Prevention of osteoarthritis by administration of anti-VEGF antibody, Bevacizumab

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INTRODUCTION:
Mature articular cartilage has a limited capacity to regenerate after degeneration or injury. For this reason, various treatments have been developed to induce restoration by regenerative medicine. At present, techniques using penetration of subchondral bone, mosaicplasty, cell transplantation, and implantation of tissue-engineered cartilage with various scaffold materials or without scaffold have been developed to overcome this obstacle. Osteoarthritis (OA) involves the coexistence of both chondral and osteochondral defect. Generally, osteochondral defects are repaired by endochondral ossification, by which the defect is first filled with reparative cells derived from bone marrow, which involves vascular invasion, and the cells are eventually replaced by bone. We hypothesized that better cartilage repair might be achieved by inhibiting the bioactivity of vascular endothelial growth factor (VEGF) in the osteochondral defect. 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, without using cultured cells or artificial scaffolds (1). The object of this study was to investigate whether cartilage degeneration is prevented following intravenous administration of anti-VEGF antibody in a rabbit model of anterior cruciate ligament transection (ACL T).

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 in Japanese white rabbits (n=31 knees; weight, 3 kg). Rabbits were assigned to two recipient groups: group B, administration of bevacizumab (n=15; 100 mg intravenous injection administered 1 week after surgery and 3 weeks later); and the controls (n=16). Rabbits were sacrificed 1 and 3 months postoperatively.

We evaluated osteophyte formation macroscopically using a score of 0-3 as absent, mild, moderate and severe (2). Sagittal sections (5µm thick) were obtained and stained with safranin-O fast green. We evaluated OA repair sites semiquantitatively using a grading and staging system (OARSI modified Mankin score) (3). This system includes six histological grades and four histological stages. The total score (grade score multiplied by stage score) ranged from 1 point (normal articular cartilage) to 24 points (no repair).

Differences in osteophyte formation and histological scores were assessed using the Mann-Whitney U test. Values of P<0.05 were accepted as significant.

RESULTS:
One month after ACLT, macroscopic evaluation of joints from both groups showed that some parts of joints included osteophyte formation and nearly smooth joint surfaces of the articular cartilage (Figure 1). However, histological assessment demonstrated that articular cartilage showed loss of Safranin O staining in the control group, whereas the staining was retained in group B (Figure 2).

Three months after ACLT, macroscopic evaluation showed marked progression of arthritis and osteophyte formation in the control group. By contrast, the joints from group B retained smooth joint surfaces in most regions of the articular cartilage but had less osteophyte formation (Figure 3). Histological assessment of control joints showed delamination of superficial layer, erosion of hyaline cartilage, lack of Safranin O staining, and cluster formation. Assessment of joints from group B showed smooth and uniform articular surfaces, fewer clusters of chondrocytes than in the control samples, and Safranin O staining throughout the articular cartilage (Figure 4).

The OARSI histological score was used to evaluate the quality of the repair tissue. One month after ACLT, the total score did not differ between the control and B group (mean ± standard deviation [SD]: 9.2 ± 4.6 in the control and 5.2 ± 4.8 in group B). Three months after ACLT, the total score was significantly lower in group B (4.6 ± 3.7) than in the control (13 ± 7.1) (Figure 5). Similarly, one month after ACLT, the osteophyte formation score did not differ between the control (1.5 ± 1.1) and group B (0.6 ± 0.7). Three months after ACLT, the score was significantly lower in group B (0.5 ± 0.5) than in the control (2.7 ± 0.7) (Figure 6).

DISCUSSION:
OA chondrocytes produce VEGF, whose expression by chondrocytes in OA joints is related to articular cartilage destruction (4). High-dose VEGF may induce the onset and progression of arthritis (5). Osteophyte formation during OA development has been reported to involve VEGF signaling (6). We studied whether blocking VEGF signaling with bevacizumab would increase the restoration of OA cartilage in a model of ACLT in Japanese white rabbits. Our results demonstrate that blocking VEGF therapy facilitates the repair of articular cartilage and restrains osteophyte formation in OA.

SIGNIFICANCE:
Intravenous administration of bevacizumab contributes to better repair of articular cartilage in the rabbit model. We suggest that this new early intervention may be useful for achieving better repair of post-traumatic osteoarthritis.

REFERENCES: