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

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Background: Meniscal injuries, associated with pain, stiffness, and localized swelling, are the most common pathology of the knee with a prevalence of 61 per 100,000.¹ Meniscal damage is a frequent finding on MRI images of knee osteoarthritis (OA)²; while a meniscal tear can lead to knee OA, knee OA can also lead to a spontaneous meniscal tear.³ Efforts to repair meniscal damage have been largely unsuccessful and do not prevent the progression of degenerative changes that lead to knee OA.⁴ The Wnt signaling pathway has been shown to be regulated during meniscal development,^{5,6} suggesting that manipulation of this pathway may influence the regenerative capacity of the meniscus. Lorecivivint (LOR; SM04690) is an intra-articular (IA), small-molecule CLK/DYRK1A inhibitor that modulates the Wnt pathway.

Objectives: LOR was evaluated in preclinical studies to determine its protective and anabolic effects in ex vivo explants and in a rat model of chemically induced inflammatory meniscus degeneration.

Methods: Effects of LOR (30 nM) on expression of matrix metalloproteinases (MMPs) in cultured rat menisci treated with IL-1 β 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 μ g) or vehicle. Knees were harvested on Days 1, 4, and 11 and menisci were isolated. Anti-inflammatory effects were evaluated by measuring *TNF α* and *IL6* expression by qPCR. 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 expression of *MMP1*, *MMP3*, and *MMP13* compared with DMSO ($P < 0.01$). In vivo, LOR significantly decreased expression of these MMPs and aggrecanase ($P < 0.05$) compared with vehicle in the rat model of inflammatory meniscus degeneration at Day 4 after MIA injection. In addition, LOR reduced expression of inflammatory cytokines *TNF α* and *IL6* at Day 4 compared with vehicle. Finally, LOR increased expression of collagen types I, II, and III at Day 11 after MIA injection.

Conclusions: LOR exhibited protective effects in the meniscus ex vivo and in vivo by reducing the expression of catabolic enzymes compared with control. Anti-inflammatory effects of LOR were demonstrated by inhibition of inflammatory cytokine expression. Compared with vehicle, LOR increased expression of collagens in vivo, indicating potential meniscal anabolic effects. These data support further investigation of LOR as a potential disease-modifying therapy for meniscal injuries.

References:

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