Psoriasis is a common skin disease that is associated with multiple coexisting conditions. The most prevalent coexisting condition, psoriatic arthritis, develops in up to 30% of patients with psoriasis and is characterized by diverse clinical features, often resulting in delayed diagnosis and treatment. Initial reports emphasized a benign course in most patients, but it is now recognized that psoriatic arthritis often leads to impaired function and a reduced quality of life. Fortunately, improved knowledge about disease mechanisms has catalyzed rapid development of effective targeted therapies for this disease. To help the clinician recognize and appropriately treat psoriatic arthritis, this review focuses on epidemiologic and clinical features, pathophysiological characteristics, and treatment.

Psoriatic Arthritis

Christopher T. Ritchlin, M.D., M.P.H., Robert A. Colbert, M.D., Ph.D., and Dafna D. Gladman, M.D.

Psoriasis is a common skin disease that is associated with multiple coexisting conditions. The most prevalent coexisting condition, psoriatic arthritis, develops in up to 30% of patients with psoriasis and is characterized by diverse clinical features, often resulting in delayed diagnosis and treatment. Initial reports emphasized a benign course in most patients, but it is now recognized that psoriatic arthritis often leads to impaired function and a reduced quality of life. Fortunately, improved knowledge about disease mechanisms has catalyzed rapid development of effective targeted therapies for this disease. To help the clinician recognize and appropriately treat psoriatic arthritis, this review focuses on epidemiologic and clinical features, pathophysiological characteristics, and treatment.

Psoriatic Arthritis and Spondyloarthritis

The classic description of the clinical features of psoriatic arthritis was published in 1973; however, skeletal remains unearthed in 1983 from a Byzantine monastery in the Judean Desert, dating to the fifth century a.d., showed visual and radiographic features consistent with psoriatic bone and joint disease. Psoriatic arthritis shares genetic and clinical features with other forms of spondyloarthritis and is grouped with these disorders. Diagnostic criteria for psoriatic arthritis have not been validated, but the Classification Criteria for Psoriatic Arthritis (CASPAR criteria), published in 2006, define psoriatic arthritis for the purpose of enrolling patients in clinical trials and provide guidance to clinicians (Table 1).

Epidemiology and Disease Burden

The prevalence of psoriatic arthritis ranges from 6 to 25 cases per 10,000 people in the United States, depending on the case definition. Psoriatic arthritis was thought to be rare, but recent studies based on CASPAR criteria indicate that it occurs in up to 30% of patients with psoriasis. These data suggest that the prevalence of psoriatic arthritis is between 30 and 100 cases per 10,000, assuming that 3% of the U.S. population has psoriasis. About 15% of patients with psoriasis who are followed by dermatologists have undiagnosed psoriatic arthritis. The annual incidence of psoriatic arthritis was reported to be 2 to 3% in a prospective study of patients with psoriasis. The manifestation of psoriasis precedes that of arthritis by 10 years on average, although in 15% of cases, arthritis and psoriasis occur simultaneously or psoriatic arthritis precedes the skin disease. Psoriatic arthritis is uncommon in Asians and blacks, and the male-to-female ratio is 1:1.

Psoriatic arthritis can begin during childhood. There are two clinical subtypes; they are not mutually exclusive. Oligoarticular psoriatic arthritis (characterized by four or fewer affected joints) has a peak onset at 1 to 2 years of age and occurs...
predominantly in girls. This form is associated with a positive test for antinuclear antibodies and chronic uveitis and is often characterized by dactylitis (diffuse swelling of a toe or finger).12 The second subtype (characterized by any number of affected joints) develops between 6 years and 12 years of age and is associated with HLA-B27; antinuclear antibodies are usually absent. This form has a 1:1 sex ratio, with dactylitis, enthesitis (inflammation at tendon, ligament, or joint-capsule insertions), nail pitting, onycholysis, and axial involvement occurring more frequently than in the first subtype. According to the International League of Associations for Rheumatology classification system, psoriatic arthritis is distinct from other forms of juvenile idiopathic arthritis and is defined by the coexistence of arthritis and psoriasis in the absence of features of other forms of juvenile idiopathic arthritis.13 A child with arthritis who does not have psoriasis but who has two or more features of psoriatic arthritis, such as dactylitis, nail pitting, onycholysis, or a family history of psoriasis (first-degree relative), meets the criteria for psoriatic arthritis.

The psychological and functional burdens of the disease are considerable and similar in magnitude to those of axial spondyloarthritis and rheumatoid arthritis.14,15 One study showed that psoriatic arthritis was significantly associated with rates of absenteeism from work and productivity at work and that these findings were correlated with measures of disease activity and physical functioning.16 Mortality rates among patients with psoriatic arthritis have fallen and are similar to those in the general population, although some centers report an increase in mortality related to cardiovascular disease.17,18

Table 1. Classification Criteria for Psoriatic Arthritis (CASPAR).10

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Explanation</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of psoriasis</td>
<td>Current psoriatic skin or scalp disease as judged by a dermatologist or rheumatologist</td>
<td>2</td>
</tr>
<tr>
<td>Personal history of psoriasis</td>
<td>History of psoriasis according to the patient or a family doctor, dermatologist, or rheumatologist</td>
<td>1</td>
</tr>
<tr>
<td>Family history of psoriasis</td>
<td>History of psoriasis in a first- or second-degree relative according to the patient</td>
<td>1</td>
</tr>
<tr>
<td>Psoriatic nail dystrophy</td>
<td>Typical psoriatic nail dystrophy (e.g., onycholysis, pitting, or hyperkeratosis) according to observation during current physical examination</td>
<td>1</td>
</tr>
<tr>
<td>Negative test for rheumatoid factor</td>
<td>Based on reference range at local laboratory; any testing method except latex, with preference for ELISA or nephelometry</td>
<td>1</td>
</tr>
<tr>
<td>Dactylitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current dactylitis</td>
<td>Swelling of an entire digit according to observation on current physical examination</td>
<td>1</td>
</tr>
<tr>
<td>History of dactylitis</td>
<td>According to a rheumatologist</td>
<td>1</td>
</tr>
<tr>
<td>Radiographic evidence of juxtaarticular new bone formation</td>
<td>Ill-defined ossification near joint margins (excluding osteophyte formation) on plain radiographs of hand or foot</td>
<td>1</td>
</tr>
</tbody>
</table>

Psoriatic arthritis is considered to be present in patients with inflammatory musculoskeletal disease (disease involving the joint, spine, or enthesis) whose score on the five criteria listed in the table totals at least three points; the “evidence of psoriasis” criterion can account for either one point or two points. The criteria have a specificity of 98.7% and a sensitivity of 91.4%. ELISA denotes enzyme-linked immunosorbent assay.

Figure 1 (facing page). Clinical Features of Psoriatic Arthritis.

Panel A shows the distal subtype of psoriatic arthritis, with adjacent onycholysis. Panel B shows the oligoarticular subtype. Panel C shows the polyarticular subtype. Panel D show arthritis mutilans, with telescoping of digits and asymmetric and differential involvement of adjacent digits. Panel E shows the spondylitis subtype. Panel F shows enthesitis of the Achilles’ tendon (arrow). Panel G shows dactylitis of the big toes.
Psoriatic Arthritis

A

B

C

D

E

F

G
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subtype affects four or fewer joints and typically occurs in an asymmetric distribution. The polyarticular subtype affects five or more joints; the involvement may be symmetric and resemble rheumatoid arthritis. The distal subtype, which affects distal interphalangeal joints of the hands, feet, or both, usually occurs with other subtypes, occurring alone in only 5% of patients. Arthritis mutilans, a deforming and destructive subtype of arthritis that involves marked bone resorption or osteolysis, is characterized by telescoping and flail digits. The axial or spondyloarthritis subtype primarily involves the spine and sacroiliac joints. These patterns may change over time. Enthesitis is observed in 30 to 50% of patients and most commonly involves the plantar fascia and Achilles’ tendon, but it may cause pain around the patella, iliac crest, epicondyles, and supraspinatus insertions. Dactylitis is reported in 40 to 50% of patients and is most prevalent in the third and fourth toes but may also involve the fingers. Dactylitis can be either acute (swelling, redness of the skin, and pain) or chronic (swelling without inflammation). Dactylitis is often associated with severe disease that is characterized by polyarthritis, bone erosion, and new bone formation.

The diagnosis of psoriatic arthritis is based on the recognition of clinical and imaging features, since there are no specific biomarkers (Fig. 1). Involvement of at least five domains is possible; these include psoriasis, peripheral joint disease, axial disease, enthesitis, and dactylitis. Patients should be carefully assessed for these domains, with the understanding that various domain combinations may be present in an individual patient. The personal history and family history of psoriasis are often positive. Inflammatory arthritis, enthesitis, dactylitis, and joint distribution provide important clues, as do extraarticular features such as inflammatory bowel disease and uveitis. It is important to look for psoriatic skin lesions, particularly in the groin, umbilical area, hairline, ears, and natal (i.e., intergluteal) cleft. Nail lesions, including pits and onychoysis, as well as the presence of spinal disease, support the diagnosis.

It is important that dermatologists and primary care physicians caring for patients with psoriasis identify psoriatic arthritis early. Patients with psoriasis should be questioned about joint pain, morning stiffness, and evidence of “sausage” digits (dactylitis). Screening questionnaires for dermatology or primary care offices have high sensitivity for the presence of musculoskeletal disease but moderate specificity for psoriatic arthritis.

### Differential Diagnosis

It is necessary to differentiate psoriatic arthritis from rheumatoid arthritis, osteoarthritis, gout, pseudogout, systemic lupus erythematosus, and other forms of spondyloarthritis (Tables 2 and 3). Rheumatoid arthritis is characterized by proximal, symmetric involvement of the joints of the hands and feet, with sparing of the distal interphalangeal joints, whereas in more than 50% of patients with psoriatic arthritis, the distal joints are affected; the involvement tends to be characterized by a “ray” distribution, with all the joints of the same digit involved and other digits spared.

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Table 2. Differentiation among Various Forms of Arthritis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Psoriatic Arthritis</th>
<th>Rheumatoid Arthritis</th>
<th>Gout</th>
<th>Osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint distribution at onset</td>
<td>Asymmetric</td>
<td>Symmetric</td>
<td>Asymmetric</td>
<td>Asymmetric</td>
</tr>
<tr>
<td>No. of affected joints</td>
<td>Oligoarticular</td>
<td>Polyarticular</td>
<td>Monoarticular or oligoarticular</td>
<td>Monoarticular or oligoarticular</td>
</tr>
<tr>
<td>Sites of hands or feet involved</td>
<td>Distal</td>
<td>Proximal</td>
<td>Distal</td>
<td>Distal</td>
</tr>
<tr>
<td>Areas involved</td>
<td>All joints of a digit</td>
<td>Same joint across digits</td>
<td>Usually monoarticular</td>
<td>Same joints across digits</td>
</tr>
<tr>
<td>Tenderness (kg on a dolorimeter)</td>
<td>7</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Purpulish discoloration</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Spinal involvement</td>
<td>Common</td>
<td>Uncommon</td>
<td>Absent</td>
<td>Noninflammatory</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>Common</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

* NA denotes not assessed.

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Psoriatic Arthritis

This is noticeable both clinically and radiographically. At its onset, psoriatic arthritis tends to be oligoarticular and less symmetric than rheumatoid arthritis, although with time, psoriatic arthritis may become polyarticular and symmetric.26,27 The affected joints are less tender in psoriatic arthritis than in rheumatoid arthritis and may have a purplish discoloration.28 Spinal involvement (sacroiliac joints or the lumbar, thoracic, or cervical spine) occurs in more than 40% of patients with psoriatic arthritis but is uncommon in patients with rheumatoid arthritis.

Psoriatic monoarthritis, particularly involving the toes, or dactylitis may be misdiagnosed as gout or pseudogout. The uric acid level may be elevated in patients with psoriatic arthritis, as well as in those with gout, making the differential diagnosis difficult, particularly if crystal analysis of joint fluid is negative or cannot be performed. The distal-joint involvement that is characteristic of psoriatic arthritis is also observed in osteoarthritis. In psoriatic arthritis, palpation of distal joints reveals soft swelling due to inflammation, whereas in osteoarthritis, swelling arises from a bony osteophyte and is solid. Moreover, involvement of distal interphalangeal joints and nail disease (pitting or onycholysis) occur frequently in psoriatic arthritis but not in osteoarthritis.

Ankylosing spondylitis typically begins late in the second decade of life or early in the third decade, whereas psoriatic spondyloarthritis is more likely to develop in the fourth decade of life. Psoriatic spondyloarthritis may be less severe than ankylosing spondylitis, with less pain and infrequent sacroiliac-joint ankylosis; an asymmetric distribution of syndesmophytes (bony growths originating inside a ligament of the spine) is more common in cases of psoriatic arthritis.29 It may be difficult to distinguish between psoriatic arthritis and reactive arthritis. Both conditions may be associated with joint and skin lesions, and the skin lesions can be difficult to ascribe pathologically to one condition or the other. The psoriasiform lesions of subacute cutaneous lupus can mimic psoriasis vulgaris, but patients with cutaneous lupus do not have the other defining features of psoriatic arthritis.

Table 3. Clinical Features of Various Forms of Spondyloarthritis.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Psoriatic Arthritis</th>
<th>Ankylosing Spondylitis</th>
<th>Reactive Arthritis</th>
<th>IBD-Associated Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (yr)</td>
<td>36</td>
<td>20</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>1:1</td>
<td>3:1</td>
<td>3:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Peripheral joints affected (% of cases)</td>
<td>96</td>
<td>30</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>Axial joints affected (% of cases)</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>Common</td>
<td>Absent</td>
<td>Uncommon</td>
<td>Absent</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>Common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Psoriasis (% of cases)</td>
<td>100</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Nail lesions</td>
<td>87% of cases</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>HLA-B*27 (% of cases)</td>
<td>40–50</td>
<td>90</td>
<td>70</td>
<td>30</td>
</tr>
</tbody>
</table>

* IBD denotes inflammatory bowel disease.

Laboratory and Imaging Findings

Tests for rheumatoid factor, anti–cyclic citrullinated peptide antibodies, or both are negative in 95% of patients with psoriatic arthritis. When a test result is positive, clinical and imaging features must be used to differentiate psoriatic from rheumatoid arthritis. Approximately 25% of patients with psoriatic arthritis are HLA-B27–positive. Increases in the serum C-reactive protein level, the erythrocyte sedimentation rate, or both are seen in only 40% of patients.

The occurrence of bone and cartilage destruction with pathologic new bone formation is one of the most distinctive aspects of psoriatic arthritis (Fig. 2). Radiographs of peripheral joints often show evidence of bone loss with eccentric erosions and joint-space narrowing, as well as new bone formation characterized by periostitis,
bony ankylosis, and enthesophytes (abnormal bony projections at the attachment of a tendon or ligament). In the axial skeleton, changes associated with psoriatic arthritis include unilateral sacroiliitis and bulky paramarginal and vertical syndesmophytes. (In contrast, in ankylosing spondylitis, sacroiliac involvement is typically bilateral and paramarginal syndesmophytes are uncommon.) Magnetic resonance imaging studies may reveal focal erosions, synovitis, and bone marrow edema in the peripheral and axial structures, particularly at entheses. Bone marrow

**Figure 2. Radiographic Features of Psoriatic Arthritis.**

Panel A shows arthritis mutilans, with pencil-in-cup deformities (arrow) and marked bone resorption (osteolysis) in phalanges of the right hand. The hand radiograph in Panel B shows joint resorption, ankylosis, and erosion in a single ray. Panel C shows enthesophytes at the planter fascia and Achilles’ tendon insertions. Panel D shows syndesmophytes involving the cervical spine, with ankylosis of facet joints (arrow). Panel E shows bilateral grade 3 sacroiliitis. Panel F shows a paramarginal syndesmophyte bridging the fourth and fifth lumbar vertebrae. Panel G shows bone marrow edema in the second and third lumbar vertebrae in a patient with severe psoriasis and a new onset of back pain. The high-frequency (15-MHz) gray-scale ultrasound image in Panel H shows synovitis of the metacarpophalangeal joint. Distention of the joint capsule is evident (arrows). The confluent red signals (box in the lower part of the image) with power Doppler ultrasonography indicate synovial hyperemia. MC denotes metacarpal head, and PP proximal phalanx. The high-frequency (15-MHz) ultrasound image in Panel I shows enthesitis. The confluent red signals with power Doppler ultrasonography represent hyperemia at the tendon near its insertion into the calcaneus. Normally, the tendon is poorly vascularized.
Psoriatic arthritis is a severe form of arthritis in which deformities and joint damage develop in a large number of patients.1,2 Bone erosions are observed in 47% of patients within the first 2 years, despite the use of traditional disease-modifying medications in more than half the patients.32 Furthermore, severe disease at presentation and an elevated C-reactive protein level are risk factors for radiographic progression.33,34 Spontaneous remission of psoriatic arthritis is extremely rare. In an observational trial involving patients treated with anti–tumor necrosis factor (TNF) agents, the rate of partial remission was 23%.35 However, relapse rates are high when biologic agents are discontinued.36,37

OUTCOMES

Psoriatic arthritis is a severe form of arthritis in which deformities and joint damage develop in a large number of patients. In psoriatic arthritis, frequencies of HLA-B*08, B*27, B*38, and B*39 have been observed, with specific subtypes of those alleles linked to subphenotypes, including symmetric or asymmetric axial disease, enthesitis, dactylitis, and synovitis.40 Genomewide association scans have shown that certain polymorphisms in the gene encoding interleukin-23 receptor (IL23R), along with variants in nuclear factor κB (NF-κB) gene expression (TNIP1) and signaling (TNFAIP3), and TNF expression are associated with psoriatic arthritis. A polymorphism at chromosome 5q31, rs715285, maps to an intergenic region flanked by the genes CSF2 and P4HA2.41 Association studies have identified additional risk alleles in patients with psoriasis and in those with psoriatic arthritis, including interleukin-12A (IL12A), interleukin-12B (IL12B), IL23R, and genes that regulate NF-κB.42,43

There are several environmental risk factors for psoriatic arthritis. These include obesity; severe psoriasis; scalp, genital, and inverse (or intertriginous) psoriasis; nail disease; and trauma or deep lesions at sites of trauma (Koebner’s phenomenon).44,45

It has been shown consistently that T cells are important in psoriasis and psoriatic arthritis. A central role for CD8+ T cells in disease pathogenesis is supported by the association with HLA class I alleles, oligoclonal CD8+ T-cell expansion, and the association of psoriatic arthritis with human immunodeficiency virus disease.46 Type 17 cells, which include CD4+ type 17 helper T (Th17) cells, and type 3 innate lymphocytes (cells that produce interleukin-17A and interleukin-22), in addition to CD4+CD8+ lymphocytes, are increased in psoriatic synovial fluid as compared with rheumatoid synovial fluid.47,48

Recent studies highlight the importance of the interleukin-23–interleukin-17 and TNF pathways in the pathogenesis of psoriasis, psoriatic arthritis, and axial spondyloarthropathies.47,49 In psoriasis, expression of interferon-α by plasmacytoid dendritic cells activates dermal dendritic cells that trigger the differentiation of type 1 helper T (Th1) cells and Th17 cells in draining lymph nodes. These lymphocytes return to the dermis and orchestrate a complex immune-mediated inflammatory response (Fig. 3).50 Additional genetic factors, environmental factors, or both are likely to trigger inflammatory arthritis.

In an alternative disease model, the enthesis is proposed to be the initial site of musculoskeletal disease.51 In support of this view, enthesitis,
Figure 3. Pathogenic Pathways in Psoriatic Arthritis.

The events that potentially link inflammation in the psoriatic skin, bone marrow, and gut with enthesitis, synovitis, and altered bone phenotypes are shown. The interaction between genetic and environmental factors triggers an inflammatory response at multiple sites. In the plaque that forms in the skin, DNA released by stressed keratinocytes binds to the antibacterial peptide LL-37 and stimulates interferon-α (IFN-α) release by plasmacytoid dendritic cells, activating dermal dendritic cells, which migrate to draining lymph nodes and trigger differentiation of type 1 helper T (Th1) and type 17 helper T (Th17) cells. The Th1 and Th17 cells home to the dermis, where they release interleukin-12, 17, and 22 (IL-12, IL-17, and IL-22, respectively) and tumor necrosis factor α (TNF-α), along with a range of chemokines and other cytokines. Additional IL-17–secreting (i.e., type 17) cells in the dermis include innate lymphoid cells and CD8+ T cells. The cytokine release in the dermis promotes keratinocyte proliferation; these keratinocytes in turn release cytokines that act in a paracrine fashion on cells in the dermis. Expansion of Th1 and Th17 cells, along with other type 17 cells and osteoclast precursors (OCPs), may also take place in the bone marrow. In the gut, microbial dysbiosis may initiate inflammation in the ileocolon and trigger IL-23 release and type 17 cells. In the enthesis, IL-23 release in response to biomechanical stress or trauma at the tendon-insertion site activates type 17 cells and other cytokines, including IL-22 and TNF, with resultant inflammation, bone erosion, and pathologic bone formation. Mesenchymal cells differentiate into osteoblasts in response to IL-22 and other signaling pathways, forming enthesophytes in peripheral entheses and joints and syndesmophytes in the spine. Type 17 cells, OCPs, and dendritic cells reach the joint from adjacent entheses or the bloodstream. Increased expression of the receptor activator of NF-κB (RANK) ligand (RANKL) by synoviocytes in the lining, coupled with increased levels of TNF, IL-17, and RANKL expressed by infiltrating cells, drives the differentiation of OCPs into osteoclasts, with synovitis and bone resorption. Pathologic bone formation proceeds as outlined above in the enthesis.
Psoriatic arthritis was characterized by synovitis, and altered bone remodeling were observed in a murine model in which the administration of interleukin-23 led to an enthesis-centered inflammatory arthritis that was similar to spondyloarthritis, with bone erosion and new bone formation. Inflammation was linked to a novel population of innate lymphocytes residing in the entheses that produce interleukin-17. Inflammation and bone erosion were mediated by TNF and interleukin-17. Another murine model has shown that overexpression of interleukin-23 can also lead to an inflammatory, erosive arthritis phenotype, which may reflect differences in the dose or timing of interleukin-23 delivery, microbial heterogeneity, or differences in mouse strains. Several other murine models of spondyloarthritis with enthesitis, psoriasiform skin lesions, and arthritis have subsequently been reported, all of which have been linked to interleukin-23. Microbial infections are known triggers of certain forms of spondyloarthritis, and reports of an elevated frequency of subclinical gut inflammation and dysbiosis (decreased microbial diversity) in patients with psoriatic arthritis, as compared with healthy controls, support a potential gut–joint axis in the pathogenesis of psoriatic arthritis.

The synovial tissues in patients with psoriatic arthritis bear a closer resemblance to the synovium in patients with spondyloarthritis than to the synovium in those with rheumatoid arthritis, with more vascularity, a greater influx of neutrophils, and the absence of antibodies to citrullinated peptides. As compared with rheumatoid synovial tissue, psoriatic synovial tissue has a lower number of infiltrating T lymphocytes and plasma cells, but the expression of TNF and interleukin-1, 6, and 18 is similar in the two diseases.

Bone involvement in psoriatic arthritis is heterogeneous both among patients and within the individual patient. Spinal involvement may be similar to that in ankylosing spondylitis, and destructive peripheral-joint features may resemble those of rheumatoid arthritis. Pathologic new bone formation, including joint ankylosis and syndesmophyte formation, typically occurs at sites of soft-tissue inflammation surrounding the enthesis. In psoriatic synovium, marked up-regulation of the receptor activator of NF-κB (RANK) ligand (RANKL) and low expression of its antagonist, osteoprotegerin, have been detected in the adjacent synovial lining. The RANKL cytokine binds to RANK on the surface of osteoclast precursors derived from circulating CD14+ monocytes. This ligand–receptor interaction triggers proliferation of the osteoclast precursors and their differentiation into multinucleated osteoclasts, which resorb bone. Moreover, a study has shown that osteoclast precursors derived from circulating CD14+ monocytes are markedly elevated in the peripheral blood of patients with psoriatic arthritis, as compared with healthy controls, and that treatment with anti-TNF agents significantly reduces the level of circulating precursors, a finding that supports a central effect of TNF in the generation of precursor formation. Molecules and pathways associated with pathologic bone formation include interleukin-17A, bone morphogenetic protein, transforming growth factor β, prostaglandin E2, and molecules in the Wnt signaling pathway, although their roles in psoriatic arthritis are unknown.

**Outcome Measures for Psoriatic Arthritis**

It is important to evaluate each of the musculoskeletal domains, along with the severity and extent of psoriasis, in patients with suspected psoriatic arthritis. Assessments should include examination of 68 joints for tenderness and 66 joints for swelling; spinal range of motion and pain; enthesitis, assessed with the use of one of the enthesitis indexes, such as the Leeds Enthesitis Index (assessment of six entheses) or the Spondyloarthritis Research Consortium Canada (SPARCC) Enthesitis Index; and dactylitis, assessed with the use of either a dactylitis digit count or the Leeds Dactylitis Index. Psoriasis should be assessed on the basis of the involved body-surface area or the Psoriasis Area and Severity Index (PASI), and nails should be examined for onycholysis or pitting. In clinical trials, outcome measures adapted from instruments used to assess outcomes of rheumatoid arthritis include the American College of Rheumatology (ACR) 20, ACR 50, and ACR 70 response rates (indicating reductions in the number of both...
tender and swollen joints of at least 20%, 50%, and 70%, respectively, with improvement in at least three of the following five additional measures: patient and physician global assessments, pain, disability, and an acute-phase reactant) and the Disease Activity Score (DAS), which is used to assess peripheral arthritis. A number of composite measures have recently been developed specifically for psoriatic arthritis, including the Psoriatic Arthritis Disease Activity Score (Table S1 in the Supplementary Appendix), available with the full text of this article at NEJM.org), the Composite Psoriatic Disease Activity Index (Table S2 in the Supplementary Appendix), and the GRACE (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis [GRAPPA] Composite Exercise) instrument (Table S3 in the Supplementary Appendix). In addition, minimal disease activity, defined by clinically significant improvement in five of seven response measures or domains is a validated instrument for assessing treatment response in psoriatic arthritis (Table S4 in the Supplementary Appendix).

**THERAPY**

The treatment of psoriatic arthritis is complicated by heterogeneity in the presentation of the disease and its course, often resulting in a delayed diagnosis. To address this complexity, it is important to identify disease activity in each of the domains. The domain with the highest level of activity drives the treatment choices, and it is very common for a patient to have involvement of several domains.

Evidence-based treatment recommendations have recently been published. Table 4 summarizes current therapies and treatment responses. For patients with a mild oligoarticular presentation, nonsteroidal antiinflammatory medications combined with intraarticular injections, when appropriate, can be effective. For patients with more severe symptoms, disease-modifying antirheumatic drugs (DMARDs) are typically prescribed as an initial treatment. Unfortunately, data from randomized clinical trials of traditional DMARDs for the treatment of psoriatic arthritis are limited. A trial of methotrexate as compared with placebo did not show a significant treatment effect, although the study may have been underpowered and the dose of oral methotrexate was lower than that typically prescribed in practice. Leflunomide is effective for peripheral arthritis but not psoriasis. Compelling data show that anti-TNF agents (adalimumab, certolizumab, etanercept, and golimumab) suppress skin and joint inflammation and retard radiographic progression. These agents are effective for enthesitis, dactylitis, and also for axial disease on the basis of data from trials involving patients with ankylosing spondylitis.

Use of the anti-p40 antibody ustekinumab, directed against the shared subunit of interleukin-12 and interleukin-23, is effective for the treatment of psoriasis and psoriatic arthritis, although results in the skin are more impressive than those in the joints. Secukinumab and brodalumab, agents that block interleukin-17 and the interleukin-17 receptor, respectively, are effective in psoriatic arthritis, with demonstrated improvement in both skin and musculoskeletal features. However, trials of brodalumab were suspended because of safety concerns that were not observed with secukinumab. Ixekizumab, another interleukin-17 blocker, showed efficacy in phase 3 trials involving patients with psoriatic arthritis and was recently approved for the treatment of psoriasis. Phosphodiesterase 4 inhibitor with apremilast has been approved for the treatment of psoriasis and psoriatic arthritis. Skin responses to treatment with apremilast are similar to those with methotrexate, but joint responses are somewhat lower than those observed with biologic agents. Finally, abatacept, a T-cell activation blocker that targets CD80 and CD86 costimulatory molecules, is moderately effective in psoriatic arthritis for joint involvement but not for skin disease. Anti-TNF agents, the interleukin-12–interleukin-23 antagonist ustekinumab, and the interleukin-17 monoclonal antibodies secukinumab and ixekizumab inhibit radiographic progression in patients with psoriatic arthritis who have peripheral-joint involvement. Apremilast, brodalumab, and secukinumab are not effective for the treatment of rheumatoid arthritis, whereas rituximab and abatacept are highly effective. Collectively, these contrasting findings from clinical trials suggest that rheumatoid arthritis and psoriatic arthritis have different underlying mechanisms. In contrast, the pathophysiological pathways that underlie psoriatic skin and joint disease overlap considerably. Nevertheless, cyclosporine and methotrexate are more effective in psoriasis than is leflunomide in psoriatic
Table 4. Efficacy and Side Effects of Drugs for the Treatment of Psoriatic Arthritis.

<table>
<thead>
<tr>
<th>Drug (Mode of Administration)</th>
<th>Dose According to Site</th>
<th>Signs and Symptoms</th>
<th>Structural Modification of Joints*</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Joints</td>
<td>Skin</td>
<td>Joints</td>
<td>Skin</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen (oral)</td>
<td>750–1000 mg/day</td>
<td>Not applicable</td>
<td>Mild response</td>
<td>—</td>
</tr>
<tr>
<td>Diclofenac (oral)</td>
<td>100–150 mg/day</td>
<td>Not applicable</td>
<td>Moderate response</td>
<td>—</td>
</tr>
<tr>
<td>Indomethacin (oral)</td>
<td>100/150 mg/day</td>
<td>Not applicable</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>DMARDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate (oral or SC)</td>
<td>15–25 mg/wk</td>
<td>15–25 mg/wk</td>
<td>Mild response</td>
<td>Moderate response</td>
</tr>
<tr>
<td>Leflunomide (oral)</td>
<td>20 mg/day</td>
<td>Not applicable</td>
<td>Mild response</td>
<td>Mild response</td>
</tr>
<tr>
<td>Sulfasalazine (oral)</td>
<td>2–3 g/day</td>
<td>Not applicable</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Anti-TNF agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab (SC)</td>
<td>40 mg every 2 wk</td>
<td>80 mg loading dose, 40 mg 1 wk later, then 40 mg every 2 wk</td>
<td>Very good response</td>
<td>Moderate response</td>
</tr>
<tr>
<td>Certolizumab (SC)</td>
<td>200 mg every 2 wk or 400 mg every 4 wk</td>
<td>Not applicable</td>
<td>Very good response</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Etanercept (SC)</td>
<td>50 mg weekly</td>
<td>50 mg twice/wk</td>
<td>Very good response</td>
<td>Mild response</td>
</tr>
<tr>
<td>Golimumab (SC, infusion)</td>
<td>50 mg monthly</td>
<td>Not applicable</td>
<td>Very good response</td>
<td>Mild response</td>
</tr>
<tr>
<td>Infliximab (infusion)</td>
<td>5 mg/kg of body weight at 0, 2, and 6 wk, then every 8 wk</td>
<td>5–10 mg/kg at 0, 2, and 6 wk, then every 8 wk</td>
<td>Very good response</td>
<td>Excellent response</td>
</tr>
<tr>
<td>Anti–interleukin-17 agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ixekizumab (SC)</td>
<td>80 mg every 2 wk</td>
<td>80 mg every 2 wk</td>
<td>Very good response</td>
<td>Excellent response</td>
</tr>
<tr>
<td>Secukinumab (SC)</td>
<td>150 mg weekly from 0–4 wk, then monthly</td>
<td>300 mg weekly from 0–4 wk, then monthly</td>
<td>Very good response</td>
<td>Excellent response</td>
</tr>
<tr>
<td>Anti–interleukin-12–interleukin-23 agent: ustekinumab (SC)</td>
<td>45 mg/kg (for body weight of &lt;100 kg) or 90 mg/kg (for body weight of ≥100 kg) at 0, 4, and 12 wk, then every 12 wk</td>
<td>45 mg/kg (for body weight of &lt;100 kg) or 90 mg/kg (for body weight of ≥100 kg) at 0, 4, and 12 wk, then every 12 wk</td>
<td>Very good response</td>
<td>Very good response</td>
</tr>
<tr>
<td>PDE4 inhibitor: apremilast (oral)</td>
<td>30 mg twice daily</td>
<td>30 mg twice daily</td>
<td>Moderate response</td>
<td>Mild response</td>
</tr>
</tbody>
</table>

* Recent trials of these agents involved patients with little disease progression, resulting in a smaller effect on structural modification as compared with earlier trials, which involved patients with more severe disease and more progression. For drugs that were not assessed with respect to structural modification of joints, observational data suggest no response. Dashes indicate that there was no appreciable response. DMARDs denotes disease-modifying antirheumatic drugs, NSAIDs nonsteroidal antiinflammatory drugs, PDE4 phosphodiesterase 4, SC subcutaneous injection, and TNF tumor necrosis factor.
arthritis. These findings, coupled with the greater response to agents that target the interleukin-12–interleukin-23 axis in the skin as compared with the joints, underscore the divergent mechanisms of inflammation in psoriatic plaques and joints.

High-level evidence supporting specific treatment algorithms for juvenile psoriatic arthritis is not available. Current recommendations follow the guidelines for juvenile idiopathic arthritis and are based on measures of disease activity, including the number of active joints, inflammatory markers (erythrocyte sedimentation rate or C-reactive protein level), and global assessments by the physician and patient or parent. Indicators of a poor prognosis, including involvement of certain joints (e.g., the hip, wrist, ankle, joints in the cervical spine, and the sacroiliac joint) and evidence of radiographic damage are also taken into account in considering both initial therapy and escalation.

In addition to pharmacotherapy, patient education about the importance of controlling inflammation is critical. Lifestyle modification, including smoking cessation, weight reduction, joint protection, physical activity, and exercise, as well as stress management, is also vital in the management of psoriatic arthritis.

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