MRI Follow-up of Knee Joint After Intra-articular Injections of Allogeneic Mesenchymal Stem Cells in a Caprine Model of Partial Medial Meniscectomy

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Synopsis: Using a goat model of partial medial meniscectomy, MRI was used to track meniscal repair in non-treated controls (n=5) and animals receiving intra-articular allogeneic mesenchymal stem cells (n=5, MSCs). Serial scans were performed prior to injection and at 6, 24, and 48 weeks post-injection. MRI showed an increase in medial meniscal size both qualitatively and quantitatively. The truncated shape of the posterior horn of the medial menisci at baseline returned to a more normal triangular shape after 6 months. MRI was unable to detect changes in the meniscus at 6 weeks. However, regrowth could be evaluated by 6 months post-treatment.

Introduction: It has been demonstrated that mesenchymal stem cells can heal clinically significant bone and cartilage defects in animal models [1]. This study's goal was to use MRI as a method to non-invasively study the knee joint to assess the efficacy of intra-articular (IA) injections of mesenchymal stem cells (MSCs) in a caprine model of partial medial meniscectomy (PMMX) for meniscal healing.

Methods: Male goats (40-80 kgs) were subjected to a medial PMMX and received either allogeneic MSCs in hyaluronan (treated, n=5) or hyaluronan only (controls, n=5) at 1, 2, and 3 weeks after surgery. MRI was performed on a 1.5 T clinical scanner (GE) at 1 week post-PMMX (immediately prior to IA injection), and 6 , 24, and 48 weeks post-injection. T1, T2-weighted and proton density (PD) images were acquired and used for visual evaluation. An observer blinded to the treatment reviewed the images. The parameters evaluated visually were: percent medial meniscus remaining after PMMX; change in shape and size of medial menisci at 6, 24, and 48 weeks; and evidence of underlying bone changes or osteoarthritis. PD sagittal images (2D fast spin echo; TR/TE=2000/34;14 cm FOV;2 NSA; ETL=8; 2 mm slice thickness; 256x192 image matrix) were used for quantitative evaluation of meniscal volume. Using a custom tool (cine, General Electric) on contiguous images, the lateral and medial meniscal regions of interest (ROIs) were traced semi-automatically using a full-width, half maximum criteria. ROIs were then manually adjusted by another observer blinded to treatment. Lateral and medial meniscal volumes were compared between treated and control animals using a linear regression analysis. A P value <0.05 was considered statistically significant.

Results: Eight animals completed the imaging protocol at all time points. Two animals (one from each group) were removed prior to study completion; one due to intra-articular infection and one due to urinary calculi. At 6 weeks, there was no difference in meniscal volume between treated and control animals. At 24 and 48 weeks post-injection, MRI showed a significant increase in medial meniscal size by visual evaluation and quantitative evaluation (1.40 ± 0.44 cc at baseline, 1.83 ± 0.32 cc at 24 weeks, 2.16 ± 0.58 cc at 48 weeks, n=8, P<0.03 vs. baseline). The posterior horn of the operated meniscus had a truncated shape at the baseline. At 6 weeks, slight smoothing of the truncation was observed progressing to a near normal triangle posterior horn shape at 24 weeks. Osteoarthritis was not observed in any of the animals. In 2 treated animals and in 1 control animal, 7-9 mm focal defects (high or low signal intensity) in medial tibial plateau were observed after 6 weeks. By quantitative analysis, there was a trend towards increased lateral meniscal volume in the treated animals as compared to the controls. Due to this slight increase in both lateral and medial meniscal volume in treated animals, the difference between the lateral and medial meniscal volumes remained constant whereas the control animals showed a diminution in the difference between lateral and medial meniscal volume (*Figure*).

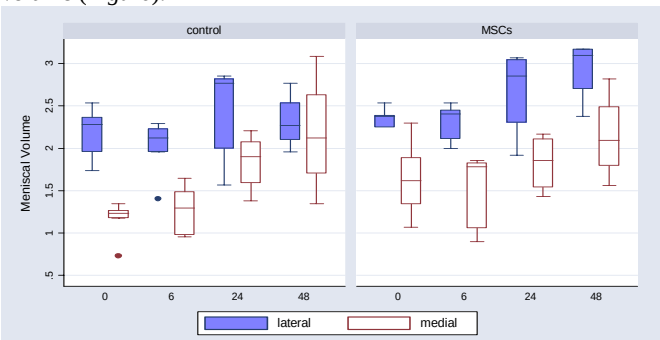

Figure: *A box whisker plot demonstrating the change in lateral and medial meniscal volumes in both control (left) and MSC-treated animals (right) from baseline to 48 weeks; the difference between medial and lateral meniscal volumes in treated animals remained constant due to the trend towards an increase in both lateral and medial meniscal volumes, whereas the difference decreases in control animals over time.*

Discussion and Conclusion: MRI can be used to non-invasively serially assess meniscal shape and volume in a goat model of meniscal injury after intraarticular injections of MSCs. In addition to quantitative evaluation of the meniscus, MRI can also be used to evaluate extra-articular changes.

Significant increase in volume and remodeling of injured menisci can be observed by MRI at 24 weeks after PMMX, but could not be appreciated at 6 weeks. Using the conventional imaging techniques, the growth in medial meniscal volume in both treated and untreated animals at 24 and 48 weeks post-injury could not distinguish fibrocartilage repair from regeneration into normal meniscal tissue. Thus, MR imaging techniques to study the underlying collagen organization would be helpful to gauge the success of stem cell therapies in future clinical trials.

References:

1. Caplan AI. Mesenchymal stem cells. J Orthop Res 9:641-650, 1991