Interleukin 6 Blockade: Tocilizumab in Psoriatic Arthritis

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ABSTRACT. Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy of unknown etiology associated with psoriasis. Joint destruction is often progressive: almost half of the patients attending an early arthritis clinic showed radiological damage 2 years after diagnosis. Proinflammatory cytokines are major mediators of systemic and local inflammation, and high levels of interleukin 1 (IL-1), IL-6, and tumor necrosis factor have been found in psoriatic skin lesions and the synovial tissue of patients with rheumatoid arthritis and PsA. IL-6 is a pleiotropic cytokine that mainly signals by membrane (neutrophil and lymphocyte) or soluble (endothelial cell) IL-6 receptors. IL-6 was originally identified as a factor in B cell differentiation, but is now known to influence T cell development: in the presence of IL-6 and transforming growth factor-β (TGF-β), naive T cells develop into Th17 cells, which are important mediators in PsA. IL-6 may also directly contribute to the epidermal hyperplasia seen in psoriatic epithelium and affect the function of dermal inflammatory cells. However, there are no data concerning the use of tocilizumab in patients with PsA, although a pilot study is currently being carried out because the role of IL-6 in the pathogenesis of PsA supports the idea that targeted treatments against IL-6 might be effective. (J Rheumatol 2012;39 Suppl 89:97–9; doi:10.3899/jrheum.120256)

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Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy of unknown etiology associated with psoriasis. It occurs in as many as one-third of patients with psoriasis and has various manifestations, including monooarticular arthritis [an erosive and destructive polyarthritis that cannot be distinguished from rheumatoid arthritis (RA)], and spondyloarthropathy with axial involvement or enthesitis. Like that associated with RA, joint destruction is often progressively erosive and leads to cortical bone resorption; however, it may be morphologically different, with bony spurs forming along entheses (enthesiophytes). Patients with PsA experience major joint damage and disability over time and, like those with RA, their quality of life is often impaired. The disease is usually easy to diagnose because it is characterized by typical clinical signs and symptoms, the presence of psoriatic skin or nail lesions, and the frequent absence of rheumatoid factor. Although RA and PsA are separate clinical entities with different etiologies, the similarities in synovial infiltrate and increased proinflammatory cytokine production support the view that, in addition to tumor necrosis factor (TNF) blockade, targeted treatments against other proinflammatory cytokines such as interleukin 6 (IL-6) might be effective.

CYTOKINES IN PsA AND PSORIASIS

Proinflammatory cytokines are important mediators of systemic and local inflammation, and high levels of IL-1, IL-6, and TNF have been observed in psoriatic skin lesions and the synovial tissue of patients with RA or PsA. The synovial infiltrate associated with both diseases is comparable in terms of the number of fibroblast-like synoviocytes and macrophages, but a number of studies have found that the synovium of patients with PsA is characterized by a less hyperplastic lining layer and fewer monocytes/macrophages.

There are also considerably fewer T cells in PsA, but because a subset of specific T cells may be sufficient to promote inflammation, and regulatory T cells may have anti-inflammatory effects, T cells are probably involved in the pathogenesis of both psoriasis and PsA. The infiltrate in psoriatic skin lesions mainly consists of activated T cells, and it has been shown that T cells are present in synovial infiltrate; further, the finding of oligoclonal T cell expansions in the skin and synovium suggest that an antigen-driven T cell response may be promoting ongoing inflammation. The role of T cells in psoriasis and PsA is also indicated by the beneficial effects of anti-T cell agents such as...
cyclosporin A and alefacept. A recent study has shown that abatacept, a selective inhibitor of T cell activation as a result of its competitive binding to CD80 or CD86, is effective on joints, but has a less marked effect on skin lesions. It is also known that T-helper cells producing IL-17 (Th17 cells) play a role in chronic inflammatory conditions. IL-23 is highly expressed in psoriatic plaques, and is responsible for stimulating Th17 cells, which also produce TNF, IL-21, and IL-22. The role of IL-23 in PsA is not clear, but the Th17-related cytokines IL-17 and IL-23 are expressed in the joints of patients with PsA or RA, and clinical studies of the Th17 axis are currently under way to establish the validity of using it in the treatment of PsA. Moreover, blocking the p40 subunit (which is shared by IL-12 and IL-23) improves arthritis in patients with PsA, who also tend to have fewer plasma cells. However, lymphoid aggregates of different sizes and levels of organization are also observed in the synovial biopsies of patients with PsA.

Increased vascularity has been found in psoriatic skin lesions and synovial tissue, and immunohistochemical analyses have shown that both over-express vascular endothelial growth factor (which is involved in angiogenesis) and other vascular markers such as von Willebrand's factor and basic fibroblast growth factor.

The expression of TNF-α, IL-18, IL-6, and IL-18 is as high in patients with PsA as in those with psoriasis. IL-6 is a pleiotropic cytokine that primarily signals through membrane (neutrophil and lymphocyte) or soluble (endothelial cell) IL-6 receptors. IL-6 was originally identified as a factor in B cell differentiation, but is now known to influence T cell development: in the presence of IL-6 and transforming growth factor-β (TGF-β), naive T cells develop into Th17 cells, which are important mediators in PsA. IL-6 is also involved in neutrophil survival, proliferation, and mobilization.

In psoriatic skin lesions, abnormal keratinocytes and other cell types synthesize IL-6, TGF-α, and IL-1α, which stimulate the growth of cultured human keratinocytes. This suggests that IL-6 may contribute to the epidermal hyperplasia seen in psoriatic epithelium and affect the function of dermal inflammatory cells.

IL-6 also inhibits effector T cell suppression by the regulatory T cells that increase effector T cell trafficking in psoriatic skin lesions. The IL-6-induced phosphorylation of STAT3 in these lymphocytes contributes to Th17 differentiation and the production of the cytokines (IL-17, IL-22, IL-6, TNF-α) that maintain inflammation.

All of these data support the view that blocking not only TNF-α but also IL-18, IL-6, and IL-18 may be effective in PsA.

**THERAPY**

Previous therapies for PsA have often been borrowed from RA without any specific studies to verify their effectiveness. There is a lack of randomized controlled trials (RCT) evaluating the effect of disease-modifying antirheumatic drugs (DMARD) therapy on PsA, but observational studies of patients receiving traditional DMARD therapy have shown that the drugs exert little control over structural damage. One observational cohort study of 23 patients who received methotrexate (MTX) for 2 years found that the treatment did not reduce radiological progression in comparison with matched controls, although other authors have found that the early administration of high-dose MTX leads to a significant decrease in actively inflamed joint counts and psoriasis and some reduction in radiological progression. Leflunomide is effective on PsA and formally approved for its treatment in Europe.

Cyclosporine can rapidly improve psoriatic skin lesions, but there is little evidence of its effectiveness on musculoskeletal disease and its use is limited by its adverse effects of hypertension and renal insufficiency. However, it has been used in combination with anti-TNF agents such as etanercept.

TNF inhibitors are effective on the joints, skin, enthesitis, and dactylitis in patients with PsA. They inhibit structural damage and significantly improve function and the quality of life. Their efficacy on the spine is presumed on the basis of their efficacy in patients with ankylosing spondylitis (AS). They are also the first agents shown to be effective at reducing active joint inflammation and radiographic damage in RCT involving patients with PsA.

**TOCILIZUMAB**

Tocilizumab (TCZ) is a recombinant humanized anti-IL-6 receptor monoclonal antibody that prevents IL-6 from interacting with both the membrane-expressed receptor and its soluble counterpart, and thus inhibits IL-6 signal transduction. It has been approved for the treatment of moderate to severe RA in adults who inadequately respond to or have been intolerant of previous therapy with 1 or more DMARD or TNF antagonists (in Europe in January 2009, and the United States in 2010). It has been shown that 24 weeks’ treatment with TCZ alone or in combination with MTX is superior to MTX alone in reducing disease activity in patients with RA. TCZ has also been reported to be efficient in treating Castleman disease, adult-onset Still’s disease, Crohn’s disease, and juvenile inflammatory arthritis.

However, there are still no data concerning TCZ use in patients with PsA, although a pilot study is currently under way and various other (mainly subcutaneously administered) IL-6 inhibitors that inhibit the receptor or the cytokine will also be studied. Further, a recent case series on 2 patients treated with TCZ reported that although it resulted in the disappearance of serum C-reactive protein in both patients, arthritis and skin lesions were not improved despite 6 months of treatment.

TCZ seems to have an acceptable tolerability profile. The most frequently reported adverse events (AE) are infec-
tions\textsuperscript{3,15} and so, as in the case of other immunosuppressive biological agents, it is likely that patients receiving TCZ are predisposed to infectious complications including tuberculosis. The other frequent AE are high liver enzyme levels, increased lipid levels, and reduced neutrophil counts, which are all consistent with the drug’s mechanism of action. Among the patients with RA, AS, and PsA, patients with PsA are the most likely to present the atherosclerotic risk factors of obesity, impaired glucose tolerance, and hypertriglyceridemia, and hence the metabolic syndrome (MS). The findings of a recent cross-sectional study indicated that MS (a cluster of traditional risk factors that includes abdominal obesity, atherogenic dyslipidemia, hypertension, and insulin resistance) is more frequent in patients with PsA than in the general population\textsuperscript{14}. In addition, given the tendency for patients with PsA to develop MS\textsuperscript{16} and fatty liver, it will be important to control hyperlipidemia and monitor liver function abnormalities (both of which are known adverse effects of IL-6 inhibitors) in every patient treated with TCZ.

Although RA and PsA are separate clinical entities of different etiology, the similarities in the synovial infiltrate and increased proinflammatory cytokine production in patients with psoriasis and PsA support the view that, in addition to TNF-\(\alpha\) blockade, treatments against other proinflammatory cytokines such as IL-6 might also be effective.

REFERENCES