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Can a Meniscus Really Regenerate So Easily? A Level-I Study Says It Can But Not for Everyone: Commentary on an article by C. Thomas Vangsness Jr., MD, et al.: "Adult Human Mesenchymal Stem Cells Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy: A Randomized, Double-Blind, Controlled Study"

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Treatment options for meniscus pathology, or more specifically meniscal deficiency, are limited, with the primary focus being on meniscal preservation. Ever since 1948, when Fairbank[1] introduced the concept of the post-meniscectomy knee, we have struggled to develop an improved treatment strategy for knees following a partial or complete meniscectomy. As the rate of meniscal injuries continues to rise, a high-level study on meniscal regeneration is timely.

This randomized, double-blind, prospective study is one of few Level-I studies that has investigated treatments for meniscal deficiency and, to my knowledge, the only one to date to study meniscal regeneration following the injection of allogeneic mesenchymal stem cells into the knee following a subtotal meniscectomy. The authors' objectives were to (1) study the safety of intra-articular injection of allogeneic mesenchymal stem cells into the knee joint, (2) determine the ability of mesenchymal stem cells to promote meniscus regeneration following a subtotal meniscectomy, and (3) report the effects on osteoarthritis in the knee joint following an injection of mesenchymal stem cells after a subtotal meniscectomy. Sixty adult patients from seven institutions were manually randomized to receive one of three different injections into the knee seven to ten days following a subtotal meniscectomy. The treatments were as follows: an injection of a low concentration of mesenchymal stem cells (50 million cells) suspended in hyaluronic acid, an injection of a high concentration of mesenchymal stem cells (150 million cells) suspended in hyaluronic acid, or a vehicle control of hyaluronic acid alone. Follow-up at the intervals of six weeks, six months, one year, and two years included clinical and safety evaluations, magnetic resonance imaging (MRI), and assessments of Lysholm knee scale scores and pain scores based on a visual analog scale (VAS). With respect to safety, there was no difference in minor or serious adverse events, no trends in terms of immunological response, and no evidence of ectopic tissue formation among the three groups. With use of MRI to assess a predefined criterion of a >15% increase in meniscal volume, five of fifty-four patients (four from the group that received the lower dose of mesenchymal stem cells and one from the group that received the higher dose) demonstrated an increase in meniscal volume compared with the control group, in which no patient met the threshold for increased meniscal volume ($p = 0.022$). However, at two years, this number decreased to three patients (all in the group that received the lower concentration of mesenchymal stem cells). The overall progression of

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osteoarthritis was unchanged in 76% of the patients among all three groups at one year, with no evidence of statistical differences between the groups. At two years, the three groups reported similar Lysholm scores. However, the relative improvement at two years in the pain scores was significantly different between the control and both the high-concentration group ($p = 0.04$) and low-concentration group ($p = 0.05$).

Studies of numerous animal models have demonstrated the regenerative effects of intra-articular injection of mesenchymal stem cells on a damaged meniscus[2,3]. Once injected, the mesenchymal stem cells adhere to the damaged meniscus, differentiate into cells resembling meniscal fibrochondrocytes, and promote type-I and type-II collagen formation. Horie et al.[2] harvested allogeneic mesenchymal stem cells (from a single rabbit) and then injected the cells into a 15-mm defect created in the avascular zone of the anterior horn of the meniscus in fifteen New Zealand rabbits. The histological quality of the regenerated tissue in those injected with the mesenchymal stem cells improved compared with the controls, achieving significance at twenty-four weeks (a tissue quality score of 6.0 versus 3.9, respectively; $p = 0.02$). A similar effect was also seen in a swine model in which there was observed not only an improvement in minimizing meniscal degeneration but also a potential protective effect on adjacent articular cartilage[3].

Clinical studies of mesenchymal stem cells and their use in meniscal regeneration have been limited, with, to my knowledge, no Level-I study to date. Other treatments for meniscal deficiency have included meniscal allograft transplantation or implantation of a collagen-based meniscal scaffold. A long-term study on allograft meniscal transplantation reported up to a 30% failure rate at ten years[4], and many experts quote a ten-year survival of meniscal transplants to their patients. Rodkey et al.[5] presented a Level-I study on meniscal scaffolds demonstrating clinical, gross, and histological improvement in patients with an acute or chronic meniscal deficiency. However, the product observed in the study is not currently available in the United States. Because of the scarcity of the options to treat meniscal deficiency and the increase in meniscal injuries, tissue regeneration by a method as simple as a postoperative injection that is safe is intriguing.

The obvious strength of the current study is in the methodology and randomization. All investigators and participants were blinded, with no one unblinded prematurely. The source of funding for this study was blinded for the purposes of this perspective. However, industry-funded studies should be reviewed critically.

An interesting finding in this study is the relative long-term improvement in pain (two years) in patients who had the mesenchymal stem cells administered compared with those treated with the control. This effect was even more apparent in those with more severe osteoarthritis and also may suggest a trend for dose-dependent pain relief in the short term, as the group that received the higher dose had a substantial improvement in pain compared with the control group at one year ($p = 0.08$). This effect may be attributable to the anti-inflammatory property of mesenchymal stem cells. These findings, performed in a double-blind study, indicate a symptom-reducing effect in an osteoarthritic knee compared with the vehicle control, hyaluronic acid, which currently is indicated for pain relief for mild to moderate osteoarthritis. Additional studies may be warranted to further investigate this finding.

Even though true manual randomization occurred in this study, the small number of subjects in each group may limit the ability to adequately compare three "equal" or similar groups and thus limit the internal validity. A majority of the demographic and baseline data appear to be similar between each group (Table E-2 in the paper by Vangsness et al.); however, the patient characteristics in the control group seem different from both of the groups that received the mesenchymal stem cells (a mean weight of approximately 4 kg less and a maximum body mass index of >10 points less than both other groups). Perhaps more importantly, as it relates to the study outcome of reported symptom reduction, seven patients in the control group presented with evidence of osteoarthritis, whereas in the two groups treated with the mesenchymal stem cells, eleven and twelve patients had evidence of osteoarthritis. These observations only suggest that the control group may have weighed less and had less osteoarthritis than either group treated with the mesenchymal stem cells and these factors may be particularly important when comparing patient outcomes or the effect of treatment on osteoarthritis progression in this study.

The authors' conclusions state that there was evidence of meniscal regeneration following treatment with allogeneic mesenchymal stem cells into the knee joint following a partial or subtotal meniscectomy. Although we cannot deny this claim, the statement may be misleading to the reader. Of the thirty-five patients included in the analysis after injection of mesenchymal stem cells, only five (14%) had evidence of increased meniscal volume at one year and three (9%) at two years. Although the authors demonstrated a statistically significant difference, does this really demonstrate clinical relevance? If so, is the effect short-lived or does this show us the possible variability in quantifying the meniscal volume on MRI? It would be interesting to see the absolute values of calculated volumes, but this was not provided by the authors. Based on this article, one should be cautious in considering this product for meniscal regeneration, particularly due to the fact that <10% of patients had an increase of >15% in meniscal volume at two years.

In summary, this Level-I study clearly demonstrates the safety of the injection of mesenchymal stem cells into the knee without the formation of ectopic tissue or additional risk above that of standard knee injection. The potential exists for use of this therapy as a pain mediator in the face of osteoarthritis in the knee, which has also been seen with other biologic injections into the knee that produce a similar anti-inflammatory effect. It remains unclear whether there is evidence of clinically relevant increases in meniscal regeneration. Only one in ten patients had a >15% increase in meniscal volume after the injection at two years postoperatively. While this intriguing avenue of research deserves additional investigation, there is not enough evidence in this Level-I study to suggest the use of this product for meniscal regeneration in humans following a subtotal meniscectomy.

References

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Fairbank TJ. Knee joint changes after meniscectomy. J Bone Joint Surg Br. 1948 Nov;30(4):664-70.

Horie M; Driscoll MD; Sampson HW; Sekiya I; Caroom CT; Prockop DJ; Thomas DB. Implantation of allogenic synovial stem cells promotes meniscal regeneration in a rabbit meniscal defect model. J Bone Joint Surg Am. 2012 Apr 18;94(8):701-12.[CrossRef]

Moriguchi Y; Tateishi K; Ando W; Shimomura K; Yonetani Y; Tanaka Y; Kita K; Hart DA; Gobbi A; Shino K; Yoshikawa H; Nakamura N. Repair of meniscal lesions using a scaffold-free tissue-engineered construct derived from allogenic synovial MSCs in a miniature swine model. Biomaterials. 2013 Mar;34(9):2185-93. Epub 2012 Dec 20.[CrossRef]

Vundelinckx B; Bellemans J; Vanlauwe J. Arthroscopically assisted meniscal allograft transplantation in the knee: a medium-term subjective, clinical, and radiographical outcome evaluation. Am J Sports Med. 2010 Nov;38(11):2240-7. Epub 2010 Aug 19.[CrossRef]

Rodkey WG; DeHaven KE; Montgomery WH 3rd; Baker CL Jr; Beck CL Jr; Hormel SE; Steadman JR; Cole BJ; Briggs KK. Comparison of the collagen meniscus implant with partial meniscectomy. A prospective randomized trial. J Bone Joint Surg Am. 2008 Jul;90(7):1413-26. [CrossRef]

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