Pharmacological Profile of the Photo-cross-linked Hyaluronate Gel (Gel-One®)

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Disclosures:

Introduction: Osteoarthritis (OA) of the knee is a common joint disorder in the aging population. Intra-articular hyaluronic acid (HA) products have been accepted as a viscosupplementation for the treatment of knee OA pain. Gel-One® is the most recently approved single injection product in the US market and is composed of Gel-200 which is a novel cross-linked hyaluronic hydrogel manufactured by Photo-Gelation technology. In Gel-200, strands of hyaluronan are bound to each other via dimers of cinnamic acid resulting in increased viscoelasticity. In a multi-center randomized controlled trial in patients with symptomatic OA of the knee, a single injection of Gel-200 was well tolerated and relieved pain associated with symptomatic OA of the knee over 13 weeks1. The purpose of this study is to investigate the pharmacological profile of Gel-200 in experimental animal models and in vitro studies.

Methods: Anterior cruciate ligament (ACL) transection-induced OA model in rabbits (in vivo)
Experimental OA was induced in 24 rabbits by transecting the unilateral ACL. Four weeks after the ACL transection, Gel-200 or PBS was administered once into the joint cavity of the left hindlimb at a volume of 50 μL/kg/joint (N=12). All animals were sacrificed 9 weeks after ACL transection. The left knee joints were removed and evaluated by morphological assessment of cartilage degeneration, biochemical analysis of synovial fluid and histopathological examination of the cartilage and synovium.

Inhibitory effect of recombinant human interleukin-1β (rhIL-1β)-induced matrix metalloproteinase (MMP) -1, -3 and -13 production in human chondrocytes (in vitro)
The normal human articular chondrocytes (NHAC) were preincubated with or without Gel-200 in the concentration range of 0.1-3.0 mg/mL for 30 minutes. The cells were then incubated with rhIL-1β (final concentration, 10 ng/mL) at 37 ºC for 16 hours to induce MMP-1, -3 and -13 productions in the presence or absence of Gel-200. The MMPs contents in the conditioned media were determined with QuantiLine ELISA kits.

Inhibitory effect of rhIL-1β-induced prostaglandin (PG) E₂ production in human synoviocytes (in vitro)
RhIL-1β was added to human synovial sarcoma cells, SW982, to stimulate PGE₂ production. The cells were incubated in the presence or absence of Gel-200 in the concentration range of 0.003-3.0 mg/mL with rhIL-1β (final concentration, 10 ng/mL) for 42 hours. The PGE₂ contents in the conditioned media were determined with PGE₂ ELISA kits.

Results: In an OA model, chondroprotective effect and improvement of synovitis by a single-dose intra-articular injection of Gel-200 were demonstrated. In the macroscopic picture, the cartilage damaged areas of the femoral condyle which were stained by the India ink were less severe in the Gel-200 group. The damaged length and width were measured by using a digital caliper and the severity of the degeneration was scored on a 7-grade scale. Progression of the cartilage degeneration was significantly suppressed in the Gel-200 group compared with the PBS group (p < 0.0001, Wilcoxon rank sum test). Using the synovium preparations, the following histopathological observations were carried out and scored on a 4-grade scale. The severity of the changes was less in the Gel-200 group (Figure 1). The modes of action for Gel-200 were assessed using in vitro studies. Gel-200 significantly inhibited MMP-13 and MMP-3 production from human chondrocytes in the range of 0.1 to 3 mg/mL in a concentration-dependent manner (Figure 2). Gel-200 showed a trend toward inhibition in MMP-1 production. At only maximum concentration (3 mg/mL), its inhibitory effect is significant. In addition, when human synoviocytes were incubated with rhIL-1ß in the presence of Gel-200, the levels of secreted PGE₂ were decreased in the range of 0.03 to 3 mg/mL in a concentration-dependent manner (Figure 3). The inhibition rates of 0.03, 0.3, and 3 mg/mL Gel-200 were 18.4, 44.9 and 49.2%, respectively.

Discussion: The mode of action of viscosupplementation is considered to improve the viscoelastic property of synovial fluid leading to protect joint cartilage against abrasion and physical stress. However, the mechanisms of long-lasting pain relief exerted by intra-articular HA therapy remain still unclear. In the previous studies, the pharmacological function of HA on several mediators related to OA pathogenesis has been investigated. It has been reported that MMPs production which is involved in cartilage destruction are suppressed by HA via CD44 which is the principal cell surface receptor for HA in vitro studies2,3,4. It has reported that PGE₂ production which is induced in synovitis are also inhibited by HA via CD44 in vitro study5. The inhibition of PGE₂ production by HA was also confirmed in a clinical study6. This is the first study that has revealed the pharmacological effects of Gel-200, novel cross-linked hyaluronate hydrogel (Gel-One®), on MMPs and PGE₂ production. The chondroprotective effect of Gel-200 in vivo study was considered to be partially caused from resulting in increased viscoelasticity due to Gel-200 injection. Furthermore, Gel-200 inhibited IL-1β-induced MMPs production in a concentration-dependent manner in human chondrocytes and decreased IL-1β-induced PGE₂ production in a concentration-dependent manner in human synoviocytes.
These findings from each study suggest that Gel-200 exerted chondroprotective and anti-inflammatory effects via multimodal HA functions.

**Significance:** In non-clinical pharmacological studies, a single-dose intra-articular injection of Gel-200 exerted chondroprotective and anti-inflammatory effects, suggesting the multimodal function by Gel-One® against symptomatic knee OA patients.

**Acknowledgments:** We wish to thank R. Zuinen and Y. Minamisawa in Seikagaku Corporation (Tokyo, Japan) for study technical support.

**References:**

Figure 1 Histopathological findings of synovial membrane
Figure 2: Effect of H2O2-induced MPP7 production in human cardiocytes
Figure 3: Inhibition of rhL-10 reduces PGE2 production in human synoviocytes.

ORS 2014 Annual Meeting
Poster No: 0341