Evaluation of rhPDGF-BB in Combination with a Bi-phasic Collagen Implant for Osteochondral Defect Repair in a Caprine Model

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INTRODUCTION: Platelet-derived growth factor-BB (PDGF-BB) is a well characterized wound healing protein known to be chemotactic and mitogenic for cells of mesenchymal origin, including osteoblasts and chondrocytes [1, 2]. Biocompatible scaffolds, combined with growth factors such as PDGF-BB, have potential to stimulate the regeneration and repair of cartilaginous tissues. The purpose of this study was to determine the efficacy and safety of recombinant human PDGF-BB (rhPDGF-BB) combined with a collagen implant to augment healing of an osteochondral defect in a caprine model.

METHODS: Treatment Groups: Five treatment groups (n=7/group; n=4/empty group) were used in the repair of a single osteochondral defect: (1) empty defect, (2) 0 µg rhPDGF-BB (buffer) + collagen implant (control), (3) 15 µg rhPDGF-BB + collagen implant, (4) 75 µg rhPDGF-BB + collagen implant, and (5) 500µg rhPDGF-BB + collagen implant. Surgical Procedure: The right stifle joint of 32 skeletally mature castrated male Boer-cross goats (+/- years) was surgically exposed and a single, unilateral 8 mm diameter x 8 mm depth osteochondral defect was created in the medial femoral condyle. Collagen implants (Chondromimetic implant; TiGenix, Inc: 8.5 mm diameter x 8 mm depth) hydrated with different concentrations of rhPDGF-BB or buffer alone were press fit into the treated defects. Post-op a modified Thomas splint was applied for 14 days. Animals were allowed to ambulate normally until sacrifice at 12 weeks post-surgery.

Gross Morphological Evaluation: All specimens were assessed macroscopically at the time of necropsy. Integration of nascent tissue to native cartilage, degree of defect filling, smoothness, and color of repair tissue were evaluated prior to fixation of specimens in 10% neutral buffered formalin [3]. Additionally, the joint space of the operated and control stifle joints were assessed.

MicroCT Analysis: All specimens were subjected to microCT analysis (Scanco MicroCT 80) to determine reconstitution in the subchondral space of the defect. Bone volume, trabecular number, connectivity density, and trabecular thickness for uniform regions of interest were determined.

Histology: Specimens were decalcified, processed, and embedded in paraffin. Sections were obtained in the sagittal plane and stained with hematoxylin and eosin, Safranin-O with fast green, or IHC for Type I and Type II collagen. All rhPDGF-BB treatment groups exhibited increased Safranin-O staining of the matrix compared to the 0 µg rhPDGF-BB control, although these did not reach statistical significance. Further, the presence of bony bridging across the central region of the defect was only noted in the 500 µg rhPDGF-BB group (Figure 1). Histology: Treatment groups had mild or no inflammatory response in the subchondral bone and normal cellularity. The total cartilage repair score (Table 1) was significantly improved (p =0.048) in the 500 µg rhPDGF-BB treatment group (14.3±0.3) compared to the 0 µg rhPDGF-BB control group (12.1±0.4). All rhPDGF-BB treatment groups exhibited increased Safranin-O staining of the matrix compared to the 0 µg rhPDGF-BB control group, and a significantly decreased incidence (p = 0.01) of subchondral cyst formation compared to the empty defect treatment group. Sizeable subchondral cyst formation was evident in all specimens in the empty defect group.

RESULTS: Animal Observations: Clinical observations revealed normal recovery, with no animals developing signs of inflammation or infection. Gross Morphological Evaluation: The total gross score was improved for specimens in all three rhPDGF-BB treatment groups (15, 75, and 500 µg) over the 0 µg rhPDGF-BB and empty defect groups. Additionally, the gross score was significantly improved (p =0.0006) in specimens treated in the 500 µg rhPDGF-BB control and empty defect groups. MicroCT Analysis: No specimens exhibited breach of the chondral region by nascent bone. MicroCT analysis (8mm diam. x 6.25mm depth cylinder) indicated a significant increase in trabecular number (p=0.004) for the 500 µg rhPDGF-BB group compared to the 0 µg control, 75 µg, and Empty groups. Average bone volume reconstitution within the defect space was increased by 59% for the 500 µg rhPDGF-BB group (44.1%±6.6) relative to the 0 µg rhPDGF-BB control (27.8%±3.4). Additional microCT parameters (trabecular thickness and connectivity density) were also increased, on average, in the 500 µg rhPDGF-BB group compared to the 0 µg rhPDGF-BB control, although these did not reach statistical significance. Furthermore, the presence of bony bridging across the central region of the defect was only noted in the 500 µg rhPDGF-BB group (Figure 1).

Table 1: Mean repair scores ± SEM for specimens at 12 weeks. Higher score for gross repair and total cartilage repair and a lower score for subchondral cyst and cartilage flow are indicative of improved repair.

DISCUSSION: The results of this study indicate that rhPDGF-BB, combined with a collagen implant, is safe and improves repair of large osteochondral defects located in a high-load bearing region in a caprine model. Blood work and local pathology demonstrated treatment by rhPDGF-BB in the joint to be safe. Increases in gross scoring and histopathologic cartilage repair score for the rhPDGF-BB treatment groups, in addition to the presence of bony bridging, especially for the 500 µg rhPDGF-BB treatment group, indicate enhanced reconstitution of the subchondral bone and overlying repair tissue. The cartilage repair score was increased, on average, in the empty defect group relative to the 0 µg rhPDGF-BB group, however this score may be partially inflated due to collapse of the surrounding native tissue into the defect. Combined with a significant decrease in cyst formation in all rhPDGF-BB treatment groups, these results suggest that rhPDGF-BB, combined with a collagen implant, may have promise as a therapeutic agent for osteochondral defect repair.