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ANTI-INFLAMMATORY PROPERTIES OF SM04690, A SMALL MOLECULE INHIBITOR OF THE WNT PATHWAY AS A POTENTIAL TREATMENT FOR KNEE OSTEOARTHRITIS

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Abstract:

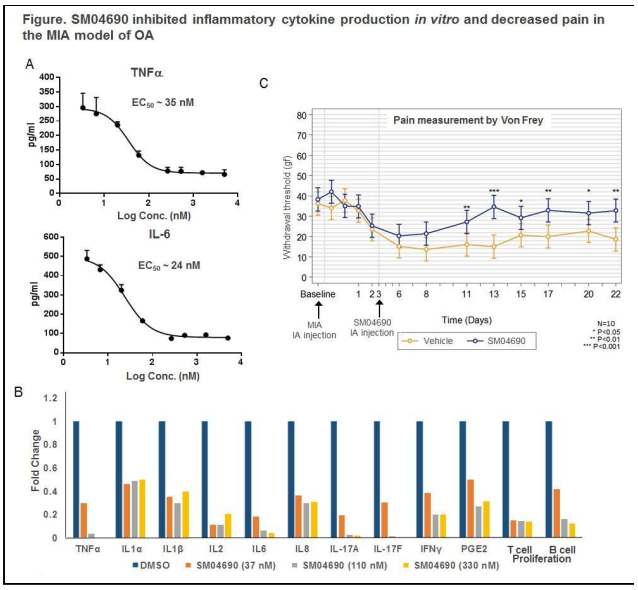
Purpose: Osteoarthritis (OA) is characterized by pain, swelling, and reduced function in the affected joint. Current therapeutic options focus on pain relief rather than disease modification. Amongst many cellular processes, increased Wnt signaling in OA joints increases cartilage breakdown and bone formation. It also modulates inflammatory pathways. SM04690 is a novel small molecule previously shown in preclinical studies to inhibit the Wnt pathway, protect cartilage, and induce chondrogenesis (Hood et al. OAC 2016, s187). It was further evaluated in a series of preclinical studies to determine its capacity to reduce inflammation, and thereby modify pain in OA.

Methods: Anti-inflammatory activity was evaluated by measuring TNF-α and IL-6 secretion using ELISA in synovial fibroblasts stimulated with IL1-β, THP-1 monocyte cells stimulated with lipopolysaccharides (LPS), and peripheral blood mononuclear cells (PBMCs) stimulated with anti-CD3/anti-CD28. A panel of pro- inflammatory cytokines (TNF-α, IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-17A, IL-17F, IFN-γ, and PGE2) was evaluated by ELISA, T and B cell proliferation by flow cytometry in PBMCs, and T and B cell co-cultures stimulated with super-antigen or LPS, compared to vehicle or benchmark immunosuppressant or steroid (cyclosporin A and prednisolone). The effect of SM04690 on the LPS-induced expression and phosphorylation of inflammatory signaling pathway mediators (JNK, NFkB, Erk, cJun, Akt, Stat3) in THP-1 cells was evaluated by qPCR and Western Blot. *In vivo* activity of SM04690 was evaluated in the rat monosodium iodoacetate (MIA) injection-induced model of OA, immediately followed by a single intra-articular (IA) injection of SM04690 or vehicle. Inflammation in the joint was evaluated by measurement of pro-inflammatory markers (TNF-α, IL-1β, and IL-6) by qPCR. Pain was measured as paw withdrawal threshold using the Von Frey apparatus at various time points during the study.

Results: SM04690 inhibited IL-1β-induced TNF-α and IL-6 secretion in synovial fibroblasts ($EC_{50} \cong 30nM$) (Figure A), and LPS- and anti-CD3/anti-CD28-induced TNF-α and IL-6 secretion in THP-1 cells and PBMCs, respectively. SM04690 significantly inhibited ($p<0.01$) superantigen and LPS stimulated production of pro-inflammatory cytokines (TNF-α, IL1-α, IL1-β, IL-2, IL-6, IL-8, IL-17A, IL-17F, IFN-γ, PGE2), and T and B cell proliferation in PBMCs and T and B cell co-cultures (Figure B), with activity comparable to or better than cyclosporin A and prednisolone. Additionally, SM4690 treatment specifically decreased LPS-induced gene expression (3-fold, $p<0.01$) and phosphorylation of NFkB in THP-1 cells with no effect on JNK, Erk, cJun, Akt and Stat3 signaling. In the MIA-injection induced OA model, a single IA injection of SM04690 significantly increased ($p<0.01$) the paw withdrawal threshold in treated rats as compared to vehicle treatment, at multiple time points after treatment (Figure C), indicating decreased pain in response to treatment. Further, SM04690 treatment reduced visible swelling of the knee and significantly ($p<0.05$) inhibited the production of pro-inflammatory cytokines in the joint as compared to vehicle.

Conclusions: SM04690 demonstrated potent anti-inflammatory properties in various cell types with activity comparable to or greater than cyclosporin A and prednisolone, and inhibited NFkB signaling *in vitro*. In a rodent model of knee OA, a single IA injection of SM04690 resulted in reduced inflammation and pain compared to vehicle. The anti-inflammatory properties of SM4690 may provide beneficial effects in the treatment of OA.

Clinical studies with SM04690 in OA are ongoing.



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