Small Molecule Inhibitor of the Wnt Pathway (SM04755) as a Potential Topical Scleroderma Treatment

Deshmukh V, Hood, A, Yazici Y
Samumed LLC

Aim

SM04755, a novel, small-molecule Wnt pathway inhibitor, was evaluated in preclinical studies to determine its potential for inhibition of inflammation, dermal fibrosis and vasculopathy in scleroderma (SCL).

Methods

Wnt pathway inhibition was measured with a cell-based reporter assay. Anti-inflammatory activity in lipopolysaccharide (LPS) stimulated monocytes and anti-CD3/anti-CD28 stimulated PBMCs was measured by ELISA for pro-inflammatory cytokines. Fibrosis in TGFβ stimulated human dermal fibroblasts (HDFs) was measured by smooth muscle actin (αSMA), plasminogen activator inhibitor (PAI-1), connective tissue growth factor (CTGF) and collagen gene expression by qPCR. Myofibroblast differentiation and reversion were measured by staining for αSMA. *In vivo* efficacy was evaluated in a bleomycin-induced mouse SCL model by measuring the thickness of the skin layers, expression of fibrotic and Wnt pathway genes and CD31 immunohistochemistry for vasculopathy.

Results

SM04755 was a potent (EC_{50} ≅152nM) and selective inhibitor of Wnt signaling and LPS, anti-CD3/anti-CD28 induced cytokine secretion (EC_{50} ≅500nM) in monocytes and PBMCs. SM04755 inhibited TGFβ stimulated fibrosis with decreased gene expression ($p<0.05$) of αSMA, PAI-1, CTGF and collagen in HDFs, and reduced αSMA stained stress fibers in myofibroblasts (EC_{50}≅400nM), thus also reversing fibrosis. In a bleomycin-induced mouse SCL model, compared to vehicle topical SM04755 reduced dermis and deep fascia thickness, increased adipose layer thickness ($p<0.01$), and reduced expression of fibrotic markers and Wnt pathway genes in the skin ($p<0.01$), thereby reversing bleomycin-induced dermal fibrosis. Decreased endothelial CD31 staining in skin suggested that SM04755 may have also improved vasculopathy.

Conclusion

SM04755 inhibited inflammation and dermal fibrosis *in vitro*. In a SCL mouse model, topical SM04755 reversed fibrosis, increased adipose tissue and may have reduced vasculopathy compared to vehicle. SM04755 has potential as a topical therapy for scleroderma.