Intra-articular Implantation of Mesenchymal Stem Cells, Part 1

A Review of the Literature for Prevention of Postmeniscectomy Osteoarthritis

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Osteoarthritis (OA) after a partial or total meniscectomy procedure is a common pathology. Because of the high incidence of meniscectomy in the general population, as well as the significant burden of knee OA, there is increasing interest in determining methods for delaying postmeniscectomy OA. Biological therapies, including mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and platelet-rich plasma (PRP), have been proposed as possible therapies that could delay OA in this and other settings. Several studies in various animal models have evaluated the effect of injecting MSCs into the knee joints of animals with OA induced either by meniscal excision with or without anterior cruciate ligament transection. When compared with control groups receiving injections without progenitor cells, short-term benefits in the experimental groups have been reported. In human subjects, there are limited data to determine the effect of biological therapies for use in delaying or preventing the onset of OA after a meniscectomy procedure. The purpose of this review is to highlight the findings in the presently available literature on the use of intra-articular implantation of MSCs postmeniscectomy and to offer suggestions for future research with the goal of delaying or treating early OA postmeniscectomy with MSCs.

Keywords: osteoarthritis; knee osteoarthritis; meniscectomy; mesenchymal stem cells

Approximately 700,000 arthroscopic partial meniscectomies are performed in the United States each year.[35] Arthroscopic meniscectomy may result in a more rapid progression to osteoarthritis (OA) in the affected knee compared with a similar knee that has undergone techniques for meniscal preservation, or is otherwise normal.[48] The degree of OA and the time until OA onset are likely most dependent on the volume of meniscus taken at the time of surgery, as studies have shown that increasing meniscectomy size results in reduced contact area within the knee joint and thus greater contact pressures on the cartilage in the ipsilateral compartment.[17,27,36,51]

Based on finite element modeling, it has been estimated that meniscectomies greater than 20% drastically increase stresses in the knee joint.[61] With resection of 65% of the meniscus, the maximal shear stress in the cartilage increases to 225% that of a knee with an intact meniscus.[61] In addition, the maximum intra-articular fluid pressure has been shown to significantly increase after partial meniscectomy and correlates with the size of meniscal resection.[31] Furthermore, resection of the superior and inferior leaflets of a horizontal meniscal tear results in significantly greater peak pressures compared with the torn meniscus before meniscectomy.[5] After arthroscopic partial meniscectomy, radiographic signs of OA may be evident at 8 to 16 years postoperatively if a significant amount of meniscal tissue is removed.[48]

Recent literature suggests the vulnerability of the cartilage after a knee injury. Using an arthroscopic indenter device, cartilage softening after rupture of the anterior

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cruciate ligament (ACL) has been demonstrated as early as at the time of ACL reconstruction.[63] On magnetic resonance imaging (MRI), articular cartilage damage can be evident at 2 to 4 years after ACL reconstruction,[37] and changes can be seen in the deep articular cartilage of the medial femoral condyle with the use of MRI after ACL tears when compared with uninjured controls.[10] Interestingly, in patients with an intact meniscus, it seems that the articular cartilage has the capacity to heal after ACL reconstruction. However, in patients with a concomitant meniscal tear, this healing capacity may be inhibited.[10] The rapid progression to OA after meniscal damage or meniscectomy is likely the result of interconnected pathways, in which increased inflammation at the time of initial meniscal damage results in cartilage degradation and pain, leading to altered gait mechanics and an increase in the mechanical loads on the knee joint.[16] Meniscal damage or partial meniscectomy may also result in loss of knee joint homeostasis, thereby initiating OA development. More specifically, the turnover rate of aggrecan, a proteoglycan found in the extracellular matrix of cartilaginous tissue, is increased after a meniscal lesion or ACL rupture.[38] In addition, collagenase (MMP-1) and aggrecanase (ADAMTS-4) gene expression is increased in the synovial fluid of animals after ACL injury,[21] leading to breakdown of the extracellular matrix found in articular cartilage.

Given the potential long-term sequelae of partial or total meniscectomy, recent literature has proposed the use of adjunctive biological augmentation in order to prevent or delay OA. Of these options, mesenchymal stem cells (MSCs) have shown recent promise. MSCs were first described by Friedenstein et al[18] in 1968 after being derived from bone marrow samples. The osteochondrogenic potential of these cells was first demonstrated in an in vivo environment in chicks by Nakahara et al[44] in 1990. However, it was not until 1994 that MSCs were used in an attempt to repair focal articular cartilage lesions in rabbits.[64] MSCs likely play a significant role in the pathogenesis of OA.[12] The proliferative rates of MSCs are not only lower in patients with OA, but these cells also have lower chondrogenic capacity.[12] Murphy et al[43] hypothesized that, due to the multipotentiality of MSCs, these stem cells may allow for active regeneration of damaged tissues. Thus, local delivery of MSCs to patients with OA could potentially enhance repair of articular cartilage and limit the progression of OA.

Recent studies in both animals and humans have evaluated the effect of intra-articular knee injections of MSCs on OA progression. The purpose of this review is to highlight the findings in the presently available literature and to offer suggestions for future research with the goal of delaying or treating early OA after meniscectomy with MSCs.

METHODS

A literature search was performed that included searches of PubMed, Medline, and Cochrane Library databases using various combinations of the search terms *knee, meniscectomy, mesenchymal stem cells*, and *osteoarthritis*. The following inclusion criterion was 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.

MESENCHYMAL STEM CELLS

The term *mesenchymal stem cells* (MSCs) was first coined by Caplan[6] in 1991. Caplan described MSCs as cells that divide and become committed to a specific phenotypic pathway, with end-stage cells forming unique tissue such as cartilage and bone. Nearly 15 years later, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy defined the minimal criteria for a human cell to be classified as an MSC: (1) the ability to adhere to plastic when maintained in standard culture conditions; (2) expression of surface antigens CD105, CD73, and CD90; (3) lack of expression of hematopoietic antigens CD45, CD34, CD14, or CD11b, CD79alpha or CD19, and HLA-DR surface molecules; and (4) the ability to differentiate to osteoblasts, adipocytes, and chondroblasts in vitro.[15] Expression of surface antigens allows for accurate identification of a cell population, and so it is critically important for cells to express and lack expression of the specific antigens listed above in order to be classified as an MSC. Without meeting the above criteria, the term MSC should not be used.

MSCs may be harvested from various tissues throughout the body, although they are most often obtained from the bone marrow. MSCs represent 0.001% to 0.01% of the bone marrow mononuclear cells (BMMCs), and typically between 1×10^7 and 1×10^8 BMMCs are obtained during harvest.[28] The therapeutic dosage of MSCs remains unclear and depends on the therapeutic application, though 1.0 to 2.0×10^6 MSCs per kilogram of body weight is generally used.[28] When cultured in vitro, MSCs can expand by a thousand-fold within 2 to 3 weeks. However, prolonged culture reduces the quality of these cells, and it has been shown that a higher number of cell passages may result in decreased activation of MSCs.[13]

Few studies have been performed on the use of MSCs to treat OA or focal cartilage defects of the knee.[7] Furthermore, none of these studies reached level 1 evidence. No major adverse events were reported in these studies, and although clinical improvement has been consistently shown in these studies by significant improvement in various patient-reported outcome scores, their methodological quality limits the conclusions that can be drawn regarding the efficacy of intra-articular MSC injections for the treatment of knee pathologies.

Normal articular cartilage is composed of a dense extracellular matrix consisting of highly complex cells known as chondrocytes.[60] In order for MSCs to repair articular cartilage to a normal state, these MSCs must be capable of regenerating mature and fully structured normal extracellular matrix. Although clinical improvement is certainly important in establishing the beneficial effects of treatment, it does not demonstrate the mechanisms by which MSCs repair cartilage tissue or the quality of the repaired

TABLE 1
Animal Studies[a]

Study (Year)	Animal Model	Induction of OA	MSC Harvest Site	Treatment Group
Delling et al[14] (2015)	Sheep	Complete lateral meniscectomy	Bone marrow	2×10^7 MSCs in 2 mL PBS
Hatsushika et al[22] (2013)	Rabbit	Partial medial meniscectomy	Synovial tissue	1×10^7 MSCs in 100 μL PBS
Hatsushika et al[23] (2014)	Pig	Partial medial meniscectomy	Synovial tissue	5×10^7 MSCs in 1 mL PBS
Horie et al[24] (2012)	Rat	Partial medial meniscectomy	Human bone marrow	2×10^6 MSCs in 50 μL PBS
Murphy et al[43] (2003)	Goat	ACL transection and complete medial meniscectomy	Bone marrow	1×10^7 MSCs in 5 mL Hylartin solution
Shen et al[56] (2014)	Rat	Partial medial meniscectomy	Human meniscal tissue	6×10^6 human MSCs in 50 μL PBS
Shen et al[57] (2013)	Rabbit	Partial medial meniscectomy	Meniscal tissue	6×10^6 MSCs in 100 μL PBS
Song et al[59] (2014)	Sheep	ACL transection and complete medial meniscectomy	Bone marrow	1×10^7 MSCs in 5 mL PBS

[a]Unless otherwise indicated, mesenchymal stem cells (MSCs) in each study were harvested from the animal model used. Outcome measures from studies using meniscal scaffolds or composite matrices are not included in this review. ACL, anterior cruciate ligament; OA, osteoarthritis; PBS, phosphate-buffered saline.

tissue. Only through detailed biochemical and biomechanical analysis of tissue samples can these characteristics be determined.

ANIMAL MODELS

Several studies have recently been published in a variety of animal models to evaluate the effects of MSCs on OA postmeniscectomy (Table 1). The models used vary between small to larger animal models with improved translational applications, including pig, goat, and sheep. In order to induce OA in animal subjects, many authors[22-26,56,57] perform bilateral partial or complete meniscectomy, typically removing a portion of the anterior horn of the medial meniscus. At least 1 week after meniscectomy, most authors perform an intra-articular injection of autologous MSCs in the order of 10^6 or 10^7 cells, with the contralateral knee receiving an injection with phosphate-buffered saline (PBS) and no cells (control). Two studies[43,59] performed concomitant ACL transection and complete medial meniscectomy in order to replicate an OA model.

For the purposes of this review, only studies involving the intra-articular injection of MSCs in solution are mentioned. Animal studies involving implantation of meniscal scaffolds or composite matrices loaded with MSCs have also been published but are beyond the scope of this review.

In Vivo Immune Response

Autologous and allogenic cells have been proposed as a source of cell line for the treatment or prevention of OA. The majority of the studies cited in this review involve the intra-articular injection of autologous MSCs derived from various harvest sites, including bone marrow, synovial tissue, and meniscal tissue. The use of autologous MSCs is advantageous in that these cells do not evoke an immune response,[2] although considerable manipulation of autologous MSCs could potentially cause an immune reaction.

In an effort to evaluate the use of allogenic MSCs as an alternative to autogenous cells, a recent study[49] reported on the effects of MSC injections in horses from allogeneic major histocompatibility complex–mismatched donors. Injections of 30 to 50×10^6 MSCs in 1 mL PBS were performed intradermally in the necks of horses. This resulted in the production of cytotoxic antibodies in all recipient horses of the treatment group, while a control group consisting of major histocompatibility complex–matched donors did not produce antibodies. Four of 7 horses developed strong antibody responses, resulting in >80% donor peripheral blood leukocyte death in microcytotoxicity assays. Two horses with weak antibody responses after an initial injection received a second injection of MSCs 5 weeks later, with 1 horse showing an increase in cytotoxic antibodies and the other horse showing no change in antibody response after the second injection. The results of this study demonstrate that MSCs are not immunoprivileged and that the use of allogenic MSCs should be used with caution. However, a balance must be determined between the risk of using allogenic MSCs and the invasiveness and potential complications of harvesting autologous MSCs in human patients.

Imaging Outcomes

Radiographic outcomes after intra-articular injection of MSCs in animal models have overall been successful. Using a porcine model, Hatsushika et al[23] isolated MSCs from synovial tissue with underlying connective tissue from the suprapatellar pouch. After bilateral partial medial meniscectomy, injection of MSCs was performed unilaterally 3 times in 2-week intervals, with the first injection occurring 2 weeks after meniscectomy. Evaluation with MRI at 1.5 T was performed at various time points after injection and scored using a modified version of the Whole-Organ Magnetic Resonance Imaging Score (WORMS). Both groups showed the development of OA at 2 weeks, when MSCs were injected in the study group. However, compared

TABLE 2
Histological Outcomes[a]

Study	Specimens Analyzed	Outcome Measures	Outcomes in Treatment Group[b]
Hatsushika et al[22] (2013)	Medial femoral condyle	OARSI	Lower score at 24 weeks postinjection
Horie et al[24] (2012)	Tibial plateau	OARSI	Less cartilage damage at 2, 4, and 8 weeks postmeniscectomy
Murphy et al[43] (2003)	Medial femoral condyle	Histological	Significantly lower scores for subchondral bone plate thickening and articular cartilage structure at 6 weeks postinjection Significant OA lesions in treatment and control groups at 20 weeks postinjection
Shen et al[56] (2014)	Tibial plateau and femoral condyles	ICRS	Significantly higher scores at 12 weeks postmeniscectomy
Shen et al[57] (2013)	Tibial plateau and femoral condyles	Modified Mankin score	No significant difference compared with control at 4 weeks postmeniscectomy Significantly lower score at 12 weeks postmeniscectomy
Song et al[59] (2014)	Femoral condyles	Modified Mankin score	Significantly lower score at 8 weeks postmeniscectomy/ACL transection compared with BMMCs and PBS

[a]ACL, anterior cruciate ligament; BMMCs, bone marrow–derived mononuclear cells; ICRS, International Cartilage Repair Society Visual Histological Assessment Scale; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International cartilage osteoarthritis histopathology grading system; PBS, phosphate-buffered saline.

[b]Lower scores represent better outcomes for all histological outcomes except the ICRS score.

with the control group, the study group achieved a significantly better WORMS score at 8, 12, and 16 weeks after the first injection of MSCs.

Shen et al[57] evaluated joint space narrowing in a rabbit model after intra-articular injection of allogeneic MSCs derived from rabbit meniscal tissue. Injections were performed at 1 and 2 weeks after meniscectomy. At 12 weeks after meniscectomy, radiographic evaluation demonstrated a significantly greater joint space between the femoral condyles and tibial plateau in the treatment group compared with control ($P < .05$). However, the results of this study are limited in that the joint dimensions in a small animal model are difficult to reproducibly assess.

Delling et al[14] evaluated the effect of intra-articular injection of autologous MSCs in an ovine model. Six weeks after lateral meniscectomy, the study group received an injection of MSCs in the lateral joint space, while the contralateral, control knees received 1 of 4 different solutions, none of which contained viable MSCs. Using a 0.5-T MRI, an original MRI evaluation score was assessed at various time points from before injection until 12 weeks after injection. Contrary to other studies, no significant differences were found in the MRI evaluation scores between study and control groups at any of these time points. Radiographs were also obtained at various time points and, using an original radiographic image evaluation scoring system, no significant differences were found between groups at 12 weeks after injection. The radiographic scores increased for both groups from the time of injection to 12 weeks later, indicating worsening OA. A potential weakness of this study was the use of a 0.5-T MRI, which is likely incapable of detecting cartilage differences between the 2 groups.

Histological Outcomes

Several histological assessment scores have been developed to quantify OA from articular cartilage stains.[1,40,52] These

scores take into account proteoglycan content, the presence of clusters, vascularization, chondrocyte hypertrophy, and cartilage surface morphology. At short-term follow-up, histological improvement has been noted in most animal models after intra-articular injection of MSCs (Table 2). The long-term success of this procedure is more controversial, however. An important limitation of histological analysis in animal models is the thickness of articular cartilage in these models. The average knee articular cartilage thickness in rabbits and sheep is less than 1 mm, compared with an average thickness in humans of 2.2 to 2.5 mm.[19] It would be difficult to obtain standardized knee joint sections from these animal models for histological analysis, and such a system would need to be validated before making any definitive conclusions.

At 1 and 2 weeks after bilateral partial medial meniscectomy, Shen et al[56] injected human MSCs into the right knees of rats, with the contralateral knees receiving injections of PBS without MSCs. At 4 weeks after meniscectomy, histological evaluation was performed using the International Cartilage Repair Society Visual Histological Assessment Scale,[40] which showed significantly more neo-tissue formation and extracellular matrix deposition in the treatment group compared with control. However, no significant differences were seen between groups in terms of gross morphology at 12 weeks postmeniscectomy.

Using the Osteoarthritis Research Society International (OARSI) cartilage osteoarthritis histopathology grading system,[52] Horie et al[24] quantified degenerative changes in the tibial plateau of rats at 2, 4, and 8 weeks after hemimeniscectomy and MSC injection. On the basis of this scoring system, the treatment group had significantly less cartilage damage compared with control at 2, 4, and 8 weeks postinjection. The OARSI system was also used by Hatsushika et al[22] on medial femoral condyle specimens in a rabbit model. At 24 weeks after injection, the control group had a significantly higher (ie, worse) OARSI score.

Murphy et al[43] isolated MSCs from the iliac crest of goats. Intra-articular injection of autologous MSCs was performed 6 weeks after ACL transection and complete medial meniscectomy. At 6 weeks postinjection, samples from the medial condyle were assessed histologically using a quantitative scoring system. Histologic scores for all parameters (reduction of articular cartilage matrix staining, changes in osteophyte formation, subchondral bone plate thickening, and articular cartilage structure) were lower (ie, closer to normal) in the treatment group specimens, with significantly lower scores for subchondral bone plate thickening and articular cartilage structure. However, at 20 weeks after injection, significant OA lesions were present in both the treatment and control groups. The authors hypothesized that this was a result of ACL transection, which resulted in an increased joint load secondary to instability that was not benefited by intra-articular MSC injection.

Shen et al[57] performed histological evaluation in a rabbit model at 4 and 12 weeks after meniscectomy using the modified Mankin score.[1] No significant difference was found between groups at 4 weeks. However, at 12 weeks, a significantly higher (ie, worse) modified Mankin score was exhibited in the control group, both in the tibial plateau and the femoral condyles. Furthermore, the score for the control group increased significantly from the 4-week mark to the 12-week mark in the tibial plateau and the femoral condyles.

A sheep model was used by Song et al.[59] At 12 weeks after complete medial meniscectomy and ACL transection, sheep were injected with bone marrow–derived MSCs, BMMCs, or PBS without cells. At 8 weeks after injection, sections of the femoral condyles were analyzed. Using the modified Mankin score, the MSC group displayed a significantly better score than the BMMC group, and the PBS group exhibited a significantly worse score than both cell groups.

HUMAN MODELS

The use of MSCs in human patients is tightly regulated by the Food and Drug Administration (FDA). Most treatments using cultured MSCs in humans are not presently approved by the FDA and are considered experimental in many settings. In terms of autologous cellular transplants, the FDA regulates treatments involving cells that are more than minimally manipulated.[50] Allogenic transplants are also regulated by the FDA, as these cells are treated similarly to traditional pharmaceutical drugs. As a result of FDA regulation, published data on intra-articular injections of MSCs in human subjects are limited. Although several studies[32,33,45,65] have analyzed the effects of MSC injections in patients with idiopathic or secondary OA, only 1 study[62] has limited its inclusion criteria to patients after a meniscectomy procedure.

Vangsness et al[62] conducted a randomized, double-blind, controlled study (level I) in which all patients were undergoing partial medial meniscectomy. Patients were randomized to 1 of 3 groups: group A (50×10^6 human allograft

MSCs), group B (150×10^6 human allograft 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. 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, the stem cell group (group A) had a significantly greater number of patients (4/18; 22%) with a minimum of 15% volume increase compared with the control group (0/19; 0%). 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. Furthermore, 0 of 18 patients in group B demonstrated a minimum 15% increase in meniscal volume at 24-month follow-up. Visual analog scales (VAS) for pain were also conducted at 6 weeks and 6, 12, and 24 months postoperatively. Compared with the control group, there were significant improvements in VAS pain scores for groups A and B at 24 months after meniscectomy.

Although this study did not directly report on osteoarthritic outcomes such as with plain radiographs, the VAS pain scores may be used as an indirect measure of pain due to OA.[4] However, it is difficult to evaluate the effectiveness of OA prevention at a final follow-up of 24 months. OA is a disease that takes several years to develop. Based on a known initiation point (in this case, partial meniscectomy), OA may take 10 to 20 years to develop.[53] Thus, long-term follow-up is likely necessary in a clinical trial to determine the true efficacy of intra-articular MSC injections in preventing OA.

There are several important limitations to note from the study by Vangsness et al.[62] This study has reported conflict of interest, and 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. In reality, this apparent meniscal volume may actually represent synovial inflammation. Given that, at 24-month follow-up, less than 10% of all patients receiving MSCs demonstrated a minimum 15% increase in meniscal volume, it is likely that this apparent meniscal volume represents some other synovial space-occupying tissue. Further studies with the use of delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) or second-look biopsy are necessary to establish the quality of the regenerated tissue.

Safety Concerns and Complications

In the study by Vangsness et al,[62] no deaths occurred and no adverse events led to treatment discontinuation or study termination. Overall, 427 adverse events occurred among 52 patients in the study population. Of these, 272 adverse events were reported as mild, 126 as moderate, 28 as severe, and 1 as life-threatening in which a patient suffered a myocardial infarction approximately 1 year after study

injection. The most common adverse events were arthralgia, joint swelling, joint stiffness, injection-site joint pain, joint effusion, headache, and peripheral edema. Thus, although intra-articular injection of MSCs was reported to produce minor side effects, it is difficult to determine which of these adverse events were directly related to the injection of MSCs. More importantly, though, the majority of all adverse events reported in this study were mild and none resulted in death or the need to terminate the study.

Ongoing Clinical Trials

Although not yet published, a phase I/II clinical trial was recently performed on 55 patients undergoing medial meniscectomy (http://osiris.com/OLD/prod_chondrogen .php). Patients were randomized to receive a single intra-articular injection of 50 million or 150 million human MSCs (Chondrogen; Osiris Therapeutics Inc) in suspension with commercial sodium hyaluronan 1 week after meniscectomy. A control group received an injection of sodium hyaluronan alone. Based on preliminary unpublished results, patients who underwent injection with Chondrogen experienced significant improvement in pain at 6 weeks, 6 months, and 12 months as compared with placebo. Furthermore, the effects on pain were seen to be dose dependent. Finally, patients in the control group were more likely to experience degenerative bone changes associated with OA, although it is unclear how this was assessed.

DISCUSSION

The main finding of this review is that successful short-term outcomes have been reported with the intra-articular injection of MSCs for the prevention of postmeniscectomy OA in animal models. Only 1 published human study[62] has involved intra-articular MSC injections after meniscectomy, although the outcomes measured in this study included knee pain and meniscal regeneration rather than radiological or histological outcomes of OA. Determining ways to slow or prevent the progression of OA, especially after meniscectomy, would significantly improve quality of life for countless patients worldwide.

Partial meniscectomy results in eventual progression to knee OA by a number of mechanisms. In particular, the amount of meniscus taken at the time of meniscectomy plays a significant role in this progression, as increasing meniscectomy size results in reduced contact area within the knee joint and thus greater contact pressures.[17,27,36,51] However, this is not the only factor involved, as appropriate joint lubrication by hyaluronic acid and lubricin,[34] proprioceptive feedback,[39,54] knee alignment,[55] and body mass index[11,66] are also involved in determining progression of knee OA.

MSCs are capable of differentiating into a specific phenotypic pathway depending on the environment in which they exist.[20] As such, these cells serve as an important potential regenerative therapy. Within the field of orthopaedics, MSCs have been used in animal models in an attempt to improve healing associated with rotator cuff repair,[46] ACL reconstruction,[29] patellar tendon repair,[30] and articular cartilage defects of the knee.[42] However, due to the novelty of these cells in therapeutic applications and federal regulations, clinical studies involving MSCs are limited.

In this review, we evaluated several studies in animal models involving the intra-articular injection of MSCs for the prevention of OA after meniscectomy. Most of these studies found successful results in terms of OA prevention. Unlike the available data in humans, most animal studies involve inducing OA by performing open or arthroscopic excision of a portion of the meniscus. It is unclear how comparable these methods are to a human population in which meniscectomy is performed after acute or chronic meniscal damage rather than excision of a healthy meniscus. It is likely that excision of a healthy meniscus allows for greater regeneration potential, and thus, the animal studies that have been published may overestimate the treatment effectiveness of MSC injections. This is evident by the results of some animal studies[25,56] in which meniscal regeneration was grossly visible even in some of the control knees that did not receive MSC supplementation. Furthermore, the ages of the animal models described in this review are much younger than a human patient who develops OA after a meniscectomy procedure. This must be taken into account when attempting to translate the findings of animal studies to humans.

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. Finally, OA is a multifactorial disease that may not be fully characterized in isolation by the postmeniscectomy state. While MSCs may improve outcomes after meniscectomy, much is still unknown with regard to OA progression in these patients.

CONCLUSION

Limited results from animal studies suggest that there is some potential for intra-articular injection of MSCs for the prevention of OA. Future studies should act to further define the comparative regeneration capacities of MSCs isolated from bone marrow, synovium, and the infrapatellar fat pad. Other stem cell characteristics such as donor sex,[41,47] donor age,[9,47] donor health,[8] culture medium,[3] and storage method[58] should also be considered, as these factors may affect regeneration capacity. In addition, further studies are needed to determine the potential for allogeneic MSC injections, as previous studies have not evaluated immune responses after intra-articular injections of these cells. Longer-term studies are needed, as the longest follow-up currently in the literature is only 24 months, and several animal studies[22,24,26,56] have shown only short-term benefit of MSC injections. With further research, the role of intra-articular injection of MSCs may be better defined.

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