Novel PTH-Based Bone-Graft Substitute for Treatment of Fractures: Results From a Large Ovine Tibial Plateau Defects Study

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Background/Purpose: A novel formulation containing a modified, covalently linkable parathyroid hormone (TGplPTH1-34) in fibrin with hydroxapatite/tricalcium phosphate (HA/TCP) granules has been developed for use as a bone-graft substitute. The formulation has been optimized such that the TGplPTH1-34 is covalently linked to the fibrin matrix during polymerization so that the product is able to provide bioactivity (through the linked TGplPTH1-34) as well as compression resistance (from the presence of fibrin-granule mixture). The product is therefore a bone-graft substitute, to be used for treating bony defects that are exposed to mechanical stresses. One prime indication has been tibial plateau fractures (TPFs), and in order to determine whether this material is appropriate for clinical use in this space, it was first tested in an ovine metaphyseal model for TPF.

Methods: Following creation of a 3.5-cm3 cuboidal defect in the cancellous bone of the proximal tibia directly below the articular surface, sheep were treated with either TGplPTH1-34 (at 0.4 mg/mL or 1.0 mg/mL) in fibrin with HA/TCP or cancellous autograft. Animals were followed up at 6 and 12 months. Primary healing measures were bone formation, as determined by micro computed tomography (CT) as well as the mechanical integrity of the newly formed tissue, measured through both nondestructive mechanical tests on the whole bone as well as destructive tests on bone cores. Safety parameters were measured including systemic PTH, PTH-specific antibodies, and serum calcium.

Results: 18 sheep were treated in the study, and all animals tolerated the material well. Micro CT measurements of the bone formation demonstrated that all three treatments were efficacious, with the autograft (40.0%) and high concentration (41.7%) creating more bone than the lower concentration (24.6%) at 6 months. This trend was also observed in the biomechanical testing. Defects treated with the 1.0-mg/mL TGplPTH1-34 in fibrin with granules had a stiffness (1502 N/mm2) that was higher than that for both autograft treated bone (1394 N/mm2) as well as noninjured, contralateral bone (1103 N/mm2). This was mirrored in the ultimate strength, where the bone following treatment with the 1 mg/mL product could bear a higher load before failure (18.7 N/mm2) than the autograft treated bone (14.7 N/mm2) and the noninjured bone (18.7 N/mm2). The data at 12 months confirmed the early stage findings.

Conclusion: Here, the efficacy of a novel bone-graft substitute based on the local retention of TGplPTH1-34 in a fibrin matrix has been shown. In a large, ovine metaphyseal defect model, healing of the bony defect was demonstrated both radiologically (with micro CT) as well as functionally (biomechanical testing). In fact, at the 6-month time point, the newly formed bone following treatment with the material was at least as strong if not stronger than both

See pages 47 - 108 for financial disclosure information.

defects treated with autograft and even uninjured, contralateral bone. The combination of this data demonstrates that this novel bone-graft substitute is a potent, efficacious tool for treating large defects.

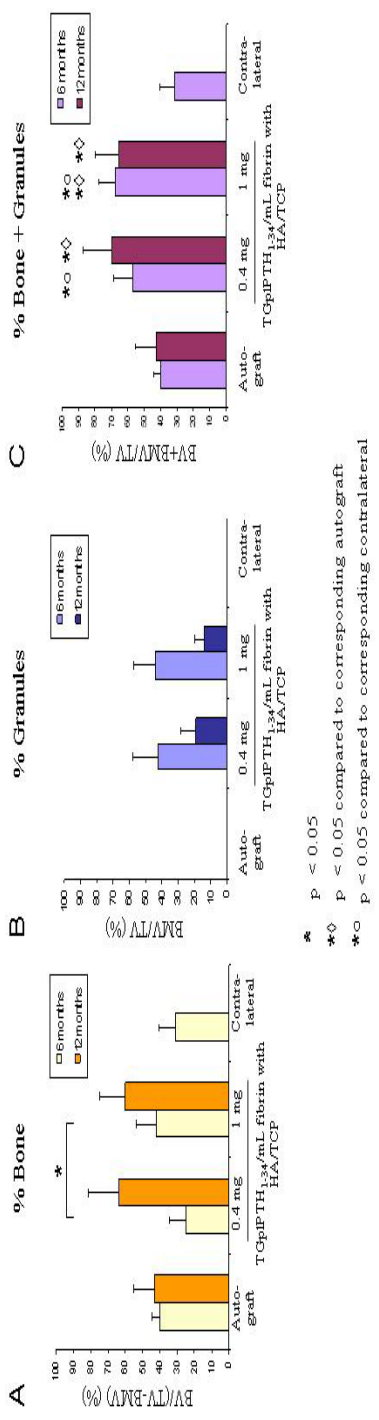

Figure: mCT analysis at 6 and 12 months of bone formation and HA/TCP granule content in the defect for the autograft group, the 0.4 mg modified TGplPTH$_{1-34}$/mL fibrin with HA/TCP granules group, the 1 mg TGplPTH$_{1-34}$/mL fibrin with HA/TCP granules group and a similar bone portion from the contralateral bone. A: Percentage of the bone volume (BV) in the available space (total volume minus the granule volume, %BV/(TV-BM). B: percentage of HA/TCP granules (BM) in the total volume (TV). C: percentage of bone (BV) plus HA/TCP granules (BM) in the total volume (TV). * p<0.05 statistically significant. *◇ p<0.05 statistically significant compared to the corresponding autograft group, *○ p<0.05 statistically significant compared to the corresponding contralateral group.