higher (p=0.01) remission rates compared with those with GPA (73%). Patients at study entry who were considered to be in relapse (67%) had significantly lower (p=0.01) remission rates compared with those who entered with a new diagnosis (81%). In all disease types, time to disease flare was longer for those patients with higher remission rates. Disease flares in the two treatment arms did not differ in number or severity.

The investigators noted that an increasing rise in ANCA titer or B-cell count was not an accurate predictor of disease flare. B-cell depletion occurred with cyclophosphamide-azathioprine, as well as rituximab, but was more prolonged with cyclophosphamide-azathioprine. Among rituximab-treated patients who achieved complete remission, flares occurred only after reconstitution of detectable B-cells. Dr. Stone noted that although flares occur in the absence of both B-cells and ANCA, as long as B-cells remain depleted and ANCA remains negative, the risk of a severe flare is low.

There were no clinically significant differences in overall or serious adverse events, deaths, infections, or malignancies. In particular, no additional malignancies occurred beyond those reported in the original study.

These results demonstrate that a single course of rituximab is as effective up to 18 months as standard therapy (cyclophosphamide-azathioprine) for remission induction and maintenance in severe ANCA-associated vasculitis. Relapses are more common in those with PR3-ANCA, GPA, and relapsing disease at baseline. Additional mechanistic studies are needed to define the immunological events that surround relapses more precisely.

JAK2 Reduces Basal Synthesis of Collagen in SSc Fibroblasts

Written by Maria Vinall

A study that explored the potential role of Janus kinase 2 (JAK2) as a molecular target for the treatment of fibrotic disease was presented by Clara Dees, PhD, University of Erlangen-Nuremberg, Erlangen, Germany. In this study, inhibition of JAK2 reduced the basal synthesis of collagen selectively in systemic sclerosis (SSc) fibroblasts but not in control fibroblasts. The profibrotic effects of transforming growth factor beta (TGFβ) were nullified with inhibition of JAK2. Inhibition of JAK2 also prevented fibrosis in inflammatory and noninflammatory fibrosis models.

SSc is characterized by an uncontrolled activation of fibroblasts, resulting in the release of excessive amounts of extracellular matrix components, leading to thickening and tightening of the skin. This study evaluated the role of JAK2 in the pathogenesis of SSc and analyzed the potential role of JAK2 inhibition as a novel antifibrotic.

Activation of JAK2 was determined by immunohistochemistry for phospho-JAK2 and phospho-signal transducers and activators of transcription 3 (STAT3; a major STAT protein that is activated by JAK2). Dermal fibroblasts were stimulated with TGFβ (a key factor in fibroblast activation in SSc) and incubated with the specific JAK2 inhibitor TG101209 at different concentrations. Fibroblast activation was determined by staining for α-smooth muscle actin (αSMA) and stress fibers. Bleomycin-induced dermal fibrosis and tight-skin 1 (Tsk-1) mice were used to evaluate the antifibrotic potential of a specific JAK2 inhibition *in vivo*.

Increased activation of JAK2 with prominent accumulation of phospho-JAK2, particularly in fibroblasts, was observed in the skin of SSc mice. JAK2 signaling persisted in cultured SSc fibroblasts, and stimulation of healthy fibroblasts with TGFβ increased the levels of phospho-JAK2, similar to those seen in SSc fibroblasts. Inhibition of JAK2 with TG101209 prevented the activation of SSc fibroblasts in the presence of TGFβ stimulation and decreased αSMA almost back to baseline levels. TGFβ-induced collagen synthesis (collagen type 1, alpha 1 [col1A1] mRNA, and collagen protein) was also reduced.

Furthermore, inhibition of JAK2 by the selective JAK2 inhibitor TG101209 abrogated the activated phenotype of SSc fibroblasts by decreasing the formation of stress fibers, the expression of αSMA, and the basal mRNA and protein levels of collagen. These inhibitory effects in the absence of exogenous stimulation were only observed in SSc fibroblasts, not in resting dermal fibroblasts from healthy individuals.

Inhibition of JAK2 consistently exerted potent antifibrotic effects in experimental fibrosis. In the model of bleomycin-induced fibrosis, treatment with TG101209 decreased dermal thickening by 95%±5% (p=0.007), collagen content by 76%±7% (p<0.001), and myofibroblast counts completely back to baseline levels (p=0.001). Potent antifibrotic effects were also observed in the Tsk-1 model. Application of TG101209 reduced hypodermal thickening, collagen content, and myofibroblast counts (p=0.01). These results suggest that JAK2 might be a promising molecular target for the treatment of SSc and other fibrotic diseases.