Prevention Of Post-traumatic Osteoarthritis By Administration Of Intra-articular Anti-vegf Antibody (bevacizumab)

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Disclosures:

Introduction:
Angiogenesis is an important factor in the development of osteoarthritis (OA). Angiogenesis also results in innervation of the articular cartilage (1), which may provide the possible source of pain in OA patients. We reported previously that intravenous administration of bevacizumab, a humanized monoclonal anti-VEGF antibody, contributes to the repair of articular cartilage in an osteochondral defect model (2) and anterior cruciate ligament transection (ACLT) model (3). While bevacizumab is a very attractive target for the treatment of neovascular disease, several complications in its intravenous (systemic) administration have been reported, including gastrointestinal hemorrhage, thromboembolism, and delayed wound healing (4). The purpose of this study was to investigate the efficacy of intra-articular (local) administration of bevacizumab in post-traumatic OA using a rabbit model of ACLT.

Methods:
Animal experiments were approved by the ethics review board of Tokai University and were performed in accordance with the guidelines on animal use of Tokai University. ACLT was performed on 18 rabbits on only one knee per rabbit to measure pain behavior in terms of weight-bearing asymmetry. Rabbits were assigned to three recipient groups: IV group (n=6; 100 mg bevacizumab intravenous injection administered at 4 and 6 weeks after ACLT, total dosage 200 mg), IA group (n=6; 25 mg bevacizumab intra-articular injection administered at 4, 5, 6 and 7 weeks after ACLT, total dosage 100 mg), and OA group (n=6; no drug treatment). We checked the pain relief assessments using Incapacitance Tester at the 4, 6 and 12 weeks after ACLT. The weight distribution of both hind legs was measured 10 times, and the following formula was used to calculate the damaged limb weight distribution ratios (%) obtained by loading the left and right limbs. Damaged limb weight distribution ratio (%) = (damaged limb load (g) / undamaged limb load (g) + damaged limb load (g)) x 100. All animals were sacrificed at 12 weeks after ACLT. We evaluated OA repair sites using a grading and staging system (OARSI modified Mankin score) (5). Statistical analyses of data were performed by Kruskal-Wallis followed by post hoc comparisons (Mann-Whitney U test). Differences were considered significant when P values were less than 0.017 between three groups.

Results:
A comparison of the weight-distribution ratio of the three groups (OA, IV and IA) following bevacizumab treatment is shown in Figure. 1. Up until 6 weeks, we measured no difference in rabbit weight distribution between the three groups. However, by 12 weeks, rabbits in the IA group showed a satisfactory improvement in the damaged limb weight distribution ratio, whereas rabbits in the OA and IV
groups failed to show such improvement, with significant difference observed (OA: 38.9±3.9%, IV 40.3±6.3%, IA 47.9±4.8%). Unfortunately, one rabbit of IV group died from complications with digestion at 8 weeks. We divided the distal portion of the femur part into femoral-tibia (FT), Corner and femoral-patella (FP) sites (Figure 2). In the OA group, diminished Safranin O staining was observed at the FT site, with clear degeneration of the cartilage. Furthermore, only minimal Safranin O staining was observed at the Corner and the FP sites (Fig. 3A). In contrast, in the IV group, matrix staining was strong at the FT site throughout the thickness of the cartilage and higher at the Corner and FP sites as compared with the OA group. Some matrix staining depletion was observed within the upper one-third of the cartilage at the Corner site and within the FP site within the full thickness of the cartilage (Fig. 3B). In the IA group, matrix staining depletion was minimal at all three sites, with staining observed throughout the full thickness of the tissue (Fig. 3C). As expected, the OARSI histological score for Safranin-O staining was not significant among the three groups at the FT site (Fig. 4A). However, at the Corner site and FP site, the histological score for the IA group was significantly lower than the score for the OA and IV groups (Fig. 4B, 4C) (Corner site; OA:19.6±3.8, IV:18.0±5.0, IA:5.5±7.8, FP site; OA:13.5±3.5, IV:7.6±9.0, IA:2.5±3.5); these results indicated a significant level of repair in the joints treated with the intra-articular injection of bevacizumab.

**Discussion:**
There are numerous potential side effects of systemic administration of bevacizumab. It is likely that the intra-articular administration of bevacizumab may decrease these adverse side effects. In this study, there was no disadvantage associated with the IA group, and in the IA group was observed significantly repair than in the OA and IV groups in terms of histological score. Furthermore, the total dose of the IA group was the half dose of the IV group. Moreover, pain improvement was significantly recognized in the IA group. Considering histological repair, pain relief and the dose and the potential adverse effects of bevacizumab, the local administration of bevacizumab is a more advantageous approach than systemic administration.

**Significance:**
In conclusion, intra-articular administration of bevacizumab recognized better histological repair and pain relief than intravenous administration. Our results indicate that intra-articular administration of bevacizumab may offer a new therapy for patients with post-traumatic OA.

**Acknowledgments:**

**References:**
(3) Nagai T, et al. Orthopaedic research society annual meeting 2013