Translational Perspectives on Psoriatic Arthritis

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ABSTRACT. The term psoriatic disease encompasses the array of disorders (arthritis, inflammatory bowel disease, uveitis, obesity, metabolic syndrome, type II diabetes, and cardiovascular disease) that are associated with psoriasis. Psoriatic arthritis (PsA) is present in about 25% of patients with psoriasis; in most cases, the psoriasis precedes joint disease by about 10 years. Previous studies revealed that osteoclast precursors (OCP) are elevated in PsA and that the frequency of these circulating cells correlates with bone destruction. More recently OCP were found to be increased also in early rheumatoid arthritis and in 25% of psoriasis patients without arthritis. Bone marrow edema, observed on magnetic resonance imaging, in PsA represents infiltration of underlying marrow with inflammatory cells based on studies in transgenic tumor necrosis factor (TNF) arthritis murine models. Studies in the TNF transgenic mouse model also revealed that changes in lymph node volume precede joint flare. These translational studies point to potential biomarkers of arthritis in psoriasis patients and generate alternative hypotheses to explain the events that lead to arthritic flare. (J Rheumatol 2009;36:30-34; doi:10.3899/jrheum.090219)

Key Indexing Terms:
Table 1. Disorders associated with psoriasis (reviewed in Ritchlin5).

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<th>Psoriasis-associated Disorder</th>
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* Associated primarily with psoriatic arthritis.

Psoriasis, a disease first described in Leviticus, was recognized by Ferdinand von Hebra as a distinct disorder in 18411,2. Over the past century and a half, our knowledge of this relatively common disease has deepened considerably, but recent literature indicates that we still have much to learn. For example, an analysis of the US National Health and Nutrition Examination Survey (NHANES) database revealed that psoriasis prevalence may be 3.4%, and that an additional 0.4% of the population may have undiagnosed psoriasis3. These estimates contrast sharply with the prevalence of 2.2%–2.6%, a widely quoted and generally accepted number. Another major advance is the understanding that psoriasis can be associated with an array of comorbidities. In fact, the term psoriatic disease has been applied to encompass the diversity of disorders4,5 that are associated with psoriasis (Table 1), and many of these extracutaneous disorders are discussed in accompanying articles included in this supplement.

One of the most common manifestations observed in psoriasis patients is psoriatic arthritis (PsA), a condition that can involve not only the peripheral joints but also entheses, tendons, and the axial skeleton. In this review, we highlight how translational research approaches and clinical trials have revealed novel insights into disease pathogenesis. In particular, we will discuss cell populations that link psoriasis and arthritis, review studies that provide a framework to understand the mechanisms responsible for bone marrow edema manifested on magnetic resonance imaging (MRI), and present data that support a new paradigm for joint flare.

CELL POPULATIONS THAT LINK PSORIASIS AND INFLAMMATORY ARTHRITIS

Analysis of clinical trial demographics and registry data reveal that psoriasis precedes joint inflammation by about 10 years. One explanation for this observation is that inflammation begins in the skin, and that a second event occurs in a subset of patients (for example an environmental insult in a specific genetic background) that results in arthritis. Many models could be envisioned to
explain the mechanisms that link joint and skin disease in patients with PsA (Figure 1). One approach to understanding the link between skin and joint disease is to examine the cellular populations that have been implicated in inflammation at both sites. The major immune cells that play a central role in psoriasis and PsA are T cells and monocytes, although a prominent mouse model discussed below provided evidence for the potential contribution of keratinocytes.

**T lymphocytes.** Immunohistochemical studies and clinical trials have underscored a central role for the T lymphocyte in the pathogenesis of psoriasis. It has been known for some time that CD4+ cells infiltrate the dermis and CD8+ cells are found in the epidermis. From a clinical trial perspective, anti-T cell therapies including cyclosporine, alefacept (LFA3-Ig), and efalizumab (anti-CD11a) have been effective in psoriasis although in the case of the latter 2 agents, efficacy is considerably less compared to anti-tumor necrosis factor (TNF) therapies. Initial studies supported a major role for Th1 cells in the pathogenesis of psoriasis, but more recent work has demonstrated a major contribution from Th17 cells (Table 2). Perhaps the most exciting data come from clinical trials with ustekinumab, an antibody to the P40 subunit, present in both interleukin 12 (IL-12) and IL-23, which has demonstrated high efficacy in moderate to severe psoriasis.

The importance of Th17 cells in psoriatic joint inflammation has not been formally established. Certainly, this subset is of critical importance in T cell-mediated osteoclastogenesis in animal models of arthritis and in rheumatoid synovium but the direct relevance of this pathway to PsA has not been demonstrated. In phase IIb PsA trials, neither efalizumab nor alefacept was particularly effective for treatment of PsA. A phase IIb clinical trial with ustekinumab did show efficacy in PsA, although the American College of Rheumatology response measures were lower than those observed with the anti-TNF agents, and radiographic endpoints were not examined. It will be interesting to compare the efficacy of another anti-T cell agent, abatacept (CTLA4 immunoglobulin Ig) construct with ustekinumab when the trial results with this molecule become available.

**Monocytes.** Monocytes can differentiate into macrophages, osteoclasts, Langerhans cells, or dendritic cells in response to cytokines and/or other signals in the microenvironment. Monocytes were required in 2 distinct animal models of psoriasis, and it is now apparent that a number of monocyte subsets are greatly expanded in psoriatic skin. In pathologic analyses of entheseal tissues, monocytes were the principal cells identified in the fibrocartilage. Monocytes are also present in the synovial lining of psoriatic joints, and they infiltrate the subsynovial lining. An increased frequency of circulating osteoclast precursors (OCP) was identified in the circulation and synovial tissues of patients with PsA. The OCP numbers dropped rapidly after treatment with TNF antagonists.

In additional studies, we demonstrated that OCP are also elevated in the circulation of patients with early RA and a subset of psoriasis patients without arthritis, an unanticipated finding. In patients with Crohn’s disease,
sacroiliac joints from patients with ankylosing spondylitis revealed a correlation between histopathologic findings and MRI scans of bone marrow edema lesions. The BME does improve considerably after treatment with an anti-TNF agent, although the rapidity of this response is highly variable.

To clarify the etiology of BME, we imaged the arthritic joints of TNF transgenic mice with gadolinium MRI. These mice develop a destructive inflammatory arthritis at about week 6 to 8. The mice with knee inflammation demonstrated prominent BME with contrast enhancement, and this finding was noted in bone adjacent to both involved and uninvolved joints (Figure 2). In contrast, BME was not noted in the nonarthritic littermates without the transgene. Histopathologic analysis of the marrow showed a transition from a normocellular yellow to a hypercellular red marrow that was packed with CD11b+ monocytes, a finding not detected in the littermates without the transgene. The BME lessened significantly following treatment with an anti-TNF agent and the marrow changed from a cellular laden red marrow to a yellow marrow as seen in the controls. Thus, our data suggest that BME reflects expansion of monocytes in the marrow, where they can differentiate into dendritic cells, osteoclasts, or macrophages depending on the signals that are present in the surrounding environment.

RELATIONSHIP BETWEEN JOINT FLARE AND DRAINING LYMPH NODE
A consistent finding on the gadolinium MRI studies of the TNF transgenic mice described above was the presence of enlarged popliteal lymph nodes draining joints with inflammatory synovitis. In parallel studies, these mice produce high levels of vascular endothelial growth factor-C, a factor that can induce lymphangiogenesis. Interestingly, the popliteal lymph nodes increased in size after 2.5 months of age, a time when TNF serum levels increase and alteration in peripheral blood mononuclear cell populations takes place. The increased lymph node

Table 2. Evidence for the involvement of the interleukin 23 (IL–23) / T helper 17 (Th17) pathway in psoriasis (reviewed in Fitch, et al).
volume was associated with pronounced synovitis (Figure 2) and both of these variables decreased following anti-TNF therapy.

In mice with established arthritis, we noted that just prior to the onset of joint inflammation, the lymph node collapses and demonstrates increased contrast enhancement. Current studies are under way to examine the mechanisms that lead to the collapse of the node and the subsequent synovitis. One potential explanation is that cells, chemokines, and cytokines that sustain joint inflammation cannot exit from the joint, resulting in persistent synovial inflammation. Additional studies are under way to better understand the relationship between synovitis and the draining node. Together, these data suggest that joint flare is precipitated by altered lymphatic flow in murine arthritis. We are now analyzing the relationship between lymph node volume and synovitis in PsA and RA using Doppler ultrasound and MRI. These studies raise the possibility that imaging biomarkers have the potential to anticipate joint flare in inflammatory arthritis.

CONCLUSION
The studies outlined above demonstrate that the skin and joint in PsA share common inflammatory pathways. One particularly intriguing immune mechanism, the Th17 response, plays a dominant role in psoriasis but the importance of this pathway in PsA remains to be determined. The understanding that the BME MRI signal is provided in part by CD11b+ monocytes underscores the importance of the underlying marrow and altered myelopoiesis in the process of joint inflammation. Lastly, compelling data point to impaired lymphatic drainage as a potential mechanism in joint flare, although additional studies are needed in humans to determine the applicability of these findings to rheumatoid and psoriatic joint disease.

REFERENCES