ISAKOS

International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine

9th Biennial ISAKOS Congress • May 12-16, 2013 • Toronto, Canada

Paper #163

Validated Methodologies for the Analysis of Tissue Quality in Cartilage Repair Randomized Controlled Trials: Polarized Light Microscopy and ICRS Histological Assessments

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Summary:
Independent and validated PLM and ICRS scoring systems proved to be useful tools in revealing significant improvement in the quality of cartilage repair following BST-CarGel® treatment compared to microfracture. Improvements in cellular and structural parameters following BST-CarGel® treatment suggest a greater durability of cartilage repair and potential for sustained clinical benefit.

Abstract:
Purpose:
Tissue biopsies are often collected during cartilage repair randomized controlled trials (RCT) to evaluate the quality of the repair cartilage. A proper assessment of the composition and structure of the repair tissue requires validated and blinded microscopic methodologies. Polarized light microscopy (PLM) and ICRS histological assessments of osteochondral biopsies were used to provide supportive data to the MRI structural primary endpoint of a cartilage repair RCT comparing BST-CarGel® treatment (Piramal Healthcare (Canada) Ltd.) to microfracture.

Materials & Methods:
During an international multicenter clinical trial that randomized 80 patients (18-55 years old) to either BST-CarGel® or microfracture control arms, 38 elective osteochondral biopsies were obtained arthroscopically at an average of 13 months post-treatment from the estimated geometric center of the treated lesion on the femoral condyle (21 BST-CarGel®; 17 Microfracture). A validated PLM score was used to evaluate the collagen architecture and zonal stratification of the repair tissue.[1,2] PLM birefringence characteristics were graded from 0 to 5 (Table 1). ICRS I (6 parameters)[3] and the validated ICRS II (14 parameters)[4] histological scores were used to evaluate tissue composition and organization. Each scoring methodology was first tested for reliability between three readers using normal and degraded human cartilage, and repair tissue. Trial biopsies were fixed in formalin, decalcified, and paraffin sections were mounted unstained (PLM scoring), or stained with Hematoxylin/Eosin and Safranin-O/FastGreen (ICRS scoring), and then scored by three blinded readers. No trial biopsies were excluded from analysis.

Results / Discussion:
The PLM analysis showed a significant improvement in collagen organization in repair biopsies following BST-CarGel® treatment ($p=0.0003$), compared to microfracture. BST-CarGel® treatment resulted in a more organized and stratified

repair tissue in three zones (deep, transitional and superficial zones). The distribution of PLM scores was positively skewed for BST-CarGel®, with only 1 score of '0' compared to 6 for microfracture. Moreover, BST-CarGel® treatment resulted in 12 biopsies with three organized zones, compared to only 3 for microfracture. Histologically, BST-CarGel® treatment led to improvements in 4 of 6 (ICRS I) and 10 of 14 (ICRS II) parameters over microfracture repair tissue. Several cell parameters were improved significantly ($p<0.05$; ICRS I: cell distribution and cell viability) or near significance ($p<0.07$; ICRS II: cell morphology) following BST-CarGel® treatment compared to microfracture. Surface parameters were superior ($p<0.05$; ICRS II: surface architecture and surface/superficial zone assessment) for BST-CarGel®, while other structural parameters were near significance ($p<0.11$; ICRS II: basal integration and overall assessment). These results are consistent with previously published findings in animal studies comparing BST-CarGel® treatment to microfracture.[5-9]

Conclusion:
Proper analysis of repair tissue requires validated and reproducible methodologies. Here, independent microscopic assessments of repair tissue using validated PLM and ICRS scoring systems proved to be useful tools in revealing significant improvement in the quality of cartilage repair following BST-CarGel® treatment compared to microfracture. Improvements in cellular and structural parameters following BST-CarGel® treatment suggest a greater durability of cartilage repair and potential for sustained clinical benefit.

References:
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TABLE 1. Polarized Light Microscopy Scoring System
Score Tissue Characteristics.
0 No vertically oriented DZ;
1 Small vertically oriented DZ;
2 Well-developed DZ and oriented zone above;
3 Three zones with vertical DZ and approximate TZ and SZ;
4 Three zones with correct orientations and approximate zonal proportions;
5 Hyaline organization and features.
DZ: Deep Zone; TZ: Transitional Zone; SZ: Superficial Zone