A Possible Therapeutic Target for Psoriatic Arthritis

Tofacitinib, a drug approved for the treatment of rheumatoid arthritis in 27 countries, could be used as a new therapeutic target for psoriatic arthritis, a new study shows.

The study, published in the Sept. 9 issue of the *Annals of Rheumatic Diseases*, is the first study to show the direct effect of tofacitinib on psoriatic arthritis synovial inflammation.

Tofacitinib is a Janus-Kinase (JAK) inhibitor, which blocks the JAK pathway inside the cell (rather than blocking upstream receptors on the surface of the cell, as other drugs do). As a result, it has the potential to interrupt the common pathways of many receptors and many cytokines. To find out its effect on those cytokines, researchers took biopsies of synovial fibroblasts from patients with psoriatic arthritis, grew them in culture and added tofacitinib to the culture media. On the molecular level, they found out which cytokines were upregulated and downregulated. On the functional level, they found out that tofacitinib inhibited fibroblast invasion, network function and migration, and reduced their secretion of inflammatory cytokines.

"This is the first study to demonstrate the effect of tofacitinib in primary PsA synovial fibroblasts and PsA explant cultures. These data further support a role for blockade of Janus-Kinase (JAK-STAT) signalling pathways in the treatment strategy for PsA," the authors wrote.

"In this study, tofacitinib significantly decreased pSTAT1, pSTAT3 in PsAFLS (psoriatic arthritis synovial fibroblasts) and PsA synovial explant cultures ex vivo," the researchers wrote.

"In parallel, tofacitinib increased SOCS3 and PIAS3 expression demonstrating negative feedback inhibition. Functionally, tofacitinib significantly decreased PsAFLS invasion, migration and network formation. Finally, tofacitinib significantly decreased spontaneous secretion of key proinflammatory cytokines, the MMP/TIMP ratio and NFκBp65 expression. Thus tofacitinib inhibits proinflammatory and invasive mechanisms which are critically involved in the pathogenesis of PsA."

Destruction of Cartilage and Bone

Psoriatic arthritis is characterized by synovitis and progressive destruction of articular cartilage and bone.

There is a distinct macroscopic vascularity in the joint characterized by elongated, tortuous vessels, associated with increased expression of cytokines, angiogenic growth factors and decreased apoptosis. This facilitates synovial fibroblasts invading adjacent cartilage and bone resulting in joint destruction. Many proinflammatory cytokines and growth factors interact at the synovium.

Recently developed agents for PsA have targeted IL12p40, interleukin (IL)-6 and IL-17, several of which signal through the Janus-Kinase (JAK) family of receptor-associated tyrosine kinases.

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