Therapeutic Effects of the Intraarticular Administration of Ultra-purified Low Endotoxin Alginate on Experimental Osteoarthritis in Rabbits

INTRODUCTION: Intrarticular administration of any therapeutic agent has been considered to be an effective strategy for preventing or delaying the progression of osteoarthritis (OA). To date, hyaluronan (HA) solutions and HA derivatives have been widely used as an agent of intrarticular administration for knee and shoulder OA. However, the therapeutic effects of HA injection on OA are still debated. Recent clinical studies have demonstrated no therapeutic effects of HA injection on preventing the disease progression. Therefore, a novel therapeutic agent for intra-articular administration must be developed. Alginate is known as a HA-like biocompatible polymer often used in biomaterials science. Previous in vitro studies have also shown that alginate enhances chondrogenesis of stem and progenitor cells. On the other hand, alginate includes mitogenic and cytotoxic impurities that induce a foreign body reaction in a living body.

METHODS: Materials. Three different molecular weight UPLE-alginate were prepared as follows: AL20 (molecular weight 0.43 x 10^6 Da), AL100 (1.0 x 10^7 Da), and AL500 (1.70 x 10^9 Da) (Mochida Pharmaceutical Co., Ltd., Tokyo, Japan). All materials had quite a low endotoxin level of 5.76 EU/µg. For comparison, sodium HA (ARTZ®, Kaken Pharmaceutical Co., Ltd., Tokyo, Japan) were used in this study. OA model and treatment protocols. Japanese white rabbits weighing 2.8–3.0 kg were used for this study according to the established ethical guidelines approved by the local animal care committee. To induce OA in both knees, anterior cruciate ligament transection (ACLT) of each knee was performed through a medial parapatellar approach. All knees were randomly divided into 5 treatment groups as follows; AL20, AL100, AL500, HA, and normal saline (NS, respectively). To test this hypothesis, we examined the activity of intra-articular administration of the UPLE-alginate using a rabbit OA model. The aims of this study were to clarify the effect of the UPLE-alginate administration on OA progression and on joint lubrication, and to determine the adequate molecular weight of the UPLE-alginate for therapeutic effects.

RESULTS: Gross Morphology (Fig.1). All rabbits exhibited some degree of mild to severe degenerative changes and joint effusion. The NS and HA groups showed extensive cartilage erosion mainly at the medial femoral condyle. The alginate injection groups exhibited milder degeneration than the HA and NS groups. The AL100 group showed lower severity grades. Severe OA changes of grade 3 (erosion) and grade 4 (erosion) at the medial femoral condyle occurred at a rate of 60%, 63%, 67%, 70%, and 90% in AL100, AL20, AL500, HA, and NS, respectively (Fig.1).

DISCUSSION: To our knowledge, the current study is the first to examine the influence of alginate materials on OA progression in vivo. Our previous in vivo studies clarified that the novel ultra-purified low endotoxin alginate (UPLE-alginate) did not evoke any macroscopical or histological inflammatory findings indicating foreign body reaction in living joints. Our hypothesis was that the UPLE-alginate could promote anti-arthritic activity in experimental OA. To test this hypothesis, we examined the activity of intra-articular administration of the UPLE-alginate using a rabbit OA model. The aims of this study were to clarify the effect of the UPLE-alginate administration on OA progression and on joint lubrication, and to determine the adequate molecular weight of the UPLE-alginate for therapeutic effects.