LORECIVIVINT (SM04690), A POTENTIAL DISEASE-MODIFYING TREATMENT FOR KNEE OSTEOARTHRITIS, DEMONSTRATED CARTILAGE-PROTECTIVE EFFECTS ON HUMAN OSTEOARTHRITIS EXPLANTA

Poster #166

Background

• Excessive Wnt pathway signaling contributes to osteophyte formation, cartilage degeneration, and inflammation in knee osteoarthritis (OA).
• Lorcivivint (LOR) is an intra-articular (IA), small-molecule drug candidate that modulates Wnt pathway activity via CLK/DYRK1A inhibition.
• LOR has demonstrated potential as a treatment for knee OA in randomized controlled trials, with improvements seen in pain and function as well as maintenance of radiographic medial joint space width in a target population.
• The cartilage-protective effects of LOR in knee OA were measured by assessing catabolic enzyme expression and activity in cartilage explants from human total knee replacement (TKR) donors.

Conclusions

• LOR impaired pro-inflammatory cytokine-stimulated cartilage catabolism in human knee explant cultures compared with controls, as shown by suppression of:
  – Gene expression of MMP1, MMP3, and MMP13
  – Stimulated secretion of all tested catabolic enzymes
  – Release of the cartilage catabolism byproducts GAG and NO
• These data indicate that LOR exerted protective effects on knee cartilage ex vivo despite previous OA-related joint damage.
• The results support the development of LOR as a potential disease-modifying treatment for knee OA. Phase 3 trials are ongoing.

Results

A. Enzyme gene expression (explants)

• Exposed to control or stimulated cartilage explants

B. Enzyme protein levels (supernatants)

• Exposed to control or stimulated cartilage explants

C. GAG and NO levels (supernatants)

• Exposed to control or stimulated cartilage explants

Methods

• Cartilage Explants: 72 hours
• DMSO or LOR: 2 hours
• IL-1β or TNF-α: 2 hours

Analysis

• Effects of LOR on cartilage catabolism (compared with DMSO) in the stimulated cultures were measured by:
  – qRT-PCR for gene expression of matrix metalloproteinases (MMPs) 1, 3, and 13
  – ELISA for release of MMP-1, MMP-3, MMP-13, and the thrombospondin motif-containing disintegrin/metalloproteinases ADAMTS-4 and ADAMTS-5
  – Dimethylmethane blue and Griss assays for release of the degradation products glycosaminoglycan (GAG) and nitric oxide (NO), respectively
• Data analyzed via mixed-effects, one-way ANOVA. Outliers identified using extreme studentized deviate test (Grubbs’ test, p<0.001). Type 1 error controlled at p<0.05 using Dunnett’s multiple comparison test.

References


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N=22; Mean ± SEM, *p<0.05, **p<0.01, ***p<0.001 vs. DMSO, one-way ANOVA.