● EFFECTS OF INTRA-ARTICULAR INJECTION OF CROSS-LINKED HYALURONATE HYDROGEL (GEL-200) ON THE ANTERIOR CRUCIATE LIGAMENT (ACL) TRANSSECTION INDUCED ARTHRITIS IN RABBITS

++Yoshioka, K; *Miyamoto, K; *Abe, R; *Takahashi, K; *Minamisawa, Y; *Maruyama, H
+Central Research Laboratories, Seikagaku Corporation, Higashiyamato, Tokyo, Japan. +81-42-563-5806, FAX: +81-42-563-5847, keiji.yoshioka@seikagaku.co.jp

Introduction:
Intra-articular injection of hyaluronan preparations is commonly utilized in the treatment of osteoarthritis (OA), however, it often required 3-5 administrations to achieve efficacy. Gel-200 is a newly developed cross-linked hyaluronate hydrogel as a novel therapeutic agent for the knee OA. The objective of this study was to examine the efficacy of Gel-200 in the rabbit ACL transection model. The ACL transection model used in this study has been accepted as an arthritis model, which produces cartilage degradation similar to OA in humans (1,2,3). Therefore, this model has been frequently used for evaluation of hyaluronan preparations (SUPARTZ®, HYLKAN®, HEALON®, SYNVISC®) (4).

Methods:
Experimental osteoarthritis (OA) was induced in 48 male rabbits by transecting the unilateral ACL. Four weeks after the ACL transection, Gel-200 was administered once or twice (at an interval of 2 weeks) into the joint cavity of the left hind knee at a dose of 0.05 mL/kg/joint. Its efficacy was compared to that of repeated administration of PBS or SUPARTZ® once a week for 5 weeks. All animals were sacrificed 9 weeks after ACL transection. The left knee joints were then removed and evaluated by morphological assessment of cartilage degeneration, volume of synovial fluid and protein content, number of infiltrated cells and glycosaminoglycans content in synovial fluid as indicators of synovitis, and histopathological examination of the cartilage and synovium.

Results:
In the morphological assessment, cartilage degeneration was less in the Gel-200 groups compared to the SUPARTZ® (Figure 1). In fact, in both the one- and two-injections Gel-200 groups the degeneration of the articular cartilage was significantly less compared with control treated with 5-weekly injections of PBS. In contrast, SUPARTZ® administration decreased the degeneration compared with control, but this efficacy was not significant. The severity comparison among the test substances were in the following order: PBS > SUPARTZ® > 1 injection of Gel-200 ≥ 2 injections of Gel-200. Efficacy of Gel-200 for suppression of cartilage degeneration was also demonstrated by a reduction of the increase in chondroitin 6-sulfate (6S) in the synovial fluid. In addition, Gel-200 appeared to improve the symptoms of synovitis, as judged from the reduction in increase of synovial fluid, protein and chondroitin 4-sulfate (4S) contents. Overall, since cartilage degeneration is milder when synovitis is not severe, these changes induced by Gel-200 may interact beneficially to relieve the progression of pathological changes. Histopathological findings of articular cartilage supported the morphological assessment (Figure 2). In the histopathological examination of synovium, cuboidal/stratified synovial epithelium, subepithelial cellular infiltration, subepithelial hemorrhage and subepithelial calcium deposition were observed in all the experimental groups. These changes were less severe in Gel-200 groups compared to those in the control group.

Conclusion:
These data show that in a rabbit ACL transection model of OA, a single intra-articular injection of Gel-200 was superior to five injections of SUPARTZ® in slowing cartilage degeneration. It is considered that this superiority of Gel-200 is attributed to its highly cross-linked structure.

References: