Accepted as poster #P1235 at the World Congress on Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (WCO-IOF-ESCEO) 2020, August 20–22, 2020

Lorecivivint (SM04690), an Intra-articular, Small-Molecule CLK/DYRK1A Inhibitor That Modulates the Wnt Pathway, as a Potential Treatment for Meniscal Injuries

Timothy Seo, MS, Vishal Deshmukh, PhD, Yusuf Yazici, MD

Samumed, LLC, San Diego, CA

Background: Meniscal damage is a common knee pathology and a frequent finding on MRI images of knee osteoarthritis (OA). Efforts to repair meniscal damage have been largely unsuccessful and do not prevent the progression of degenerative changes that lead to knee OA. The Wnt signaling pathway has been shown to be regulated during meniscal development, suggesting that manipulation of this pathway may influence the regenerative capacity of the meniscus. Lorecivivint (LOR; SM04690), an intra-articular (IA), small-molecule CLK/DYRK1A inhibitor that modulates the Wnt pathway, was evaluated in preclinical studies to determine its protective and anabolic effects in ex vivo explants and a rat model of chemically induced inflammatory meniscus degeneration.

Methods: Effects of LOR (30 nM) on matrix metalloproteinase (MMP) expression in IL-1β-treated and cultured rat menisci were measured by qPCR. In vivo, LOR activity was evaluated in a rat model of monosodium iodoacetate (MIA) injection-induced inflammatory meniscus degeneration. A single IA injection of MIA was immediately followed by a single IA injection of LOR (0.3 μg) or vehicle. Knees were harvested on Days 1, 4, and 11 and menisci were isolated. Inflammation was evaluated by qPCR for *TNFα* and *IL6* expression. Meniscus protection was evaluated by qPCR for MMPs and aggrecanase and anabolic effects by qPCR for collagens.

Results: In ex vivo meniscal explants, LOR inhibited *MMP1*, *MMP3*, and *MMP13* expression compared with DMSO ($P<0.01$). In vivo, LOR significantly decreased MMP expression and aggrecanase ($P<0.05$) and reduced inflammatory cytokine expression (*TNFα* and *IL6*) compared with vehicle in the rat model of meniscus degeneration at Day 4 after MIA injection. LOR also increased expression of collagen types I, II, and III at Day 11 after MIA injection.

Conclusion: LOR exhibited protective effects in the meniscus ex vivo and in vivo by inhibiting catabolic enzyme expression compared with controls. Anti-inflammatory effects of LOR were demonstrated by reduced inflammatory cytokine expression. Compared with vehicle, LOR increased collagen expression in vivo, indicating potential meniscal anabolic effects. These data support further investigation of LOR as a potential disease-modifying therapy for meniscal injuries.