Intra-Articular Injections of Mesenchymal Stem Cells for Knee Osteoarthritis


Authors:
Rodríguez-Merchán EC

Author Affiliation | Disclosures

Emérito Carlos Rodríguez-Merchán, MD, PhD

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Knee osteoarthritis (KOA), a common disabling disease with a high impact on quality of life, has a large societal cost. Yet no procedure halts progressive degeneration of the osteoarthritic knee joint.¹,²

According to Barry,³ mesenchymal stem cells (MSCs) differentiate into many different connective tissue cells, including cartilage. MSCs can be isolated from bone marrow, skeletal muscle, fat, and synovium. MSCs are multipotent cells with the capacity for self-renewal. Therefore, adult MSCs may regenerate tissues damaged by disease. In OA, the proliferative capacity and ability to differentiate are reduced in MSCs. Intra-articular injections of MSCs (MSC therapy) could repair progressively degenerated knee cartilage.

This review article summarizes the knowledge on the role of intra-articular injections of MSCs in the treatment of KOA, based on studies published in PubMed and the Cochrane Library. The article also reviews the methodology and results of the animal and clinical studies published so far on the topic.

**Materials and Methods**

PubMed (Medline) and the Cochrane Library were searched for literature on the role of MSC therapy in treating KOA. The key words used were *stem cells* and *knee osteoarthritis*. The period searched was from when these search engines began until January 31, 2014. One hundred thirty-five articles (including negative studies) were found, but only the 25 deeply focused on the topic were reviewed. The Figure shows the flow diagram of this study.
Results

Several experimental models of KOA have shown that MSC therapy can delay progressive degeneration of the knee joint (Appendix 1).\(^4\)\(^-\)\(^15\) Using a rabbit massive meniscal defect model, Hatsushika and colleagues\(^13\) found that a single intra-articular injection of synovial MSCs into the knee adhered around the meniscal defect and promoted meniscal regeneration. Park and colleagues\(^14\) conducted an experimental study in dogs—the first demonstrating regional and systemic safety and systemic immunomodulatory effects of repeated local delivery of allogeneic MSCs in vivo. Regarding the observed systemic immunomodulatory effects, clinical and pathologic examinations revealed no severe consequences of repeated MSC transplantsations. Results of mixed leukocyte reactions demonstrated suppression of T-cell proliferation after MSC transplantsations.

Of the human studies published so far, only 3 were prospective randomized trials (level II evidence) included in the Cochrane Library (Appendix 2).\(^16\)\(^-\)\(^18\) Varma and colleagues\(^16\) found that intra-articular injections of MSCs considerably improved overall KOA outcome scores. Fifty patients with mild to moderate KOA were divided into 2 groups. Group A underwent arthroscopic débridement, and group B had buffy coat (MSC concentrate) injection and arthroscopic débridement. Patients were assessed on the basis of their visual analog scale (VAS) pain scores and osteoarthritis outcome scores.

Wong and colleagues\(^17\) analyzed 56 knees in 56 patients (mean age, 51 years) with unicompartmental KOA and genu varum. Patients were randomly assigned to 2 groups, MSC and control. All patients underwent high tibial osteotomy (HTO) and microfracture. Patients in the MSC group received intra-articular injection of cultured MSCs with hyaluronic acid (HA) 3 weeks after surgery. Patients in the control group received only HA. The primary outcome measure was International Knee Documentation Committee (IKDC) score 6 months, 1 year, and 2 years after surgery. Secondary outcome measures were Tegner and Lysholm clinical scores and 1-year postoperative Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scores. Both treatment arms achieved improvements in Tegner, Lysholm, and IKDC scores. After adjustment for age, baseline scores, and time of evaluation, the MSC group had significantly better scores. One year after surgery, magnetic resonance imaging (MRI) scans showed significantly better MOCART scores for the MSC group. Intra-articular injection of MSCs appeared to be effective in improving short-term clinical and MOCART outcomes in patients who underwent HTO and microfracture for varus knees with cartilage defects.

Saw and colleagues\(^18\) compared histologic and MRI evaluation of articular cartilage regeneration in patients with chondral lesions treated by arthroscopic subchondral drilling followed by postoperative intra-articular injections of HA with and without peripheral blood stem cells (PBSCs). Fifty patients (ages, 18-50 years) with International Cartilage Repair Society grades 3 and 4 lesions of the knee joint underwent arthroscopic subchondral drilling; 25 patients were randomized to the intervention group (HA + PBSC) and 25 to the control group (HA). Both groups received 5 weekly injections starting 1 week after surgery. Three additional injections of either HA + PBSC or HA only were given at weekly intervals 6 months after surgery. After arthroscopic subchondral drilling into grades 3 and 4 chondral lesions, postoperative intra-articular injections of autologous PBSC combined with HA resulted in improved quality of articular cartilage repair over the same treatment without PBSC.

The other human studies analyzed had a low level of evidence (grade IV, case series) but found that intra-articular injections of MSCs reduced pain and improved function in patients with KOA over the short term, 1 year (Appendix 3).\(^19\)\(^-\)\(^25\)
Discussion

This review aimed to define the role of MSC therapy in the treatment of KOA. MSC therapy has yielded encouraging outcomes in experimental models of KOA.4-15 These experimental studies have suggested that MSCs can halt cartilage degeneration in KOA. So far, however, only 3 human studies with grade II evidence (randomized prospective trials) have been reported on the role of MSCs in KOA, but results of these studies have suggested that MSCs can reduce pain and improve function.16-18

Previous reviews of the literature1,2 have analyzed the role of MSC therapy in KOA. Barry and Murphy1 reported that several early-stage clinical trials, initiated or under way in 2013, were testing MSC delivery as an intra-articular injection into the knee, but optimal dose and vehicle were yet to be established. Filardo and colleagues2 reported that, despite growing interest in this biological approach to cartilage regeneration, knowledge on the topic is still preliminary, as shown by the prevalence of preclinical studies and the presence of low-quality clinical studies.

Study design weakness prevents effective comparison of the efficacy of MSC therapy with that of other treatments for relief of pain and other outcomes in KOA. The consistency of evidence of the clinical studies is low because of many uncontrolled variables.1-3

Conclusion

The results of MSC therapy in KOA are encouraging. However, optimal dose and vehicle are yet to be established.1 Knowledge on this topic is still preliminary. Many aspects have to be optimized, and further randomized controlled trials are needed to support the potential of this biological treatment for cartilage repair and to evaluate advantages and disadvantages with respect to the available treatments. The relative short duration of these studies is also a limitation for the technique at present.

Key Info

Figures/Tables

References

References


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