (Humira), etanercept (Enbrel), golimumab (Simponi), and infliximab (Remicade). Recently, ustekinumab—a new biologic DMARD that targets the interleukin (IL)-12 and IL-23 cytokines—became available for the treatment of patients with PsA.

Stelara Injection: A New Biologic Option for Patients with PsA

In September 2013, the US Food and Drug Administration (FDA) approved a new indication for ustekinumab (Stelara; Janssen Biotech), alone or in combination with methotrexate, for the treatment of adult patients (aged ≥18 years) with active PsA. Ustekinumab, a human immunoglobulin (Ig)G1κ monoclonal antibody that targets the shared p40 protein subunit of the IL-12 and IL-23 cytokines, is the first and only anti–IL-12/23 therapy approved by the FDA for adults with PsA.

According to study investigator Alice B. Gottlieb, MD, Chief and Dermatologist-in-Chief in the Department of Dermatology at Tufts Medical Center, “It is
critical for dermatologists and rheumatologists to be able to offer new and novel treatment options to our adult patients living with psoriatic arthritis, a disease where additional biologic options are very much needed.”

She further commented, “Therapy that targets the cytokines interleukin-12 (IL-12) and interleukin-23 (IL-23), two naturally occurring proteins believed to play a role in the development of this debilitating immune-mediated inflammatory disease, could improve patient care.”

**Mechanism of Action**

Ustekinumab is a human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit used by the IL-12 and IL-23 cytokines. These naturally occurring cytokines are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation.7

Levels of IL-12, IL-23, and p40 are elevated in the skin and blood of patients with psoriasis, and in the blood of patients with PsA, implicating IL-12 and IL-23 in the pathophysiology of psoriatic inflammatory diseases. In in vitro models, ustekinumab was shown to disrupt IL-12– and IL-23–mediated signaling and cytokine cascades by upsetting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1.7

**Dosing**

Ustekinumab is administered by subcutaneous injection. For the treatment of PsA, the initial recommended dose is 45 mg followed 4 weeks later by 45 mg every 12 weeks. For patients with coexistent moderate-to-severe plaque psoriasis weighing >100 kg (220 lb), the recommended dose is 90 mg initially and, 4 weeks later, followed by 90 mg every 12 weeks.7

Ustekinumab injection is available in several dosage forms and strengths: 45 mg/0.5 mL in a single-use prefilled syringe, 45 mg/0.5 mL in a single-use vial, and 90 mg/mL in a single-use prefilled syringe.

Ustekinumab is intended for use under the guidance and supervision of a physician. It should only be administered to patients who will be closely monitored and who will have regular follow-up visits with a physician. After proper training in subcutaneous injection technique, a patient may self-inject with ustekinumab if a physician determines that it is appropriate.7

**Clinical Studies**

The safety and efficacy of ustekinumab were evaluated in 927 patients in 2 randomized, double-blind, placebo-controlled studies of patients aged ≥18 years with active PsA (≥5 swollen joints and ≥5 tender joints), despite therapy with NSAIDs or DMARDs. The patients enrolled in these studies had a diagnosis of PsA for a minimum of 6 months. The patients had the following subtypes of PsA: polyarticular arthritis with the absence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%), and arthritis mutilans (0.5%). More than 70% of the patients had enthesitis (ie, inflammation of the sites where tendons, ligaments, and joint capsules of the fascia attach to the bone) at baseline, and more than 40% had dactylitis (ie, inflammation of a finger or toe) at baseline.7

The patients in study 1 (N = 615) and study 2 (N = 312) were randomized to receive treatment with ustekinumab 45 mg or 90 mg or with placebo subcutaneously at weeks 0 and 4, followed by dosing every 12 weeks. Approximately 50% of the patients continued to receive stable doses of methotrexate (≤25 mg weekly).7

In study 1, 80% of the patients had previously received DMARDs; previous treatment with an anti–TNF-α agent was not allowed. In study 2, 86% of the patients had previously received DMARDs, and 58% had previously received an anti–TNF-α agent, of whom more than 70% had discontinued their anti–TNF-α treatment for lack of efficacy or intolerance at any time.7

The primary end point in study 1 and study 2 was the percentage of patients achieving an ACR20 response at week 24.7 ACR20 is defined by the American College of Rheumatology (ACR) as a 20% improvement in tender and swollen joint counts and a 20% improvement in at least 3 of the 5 following ACR core set measures: patient and physician global assessments, patient-assessed pain, patient self-assessed disability, and an acute-phase reactant.9 Other responses measured included the presence of lesions over the body surface area (0%-3% = mild; 3%-10% = moderate; and >10% = severe)10; and the Psoriasis Area and Severity Index (PASI), which measures 3 features of psoriatic plaque—redness, scaling, and thickness—where each is assigned a rating of 0 to 4, with 4 being the worst.11 The extent of involvement of each region of the body is given a rating of 0 to 6; the subsequent total score can range from 0 to 72.11

The clinical response results for studies 1 and 2 are shown in Table 1. In both studies, at week 24 a greater proportion of patients achieved ACR20, ACR50, and PASI 75 response in the ustekinumab 45-mg and 90-mg groups compared with those receiving placebo. ACR70 responses were also higher in the ustekinumab 45-mg and 90-mg cohorts, although the difference was not statistically significant in study 2. The responses were similar in patients regardless of previous TNF-α exposure.7

The results of the components of the ACR response criteria from study 1 are shown in Table 2. In the 2 groups receiving ustekinumab (45 mg and 90 mg), improvements in enthesitis and dactylitis scores were ob-
served at week 24 compared with placebo. The patients receiving ustekinumab also showed improvement in physical function compared with patients receiving placebo, as assessed by the Health Assessment Questionnaire–Disability Index at week 24.7

Safety
The safety of ustekinumab was assessed in 927 patients in 2 randomized, double-blind, placebo-controlled studies in adult patients with active PsA. The overall safety profile of ustekinumab in patients with PsA was consistent with the safety profile seen in clinical trials of patients with psoriasis. In the placebo-controlled groups of the PsA clinical trials, a higher incidence in several adverse events was seen in patients receiving ustekinumab compared with patients receiving placebo, including arthralgia (3% vs 1%, respectively), nausea (3% vs 1%, respectively), and dental infections (1% vs 0.6%, respectively).7

The most common adverse events (incidence ≥3% and more than with placebo) were nasopharyngitis, upper respiratory tract infection, headache, and fatigue.7

Drug Interactions
Drug interaction studies have not been conducted with ustekinumab.7 Live vaccines should not be given concurrently with ustekinumab.

CYP450 substrates. The formation of cytochrome (CY) P450 enzymes can be altered by increased levels of certain cytokines during chronic inflammation. Thus, ustekinumab, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. On initiation of ustekinumab in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect or drug concentration should be considered.

Allergen immunotherapy. Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. Ustekinumab may decrease the protective effect of allergen immunotherapy, which may increase the risk for an allergic reaction.

Contraindications
Ustekinumab is contraindicated in patients with clinically significant hypersensitivity to ustekinumab or to any of the excipients.7

Warnings and Precautions
Infections. Ustekinumab may increase the risk for infections and the reactivation of latent infections. Serious bacterial, fungal, and viral infections were observed in patients receiving ustekinumab. In the PsA clinical studies, serious infections included cholecystitis. Ustekinumab should not be started during any clinically important active infection. If a serious infection develops, ustekinumab should be stopped until the infection resolves.

Serious infections from mycobacteria, Salmonella, and Bacillus Calmette–Guérin vaccinations have been reported in patients who are genetically deficient in IL-12 or IL-23. Diagnostic tests for these infections should be considered as dictated by the clinical circumstances.

Tuberculosis. Patients should be evaluated for tuberculosis infection before initiating treatment with ustekinumab, which should not be administered to patients with active tuberculosis. Patients receiving ustekinumab should be monitored closely for signs and symptoms of active tuberculosis. Treatment of latent tuberculosis should be initiated before administering ustekinumab.
**Malignancies.** Ustekinumab is an immunosuppressant, and it may increase the risk for malignancy.  

**Hypersensitivity reactions.** Anaphylaxis and angioedema have been reported postmarketing. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, the appropriate therapy should be given and ustekinumab should be discontinued.

**Reversible posterior leukoencephalopathy syndrome (RPLS).** One case of RPLS was observed during the psoriasis clinical development program; no additional cases of RPLS were observed in the PsA clinical development program.7

**Pregnancy.** There are no adequate and well-controlled studies of ustekinumab in pregnant women. Ustekinumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.7

**Nursing mothers.** Caution should be used when ustekinumab is administered to a nursing woman.7

**Pediatric/geriatric use.** The safety of ustekinumab in pediatric patients has not been established. And although no differences in safety or efficacy were observed between older and younger subjects in clinical trials, the number of adults aged ≥65 years was not sufficient to compare their response to younger patients.7

**Conclusion**

A novel biologic option became available for patients with PsA with the approval of a new indication for ustekinumab, the first and only anti–IL-12/23 therapy approved by the FDA for this complex and potentially debilitating condition. Previously approved by the FDA for the treatment of adults with moderate-to-severe plaque psoriasis, ustekinumab is now also indicated for the treatment of patients with active PsA. Evidence from phase 3 randomized, double-blind, placebo-controlled studies shows the benefits of ustekinumab for adults with PsA. Patients who received ustekinumab showed improvement in physical function compared with patients who received placebo at week 24. ■

**References**

7. Stelara (ustekinumab) injection [prescribing information]. Horsham, PA: Janssen Biotech, Inc; September 2013.

### Table 2

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Placebo (N = 206)</th>
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</table>

*VAS score: 0 = best, 10 = worst.

*HAQ-DI: 0 = best, 3 = worst; measures the patient’s ability to perform daily activities.

*CRP normal range, 0–1 mg/dL.

*ACR indicates American College of Rheumatology; CRP C-reactive protein; HAQ-DI, Health Assessment Questionnaire–Disability Index; PsA, psoriatic arthritis; VAS, visual analog scale.

Source: Stelara (ustekinumab) injection prescribing information; 2013.