Psoriatic Arthritis for the Dermatologist

Suzanne J. Tintle, MD, MPH*, Alice B. Gottlieb, MD, PhD

KEYWORDS

• Psoriatic arthritis • Synovitis • Dactylitis • Enthesitis • Joint • Osteoclastogenesis • Interleukin-17

KEY POINTS

- Psoriatic arthritis (PsA) is underdiagnosed and undertreated, and dermatologists are in a unique position to recognize symptoms of the disease early and initiate disease-modifying therapy before significant effects on patients' quality of life and functional capacity occur.
- All patients with psoriasis require screening for PsA.
- Characteristics of PsA include enthesitis, dactylitis, spondylitis and sacroiliitis, stiffness after inactivity, and involvement of the distal interphalangeal joints and nails.
- Joint damage begins early in the course of the disease, and a tumor necrosis factor α inhibitor is required to halt progression of synovitis, bone resorption, formation of osteophytes, enthesitis, and dactylitis.
- Apremilast and tofacitinib are promising new orally administered medications for PsA.
- The interleukin (IL)-17 inhibitors and IL-23p19 inhibitors have been developed in response to improved understanding of the immunopathogenesis of PsA and osteoclastogenesis; these targeted therapies have shown excellent efficacy in PsA in early investigational studies.

OVERVIEW: NATURE OF THE PROBLEM

Psoriatic arthritis (PsA) is an underdiagnosed, undertreated, chronic, progressive spondyloarthropathy occurring in 11% to 42% of patients with cutaneous psoriasis.[1–5] Similar to psoriasis, PsA affects men and women equally, and usually develops between the ages of 30 and 50 years, although it can develop in childhood.[2] Patients with PsA have significantly impaired physical functioning and quality of life (QOL), with high rates of anxiety, depression, and poor self-image.[5] The disease is characterized by flares and remissions; but only about 18% of patients will experience sustained periods of remission, lasting on average 2.5 years.[6] Many patients with PsA are undertreated or are not treated systematically.[1] For instance, in Lebwohl and colleagues'[1] 2014 multinational study, approximately 15% of patients with PsA had not seen a health care provider in the past year, and almost 60% were not being treated for their joint disease.

Our understanding of the immune dysregulation that triggers psoriatic pathophysiology has greatly improved over the past 20 years and has driven the development of targeted therapies for psoriasis and PsA. Innate and adaptive immune

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Department of Dermatology, Tufts Medical Center, 800 Washington Street, Box #114, Boston, MA 02111, USA
* Corresponding author.
E-mail address: suzanne.tintle@gmail.com

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responses are abnormally activated in PsA, and, in genetically susceptible patients, may acquire the ability to attack peripheral joints and other sites following an environmental trigger or inciting event (eg, mechanical stress and trauma including microtrauma).[7] PsA is highly heritable: In a 2009 study, 7.6% of first-degree relatives of patients with PsA also had PsA (17.7% of first-degree relatives had psoriasis).[8] Genome-wide studies have identified important risk loci for the disease; the psoriasis susceptibility 1 locus (*PSORS1*) was among the first identified and mapped to the major histocompatibility complex class I region.[9,10] The presence of the HLA-Cw*0602 allele accounts for an estimated one-third to one-half of genetic susceptibility to psoriasis, whereas the human leukocyte antigen (HLA)-B27, HLA-B38, and HLA-B39 alleles are more highly associated with PsA (specifically, HLA-B27 is linked to spinal involvement, and HLA-B38 and HLA-B39 to peripheral polyarthritis).[9,11] A strong genetic association of PsA with variants of the interleukin (IL)-23 receptor (IL-23R) and the IL-23p40 subunit has also been demonstrated, implicating the central pathophysiologic function of the IL-23/IL-17 axis in triggering the joint inflammation and downstream effects seen in the disease.[12]

PsA is characterized by inflammation of the tendons, ligaments, synovia, and bone, with the development of focal bone erosions mediated by osteoclasts at the bone-pannus junction. Histopathologically, PsA displays an influx of Th17 cells, a thin layer of synovial epidermal hyperplasia, and increased levels of proinflammatory, osteoclastogenic cytokines.[13] This cytokine milieu includes elevated levels of tumor necrosis factor (TNF)-α, IL-1B, IL-17, IL-12, IL-23, interferon-γ (IFN-γ), and receptor activator of NF-kappa B ligand (RANKL), together acting as potent inducers of the proliferation and activation of synovial and epidermal fibroblasts.[14] Long-term inflammation at this site leads to bone erosions alongside new bone formation in the form of syndesmophytes, enthesophytes, and ankylosis (peripheral bony fusion). IL-23 is a crucial upstream mediator of this process. Comprising a specific p19 subunit and a p40 subunit which it shares with IL-12, IL-23 is a mucosal defense factor derived from resident lymphoid or epidermal cells in the skin that acts synergistically with IL-6 and transforming growth factor β1 to promote rapid Th17 development, potentiating IL-17 and IL-22 release.[15] Mouse models of spondyloarthropathy have shown that early features of bone remodeling (early enthesitis, arthritis, and bone formation) are ameliorated by the addition of anti–IL-23 antibodies.[16,17] Following induction by IL-23, IL-17 and IL-22 stimulate proliferation of synovial fibroblasts and subsequent joint inflammation,[9] and STAT-3 (signal transducer and activator of transcription 3) dependent osteoblast-mediated bone remodeling.[17] In addition to induction of enthesitis and synovial hyperplasia, IL-17 and IL-23 are associated with changes in the RANKL-RANK axis, which further increases osteoclast formation and promotes bone remodeling in PsA.[18,19] Further knowledge regarding how simultaneous bone formation and bone resorption in PsA occurs, and how the osteoclast-osteoblast homeostasis becomes dysregulated in the psoriatic joint, is required and will further guide therapeutic development. IL-33, which may abrogate the effects of TNF-α on the RANKL pathway, and drugs inhibiting IL-1 and Bruton tyrosine kinase, both of which are costimulatory signals for osteoclastogenesis, are additional targets being studied that may have potential in PsA treatment.[20]

Juvenile psoriatic arthritis (JPsA) has traditionally been considered a subset of juvenile idiopathic arthritis (JIA), representing about 7% of all JIA cases. JPsA epidemiologically, pathologically, and clinically manifests similarly to adult PsA. As in adults, cutaneous psoriasis may not be present and joint symptoms may significantly precede cutaneous disease.[21] Treatment options for JPsA are discussed within each medication section that follows.

PATIENT EVALUATION

Patients with PsA typically present with an inflammatory arthritis, have a personal or family history of psoriasis, and are seronegative for rheumatoid factor. The clinical spectrum of PsA includes 5 major components, although not all are necessary for diagnosis: peripheral arthritis; axial disease/spondylitis; skin disease; dactylitis; and enthesitis.[22] Approximately 50% to 60% of patients have peripheral arthritis only, 6% have spondylitis only, and 35% to 40% have both peripheral arthritis and spondylitis.[23] Pain and stiffness are usually worse with rest and improved with activity, and patients may complain of morning stiffness (often >30 minutes in duration).[4] Joint symptoms typically improve with activity but can present, regardless of activity level, as inflamed, warm, tender, and swollen, with limited range of motion.[24] Dystrophy of the fingernails and/or toenails (eg, onycholysis, pitting, oil spots, hyperkeratosis, leukonychia, and/or nail plate crumbling) is strikingly common in PsA: up to 87% of PsA patients will present with this component of disease.[4] Risk factors for the development of PsA include: scalp involvement, increased extent of body surface