Intra-articular Implantation of Mesenchymal Stem Cells, Part 2

A Review of the Literature for Meniscal Regeneration

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Knee osteoarthritis (OA) after partial or total meniscectomy is a prevalent issue that patients must face. Various methods of replacing meniscal tissue have been studied to avoid this progression, including meniscal allograft transplantation, meniscal scaffolds, and synthetic meniscus replacement. Studies have shown that meniscal scaffolds may improve symptoms but have not been shown to prevent progression of OA. Recently, mesenchymal stem cells (MSCs) have been proposed as a possible biological therapy for meniscal regeneration. Several animal studies and 1 human study have evaluated the effect of transplanting MSCs into the knee joint after partial meniscectomy. The purpose of this review was to assess the outcomes of intra-articular transplantation of MSCs on meniscal regeneration in animals and humans after partial meniscectomy. Limited results from animal studies suggest that there is some potential for intra-articular injection of MSCs for the regeneration of meniscal tissue. However, further studies are necessary to determine the quality of regenerated meniscal tissue through histological and biomechanical testing.

Keywords: osteoarthritis; mesenchymal stem cells; meniscectomy; meniscal regeneration

The menisci serve an important function in distributing the load that the femur exerts on the tibia. When a meniscus is torn, this cushioning effect is no longer present, resulting in bone-on-bone forces that eventually cause osteoarthritis (OA).[27] Studies have shown that patients develop OA of the knee at a higher rate than normal after a meniscectomy procedure,[13,22,24] and that the strongest predictor of eventual OA is the amount of meniscal tissue removed during meniscectomy.[22] While radiographic signs of OA may be present at 8 to 16 years after arthroscopic partial meniscectomy, clinical symptoms of OA do not begin until later.[24]

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Meniscal allograft transplantation (MAT),[4,5,20] meniscal scaffolds,[6,19,29] and synthetic meniscus replacement[25,30] have been historically used to decrease pain and replace meniscal tissue in patients with large symptomatic meniscal tears. However, new evidence has allowed for increased enthusiasm regarding the possibility of meniscal preservation or regeneration, as recent studies have shown a beneficial effect, at least in the short term, of the intra-articular injection of mesenchymal stem cells (MSCs) on the prevention of knee OA after partial or complete meniscectomy.[18] In addition to measuring OA outcomes, several studies have also evaluated the effect that MSC transplantation has on meniscal regeneration. The purpose of this review is to assess the outcomes of intra-articular transplantation of MSCs on meniscal regeneration in animals and humans after partial meniscectomy. The authors hypothesized that transplantation of MSCs would result in significantly more postoperative meniscal regeneration compared with control groups receiving no MSCs.

METHODS

A literature search was performed that included searches of PubMed, Medline, and Cochrane Library databases using various combinations of the search terms "meniscectomy,"

TABLE 1
Meniscal Area Quantification[a]

Study (Year)	Animal Model	MSC Harvest Site	Outcomes in Treatment Group
Hatsushika et al[8] (2013)	Rabbit	Synovial tissue	Ratio of medial meniscal area to intact lateral meniscal area significantly higher at 4 and 12 weeks postinjection, but not at 16 and 24 weeks
Horie et al[12] (2009)	Rat	Synovial tissue	Significantly larger meniscal areas at 2, 4, and 8 weeks postmeniscectomy, but not at 12 weeks
Horie et al[10] (2012)	Rat	Human bone marrow versus rat bone marrow	Significantly larger meniscal areas of human and rat MSCs compared with control at 2 and 4 weeks postinjection, but not at 8 weeks; no difference between meniscal areas of human versus rat MSCs
Katagiri et al[15] (2013)	Rat	Synovial tissue	Significantly more regenerated meniscal areas in the 500 cells × 50 and 5000 cells × 5 aggregate groups compared with control at 4 and 12 weeks postmeniscectomy
Kondo et al[17] (2016)	Macaque	Synovial tissue	Larger medial meniscal areas in MSC group compared with control at 8 and 16 weeks after MSC transplantation (statistical significance not mentioned)
Qi et al[25] (2016)	Rabbit	Adipose tissue	Improved meniscal regeneration and meniscal shape compared with control at 6 and 12 weeks postinjection (statistical significance not mentioned)
Shen et al[26] (2013)	Rabbit	Meniscal tissue	Significantly higher ratio of repaired meniscus area to surplus normal meniscus at 4, 8, and 12 weeks postmeniscectomy

[a]Unless otherwise indicated, mesenchymal stem cells (MSCs) in each study were harvested from the animal model used.

"mesenchymal stem cells," "meniscal," and "regeneration." The following inclusion criteria were used: animal or human studies in which subjects received MSC transplantation into the knee joint after partial or complete meniscectomy. Studies in which subjects received intra-articular MSCs for knee OA unrelated to a meniscectomy procedure were excluded.

ANIMAL MODELS

The animal models presented in this review include rabbits, rats, sheep, pigs, and macaque monkeys. Most studies involving animal models induced OA by performing bilateral meniscectomy of the medial or lateral meniscus. After meniscal resection, at various predetermined time points, a solution of MSCs in the order of 10^6 or 10^7 is injected unilaterally. The contralateral knee of the animal typically serves as a control and receives an injection of saline with no cells. During the performance of such studies, MSCs can be inoculated either in solution or aggregates. Cell aggregates may be formed by plating cells in a particular volume of solution on an inverted culture dish lid and then allowing these cells to culture in hanging droplets.[17]

Assessment of Meniscal Regeneration

Quantifying the area of the meniscus after partial meniscectomy and transplantation of MSCs is an objective way to evaluate the degree of meniscal regeneration. However, quantification of meniscal area after MSC transplantation is limited in that meniscal volume would be a more reliable assessment of meniscal regeneration. Assessment of meniscal volume is certainly more difficult (requiring magnetic resonance imaging in small animal models), but it can be done for more accurate results. Another disadvantage of relying on meniscal area quantification is that a larger area may simply be due to flattening of meniscal tissue. For example, if the extracellular matrix of the meniscus is being degraded by excess loading, the meniscus could be flattening, thereby resulting in larger surface area at the expense of volume. Finally, assessment of meniscal area does not take into account the nature and quality of the regenerated tissue. The meniscus has dense collagen packing to resist not only tensile loading but also shear and compressive loading. Thus, biomechanical testing of these properties of the regenerated tissue is necessary to determine the true effect of MSC transplantation after partial meniscectomy.

Horie et al[10,12] performed 2 studies in rat models to analyze the effects of MSC injections on meniscal area (Table 1). In 1 of these studies,[12] MSCs were isolated from 2 sites: synovial membranes and bone marrow from the femoral shaft and tibia. Immediately after partial medial meniscectomy, an injection was performed in the femoral intercondylar space with 1 of 3 solutions: 5×10^6 synovium-MSCs in 50 μL phosphate-buffered saline (PBS), 5×10^6 bone marrow (BM)–MSCs in 50 μL PBS, or 50 μL PBS without cells (control group). Meniscal areas of the synovium-MSC and control groups were measured. The synovium-MSC group had significantly larger meniscal areas at 2, 4, and 8 weeks postmeniscectomy but not at 12 weeks. Using luciferase-based in vivo imaging, the group found that MSC-derived photons were still observed in the knee joint 28 days after injection into meniscectomized knees. Furthermore, real-time polymerase chain reaction was used on various organ systems (brain, lung, liver, spleen, kidney, knee synovium) 3 days after intra-articular injection of synovium-MSCs, and it was found that LacZ gene expression remained only in the knee synovium sample, indicating that MSC injections into the knee joint remain in the knee and do not travel to other organs.

In another study,[10] bilateral hemimeniscectomy was performed on a series of rats, immediately followed by intra-articular injection of human BM-MSCs. A positive control group of rats received injections of rat BM-MSCs. The medial meniscus was removed and photographed for quantification of the meniscus area. At 2 and 4 weeks after

injection, the meniscal areas of both the human and rat MSC groups were significantly larger than that of the control group, but no difference was found between the human and rat MSC groups. At 8 weeks, no significant difference was found in area between any groups, suggesting no major differences between allogenic and autologous cells.

Hatsushika et al[8] performed a similar analysis using a rabbit model. Two weeks after bilateral partial medial meniscectomy, synovial MSCs were injected into the meniscal defect in the right knees of rabbits, with the left knees receiving PBS without cells. The ratio of the medial meniscal area to the intact lateral meniscal area was quantified at 4, 12, 16, and 24 weeks after injection. This ratio was significantly higher in the treatment group compared with control at 4 and 12 weeks but not at 16 and 24 weeks. In these rabbit models, it is possible that the early response of the synovium to surgical trauma resulted in the higher "apparent" meniscal area, with this response declining over time.

Shen et al[26] also used a rabbit model, with MSCs isolated from rabbit meniscal tissue. Intra-articular injection of MSCs was performed at 1 and 2 weeks after partial medial meniscectomy. At 4, 8, and 12 weeks after meniscectomy, gross morphology showed more neo-tissue formation and a significantly higher ratio of repaired meniscus area to surplus normal meniscus in the MSC-treated group compared with control.

Qi et al[25] used a rabbit model with MSCs derived from the subcutaneous fat of the nape of the neck. Seven days after bilateral excision of the anterior half of the medial meniscus, intra-articular injection of 2×10^6 MSCs in 100 μL PBS was performed in 2 treatment groups: one with superparamagnetic iron oxide (SPIO)–labeled MSCs and one with unlabeled MSCs. Magnets were fixed to the outside of the treated joints for 1 day for the purposes of targeted magnetic cell delivery in the SPIO-labeled group. A control group received an injection of PBS without cells. At 6 weeks postinjection, the treatment groups exhibited improved meniscal regeneration in comparison with the control groups, with the SPIO-labeled group demonstrating the highest level of meniscal regeneration and a good meniscal shape. At 12 weeks, the meniscal tissue in the control group had deteriorated, while the majority of the menisci had regenerated in the unlabeled MSC group and almost normally shaped menisci were found in the SPIO-labeled group. However, this study did not mention any statistically significant differences between groups in terms of meniscus size, and therefore, the results of this study are limited.

Katagiri et al[15] used ImageJ software (National Institutes of Health) to quantify the area of regenerated meniscal tissue in rats after bilateral resection of the anterior half of the medial meniscus. Treatment groups received various aggregates of 25,000 synovial MSCs placed on the meniscal defects: group A, 25,000 cells × 1 aggregate; group B, 5000 cells × 5 aggregates; or group C, 500 cells × 50 aggregates. Two additional treatment groups received suspensions in PBS of 25,000 cells (group D) and 5×10^6 cells (group E) injected intra-articularly. Compared with an untreated control group, groups B and C demonstrated significantly greater areas of regenerated meniscus at 4 and 12 weeks postmeniscectomy. Furthermore, significantly more meniscal tissue was regenerated in groups B and C compared with group D at 4 weeks postmeniscectomy. Thus, transplanted cell aggregates at the site of meniscal defects may be more beneficial for meniscal regeneration compared with intra-articular injection of MSC suspensions. However, the follow-up time points used in this study are very short, and longer follow-up is necessary to determine the clinical significance of these results.

Finally, Kondo et al[17] also used ImageJ software to quantify the area of regenerated meniscal tissue in macaques after resection of the anterior half of the medial meniscus. Four weeks after synovial tissue–derived MSCs were isolated, an average of 14 aggregates of these MSCs were placed in the meniscal defects of the treatment group, while no aggregates were transplanted in the contralateral control knee. Each aggregate was initially formed from 2.5×10^5 synovial MSCs in 35 μL of culture medium, plated on an inverted culture dish lid for 3 days in hanging droplets. Although meniscal regeneration was found to occur in both groups, the regenerated meniscal area was larger in the treatment group of all primates at 8 ($n = 3$) and 16 weeks ($n = 4$) after MSC transplantation. However, statistical significance was not mentioned, which limits the conclusions that can be drawn from this study.

Histological Outcomes

Hatsushika et al[8,9] performed 2 studies to determine histological outcomes after intra-articular injections of synovial MSCs (Table 2). Both studies used a modified version of the Pauli et al[23] scoring system, which takes into account the surface integrity, cellularity, matrix/fiber organization and collagen alignment, and safranin-O staining intensity. In the first study,[8] rabbit meniscal sections were analyzed and found to exhibit better scores in the treatment group compared with control at 4, 12, 16, and 24 weeks after MSC injection. In their next study,[9] the anterior half of the medial meniscus was excised bilaterally in a series of pigs. Two weeks after meniscectomy, 5×10^7 synovial MSCs were suspended in 1 mL of PBS and injected into the right knee at 0, 2, and 4 weeks. At 16 weeks after the initial injection, the menisci were harvested and the modified Pauli score was found to be significantly better in the treatment group.

Katagiri et al[15] also used the modified Pauli scoring system to analyze histological outcomes of meniscal regeneration in rats. After bilateral resection of the anterior half of the medial meniscus, treatment groups received various aggregates of synovial MSCs placed on the meniscal defects, as mentioned above. Two additional treatment groups received intra-articular injections of MSCs suspended in PBS. Four weeks after meniscectomy, the modified Pauli score was significantly better in each of the cell aggregate groups compared with an untreated group, though no significant difference was found between the control groups and either of the cell suspension groups. At 12 weeks, the control group was found to have a significantly worse score compared with 2 of the aggregate

TABLE 2
Histological Outcomes[a]

Study (Year)	Animal Model	Outcome Measure	Outcomes in Treatment Group
Caminal et al[3] (2014)	Sheep	Kon et al[16] histological scoring system	Significantly better scores at 6 months postinjection; no significant difference compared with control at 12 months postinjection
Hatsushika et al[8] (2013)	Rabbit	Modified Pauli et al[23] scoring system	Significantly better scores compared with control at 4, 12, 16, and 24 weeks postinjection
Hatsushika et al[9] (2014)	Pig	Modified Pauli et al[23] scoring system	Significantly better score at 16 weeks after first MSC injection
Horie et al[11] (2012)	Rabbit	Ishida et al[14] histological scoring system	Significantly better scores at 12 and 24 weeks postmeniscectomy
Katagiri et al[15] (2013)	Rat	Modified Pauli et al[23] scoring system	Significantly better scores in cell aggregate groups compared with control at 4 and 12 weeks postmeniscectomy; no significant difference between control and cell suspension groups at 4 weeks postmeniscectomy
Kondo et al[17] (2016)	Macaque	Modified Pauli et al[23] scoring system	Higher scores compared with control at 8 and 16 weeks after MSC transplantation (statistical significance not mentioned)

[a]MSC, mesenchymal stem cell.

groups: 500 cells × 50 and 5000 cells × 5. This adds further evidence that MSC aggregates may have improved regenerative capacity compared with cells inoculated in suspension.

Similar to the study by Katagiri et al,[15] Kondo et al[17] used the modified Pauli scoring system to quantify meniscal regeneration outcomes in macaques. As described above, resection of the anterior half of the medial meniscus was performed bilaterally in 7 macaques. The treatment groups received transplanted aggregates of synovial MSCs while the contralateral control knees received no aggregates. The modified Pauli score was higher in all primates of the treatment group at 8 (n = 3) and 16 weeks (n = 4) after MSC transplantation, although statistical significance was not mentioned in this study, thereby limiting the conclusions that can be drawn from this study.

Horie et al[11] used a histological scoring system developed by Ishida et al[14] on rabbit meniscal sections. This scoring system takes into account bonding between native and postintervention meniscus, fibrochondrocyte existence, and safranin-O staining intensity. Synovium-derived allogeneic MSCs were inserted into cylindrical defects made in the avascular portion of the anterior medial meniscus. Histological analysis was performed on meniscal sections at 4, 12, and 24 weeks postmeniscectomy. The histological scores of the treatment group were significantly better compared with control at 12 and 24 weeks. In addition, grossly visible, full-thickness defects remained in 4 out of 5 control specimens at 4 and 12 weeks compared with 1 and 0 specimens in the treatment group at the same time points. However, by 24 weeks postmeniscectomy, gross inspection showed only 1 full-thickness defect remaining in the control group, compared with none in the treatment group. With only a 24-week follow-up in this study, it is possible that the allogeneic MSCs used would have resulted in an adverse immune response had a longer follow-up period been used. Furthermore, although quality of the regenerated tissue was assessed via existence of fibrochondrocytes and extent of bonding between regenerated tissue and borders of the meniscal defects, the authors did not test collagen fibril packing density, aggrecan density, or resistance to compressive loading in comparison to normal meniscal tissue.

Caminal et al[3] performed a study in 10 sheep. The anterior horn of the medial meniscus was pierced bilaterally in the posterior legs of the sheep and, in addition, chondral lesions of approximately 60 mm^2 were created in both femoral medial condyles. At 1 month after these procedures, BM-MSCs were injected intra-articularly in randomly assigned joints of the animals, with the remaining joints receiving injections of cell-free fluid. At 6 and 12 months after these injections, meniscal sections were analyzed according to a histological scoring guide described by Kon et al.[16] The treatment group demonstrated a significantly better histological score at 6 months, though by 12 months no significant difference was found compared with control. However, as in other studies described in this review, Caminal et al[3] did not perform biomechanical testing of the postoperative meniscal sections, thereby limiting the conclusions that can be drawn from this study.

Qi et al[25] performed a qualitative histological analysis on meniscal sections taken from a rabbit model. At 6 and 12 weeks after injection, meniscal sections were stained with hematoxylin and eosin for morphological evaluation and with safranin for glycosaminoglycan distribution. At 6 weeks, the control group demonstrated regeneration of fibroblast-like tissue and less hypercellular fibrocartilaginous tissue. In the unlabeled MSC group, partial repair of the anterior horn of the medial meniscus had occurred with hypercellular fibrocartilaginous tissue and less fibrous-like tissue. In the SPIO-labeled MSC group, meniscal regeneration had occurred with a greater mass of hypercellular fibrocartilaginous tissue and extracellular matrix (ECM). At 12 weeks postinjection, the control group demonstrated meniscal atrophy with reduced ECM. The unlabeled MSC group exhibited abnormally shaped neomeniscus with a low quantity of ECM. Finally, in the SPIO-labeled MSC group, the anterior portion of the medial meniscus was found to consist of typical fibrochondrocytes surrounded

by collagen-rich ECM bridging the interface between native and neomeniscus.

HUMAN MODELS

Published data on intra-articular injections of MSCs in human subjects is limited. To date, only 1 study[28] has analyzed the effects of MSC intra-articular injections on meniscal regeneration after a partial meniscectomy procedure. Compared with the available animal studies, there is significantly longer follow-up data available in this study. As mentioned previously,[18] tight regulation of MSC use in humans by the Food and Drug Administration is likely a significant reason for the lack of clinical studies on this topic.

Vangsness et al[28] conducted a randomized, double-blind, controlled study in which all patients were undergoing partial medial meniscectomy. Patients were randomized to 1 of 3 groups: group A (50×10^6 human MSCs), group B (150×10^6 human MSCs), and a control group consisting of sodium hyaluronate without MSCs. Patients received their respective injection 7 to 10 days postoperatively into the superolateral aspect of the suprapatellar pouch. The cells used were derived from bone marrow aspirates of unrelated donors. Magnetic resonance imaging (MRI) was performed preoperatively, on the day of the injection, and at 6, 12, and 24 months postoperatively. A predefined criterion of >15% increase in meniscal volume compared with the first postoperative MRI was used. At 12 months after surgery, group A had a significantly higher number of patients (4/18) fitting this criterion compared with the control group (0/19), suggesting a regeneration of meniscal volume with the use of a moderate dose of MSCs. However, there were no other significant differences between either of the treatment groups and the control group at any time point, including 24 months when the number of patients in group A who fit the selected criterion decreased from 4 to 3.

The most significant limitation of the study by Vangsness et al[28] is that the primary outcome of this study, increase in meniscal volume, was quantified by MRI and therefore represents apparent meniscal volume rather than normally functioning meniscal tissue. Further histological and biomechanical testing would be necessary to delineate the quality of the regenerated tissue in these patients. In particular, compression and tensile testing of the regenerated tissue should be compared with normal meniscal tissue.

DISCUSSION

The main finding of this study is that there exists a limited body of literature on the use of MSCs for meniscal tissue regeneration. The studies reviewed are highly heterogeneous in regards to the indications, methodology, evaluation time points, and objective outcomes evaluated. Standardized characterization of the progenitor cells should be described in order to assess and compare the true differences between studies. Furthermore, some of the studies presented in this review do not describe statistical outcomes between treatment and control groups, and therefore, it is not possible to determine from these studies whether the effects seen with MSC transplantation are significant.

Arthroscopic knee partial meniscectomy is the most common orthopaedic surgery procedure performed in the United States.[7] With recent evidence showing that patients develop OA of the knee at a higher rate than normal after a partial or total meniscectomy procedure,[13,22,24] it would be remarkably valuable to determine a method of regenerating torn/excised meniscal tissue. Many studies have been performed on various animal models involving the intra-articular transplantation of MSCs after partial meniscectomy. Most of these studies found successful results in terms of meniscal regeneration. However, the outcomes of these animal studies are limited in follow-up to a maximum of 12 months posttreatment, and a common theme in these studies is that the effect of MSC transplantation on meniscal area enlargement is transient, possibly due to the ability of some animal menisci to regenerate naturally. In addition, it is possible that the transient nature of meniscal regeneration is not actually regeneration of meniscal tissue but rather synovial inflammation after surgical trauma, which may appear with some imaging modalities as enlargement of the meniscus.

In both human and animal models, it is erroneous to state that meniscal regeneration has occurred without detailed histological and biomechanical testing to compare the quality of the regenerated tissue to that of normal, control meniscus. The ECM composition of the menisci (collagen, glycosaminoglycans, water) plays a significant role in the complex biomechanics of the knee joint.[1,2,21] Even within a normal meniscus, the ECM varies continuously across its width to account for different loading conditions in different regions of the knee joint.[21] Determination of the glycosaminoglycan and water content in the ECM of regenerated tissue, as well as biomechanical loading characteristics of this tissue, is important to assess the quality of meniscal tissue after MSC transplantation.

To date, only 1 study[28] has evaluated the effect of intra-articular injections of MSCs on meniscal regeneration in humans. To the best of our knowledge, no studies have described the results of composite matrices loaded with MSCs in human subjects with large meniscal lesions. The use of composite matrices allows for a more stable system of MSC implantation compared with the intra-articular injection of MSC suspensions in which a relatively small proportion of cells reach the site of interest, though the use of targeted magnetic cell delivery may improve localization of MSC treatment.[25] Katagiri et al[15] showed that placement of cell aggregates at the site of meniscal lesions was more effective, both in terms of meniscal area quantification and histological analysis, compared with the intra-articular injection of MSCs, which further supports the use of MSC-loaded matrices. In addition, matrices may be supplemented with various products such as platelet-rich plasma or bone morphogenetic protein 7, which not only secrete growth factors and stimulate healing but also may promote chondrogenic differentiation of MSCs.[31]

The intra-articular injection of MSCs postmeniscectomy has only been studied in humans in 1 study,[28] a

randomized, double-blind clinical trial. Of a total of 55 patients included in this study, there were no deaths reported and no adverse events that resulted in treatment discontinuation for any patients. There was only 1 life-threatening adverse event (a myocardial infarction) and 9 serious adverse events, all of which were deemed unlikely to be related to the MSC injections. Finally, no ectopic tissue formation was noted in any patients. The study by Vangsness et al[28] showed that MSCs may be safely delivered to the human knee joint. However, the efficacy of intra-articular injections of MSCs on meniscal regeneration may be temporary at best, as the number of patients with an increase in meniscal volume decreased from 12 to 24 months postoperatively. This temporary effect may be the result of MSCs migrating elsewhere in the knee joint, whereas a matrix system with loaded MSCs would retain cells at the site of interest. Future studies should focus on determining the effects of MSC-loaded matrices in human subjects, and the study by Vangsness et al[28] has provided some verification of the safety of this procedure.

As previously mentioned,[18] although these studies serve as important preliminary outcomes, animal models likely cannot be fully extrapolated to humans, and the available data in humans are limited. In addition, caution should be taken when interpreting much of the existing data on stem cells due to inaccurate nomenclature, lack of standardization in testing protocols, and unknown long-term side effects.

CONCLUSION

Limited results from animal studies suggest that there is some potential for intra-articular injection of MSCs in the regeneration of meniscal tissue. Within these studies, there is some evidence that MSCs transplanted as cell aggregates may carry improved regenerative capacity compared with cells inoculated in suspension. Further research is necessary to determine the quality and ECM composition of regenerated meniscal tissue in these experiments through both histological and biomechanical testing. Further studies in human subjects are necessary to determine the effects of MSC transplantation on meniscal regeneration, especially as it may be possible in some animal models for menisci to regenerate without intervention, whereas this is likely not the case in humans. Finally, it is imperative for long-term studies to be performed to determine whether the effects of MSCs on meniscal regeneration are transient or long-lasting.

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