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The use of mesenchymal stem cells for cartilage regeneration in knee osteoarthritis

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ABSTRACT

Background: Knee osteoarthritis (OA) represents an enormous societal burden. Yet no approved procedure prevents the progressive destruction of the articular cartilage. **Question:** This review aims to update the use of mesenchymal stem cells (MSCs) for cartilage regeneration in knee OA. **Methods:** A PubMed (MedLine) search related to MSCs and knee OA were analyzed. Articles related to the use of MSCs in knee OA were searched using the following key words: Knee OA stem cells and stifle joint stem cells. A total of 210 reports were found, but only 19 very selected and reviewed. The main criterion for selection was that the articles were focused in the aforementioned question. **Results:** Local delivery (intra-articular injection) of autologous MSCs has produced promising outcomes in 16 experimental models of knee OA. However, only 3 low-quality clinical studies have been reported so far on the role of MSCs injections in knee OA. Study design weakness prevented effective comparison of the efficacy of MSC injections with that of other treatments for relief of pain and other outcomes in human knee OA. The consistency of evidence of the clinical studies was low because of many uncontrolled variables. **Conclusions:** Animal experiments suggest that intra-articular injections of autologous MSCs can have the potential to promote cartilage regeneration in knee OA. Taking into account the low-quality of the data reported in clinical studies, my conclusion is that intra-articular injections of autologous MSCs in knee OA is a treatment that is still experimental.

KEY WORDS: Autologous, injections, intra-articular, knee, mesenchymal stem cells, osteoarthritis

INTRODUCTION

Knee osteoarthritis (OA), a prevalent chronic disease with a striking impact on quality of life, represents an enormous societal burden. Yet no pharmacological intervention, biologic therapy or procedure prevents the progressive destruction of the articular cartilage [1].

According to Barry [2], mesenchymal stem cells (MSCs) have the capacity to differentiate into a variety of connective tissue cells including cartilage. These multipotent cells have been isolated from bone marrow and from other adult tissues including skeletal muscle, fat, and synovium. Because of their multipotentiality and capacity for self-renewal adult MSCs may represent units of active regeneration of tissues damaged as a result of the disease.

In certain degenerative diseases such as OA, MSCs are depleted, and have reduced proliferative capacity and reduced ability to differentiate [1,2]. The delivery of MSCs to these patients may, therefore, increase repair or inhibit the progressive destruction of the joint. Delivering MSC preparations to the osteoarthritic joint we could stimulate regeneration of cartilage and retard the progressive destruction of the joint.

The purpose of this review article is to summarize the existing knowledge on the role of autologous MSCs in the treatment of knee OA based on the studies published in PubMed, and to make a rigorous review of the methodology and results of the various animal and clinical studies published so far on the topic.

METHODS

A review has been performed on the role of intra-articular injections of autologous MSCs in patients with knee OA. The search engine was MedLine (PubMed). The keywords used were: Knee OA stem cells (177 articles found in PubMed) and stifle joint stem cells (33 articles found in PubMed). Two hundred and ten articles were found, but only nineteen were selected and reviewed because they were deeply focused on the topic.

RESULTS

Local delivery (intra-articular injection) of autologous MSCs has produced promising outcomes in 16 experimental models of knee OA. However, only 3 low-quality clinical studies have been reported so far on the role of MSCs injections in knee OA. Study design weakness prevented effective comparison of the efficacy of MSC injections with that of other treatments

for relief of pain and other outcomes in human knee OA. The consistency of evidence of the clinical studies was low because of many uncontrolled variables.

Experimental Studies

In 2003 Murphy *et al*., [3] explored the role that implanted MSCs may play in tissue repair or regeneration of the knee joint, by delivery of an autologous preparation of MSCs to caprine knee joints following induction of OA. Local delivery of adult MSCs to the joints retarded the progressive destruction normally seen in this model of OA.

In 2007, Wilke *et al*., [4] analyzed twelve full-thickness 15 mm cartilage lesions in the femoropatellar joints of six young mature horses; such lesions were repaired by injection of a self-polymerizing autogenous fibrin vehicle containing MSCs or autogenous fibrin alone in control joints. Arthroscopic second look and defect biopsy were obtained at 30 days, and all animals were euthanized 8 months after repair. They found that MSCs improved the early healing response, but did not significantly enhance the long-term histologic appearance or biochemical composition of full-thickness cartilage lesions.

In 2008, Al Faqeh *et al*., [5] determined if autologous bone marrow MSCs (BMSCs) cultured in the chondrogenic medium could repair surgically induced OA in a sheep model. The results indicated that knee joints treated with autologous BMSCs cultured in chondrogenic medium showed clear evidence of articular cartilage regeneration.

In 2009, Grigolo *et al*. [6] performed an experimental animal study of OA in rabbits. They demonstrated that Hyaff-11, a hyaluronan-based scaffold has the potential for MSC implantation, and that may have application for the treatment of early OA in humans.

In 2011, Toghraie *et al*. [7] used scaffold free MSCs obtained from the infrapatellar fat pad in an experimental animal model (rabbit) of OA by direct intra-articular injection. They stated that, infrapatellar fat pad derived MSCs could be the promising cell sources for the treatment of OA.

In 2011, McIlwraith *et al*. [8] studied ten horses (aged 2.5-5 years) after creating 1 cm^2 defects arthroscopically on both medial femoral condyles of the stifle joint (analogous to the human knee). Defects were debrided to subchondral bone followed by microfracture. One month later, 1 randomly selected medial femorotibial joint in each horse received an intra-articular injection of either 20 × 10(6) BMSCs with 22 mg of hyaluronan or 22 mg of hyaluronan alone. Horses were confined for 4 months, with hand walking commencing at 2 weeks and then increasing in duration and intensity. At 4 months, horses were subjected to strenuous treadmill exercise simulating race training until completion of the study at 12 months. Horses underwent musculoskeletal and radiographic examinations bimonthly and second-look arthroscopy at 6 months. Horses were euthanized 12 months after the defects were made, and the affected joints underwent magnetic resonance imaging and gross, histologic, histomorphometric, immunohistochemical, and biochemical examinations. Although, there was no evidence of any clinically significant improvement in the joints injected with BMSCs, arthroscopic and gross evaluation confirmed a significant increase in repair tissue firmness and a trend for better overall repair tissue quality (cumulative score of all arthroscopic and gross grading criteria) in BMSC-treated joints. Immunohistochemical analysis showed significantly greater levels of aggrecan in repair tissue treated with BMSC injection. There were no other significant treatment effects. Although there was no significant difference clinically or histologically in the 2 groups, this study confirmed that intra-articular BMSCs enhance cartilage repair quality with increased aggrecan content and tissue firmness.

In 2012, Sato *et al*. [9] tested the outcome of intra-articular transplantation of MSCs suspended in hyaluronic acid (HA) in the knee joints of Hartley strain guinea pigs with spontaneous OA. Commercially available human MSCs were cultured, labeled with carboxyfluorescein diacetate succinimidyl ester (CFDA-SE), suspended in either phosphate-buffered saline (PBS) or HA, and injected into the knee joints of 7-month-old animals. The control animals were injected with either PBS or HA alone. The animals were sacrificed at 1, 3, and 5 weeks post-transplantation, the knee joints harvested, and fluorescent microscopic analysis was performed. Histological and immunohistochemical analysis were performed at 5 weeks post-transplantation. At 5 weeks post-transplantation, partial cartilage repair was noted in the HA-MSC group but not in the other groups. Examination of CFDA-SE-labeled cells demonstrated migration, differentiation, and proliferation of MSC in the HA-MSC group. There was strong immunostaining for type II collagen around both residual chondrocytes and transplanted MSCs in the OA cartilage. The findings of this study suggested that intra-articular injection of HA-MSC mixture is potentially beneficial for OA.

In 2012, Suhaeb *et al*. [10] examined the effects of MSCs, HA, and the combination of HA-MSC in treating OA in a rat model. The study suggested that the use of either HA or MSCs effectively reduced OA progression better than their combined use.

In 2012, Al Faqeh *et al*. [11] studied whether or not an intra-articular injection of a single dose of autologous chondrogenic induced BMSC could retard the progressive destruction of cartilage in a surgically induced OA in sheep. They concluded that the intra-articular injection of a single dose of BMSCs either chondrogenically induced or not, could retard the progression of OA in a sheep model.

In 2012, Toghraie *et al*. [12] induced OA in adult white New Zealand rabbits by unilateral anterior cruciate ligament transection. The study suggested that autologous stem cells obtained from subcutaneous adipose tissue could be a viable approach for treating OA.

In 2012, ter Huurne *et al*. [13] explored the effect of intra-articular injection of autologous stem cells on synovial lining thickness and its relation to joint pathology in experimental

mouse OA. The findings indicated that a single injection of autologous stem cells into the knee joints of mice with early-stage collagenase-induced OA inhibits cartilage destruction.

In 2015, Frisbie *et al*. [14] in an equine model created cartilage defects (15 mm) on the medial trochlear ridge of the femur. The following experimental treatments were compared with empty-defect controls: Fibrin only, autologous chondroprogenitor cells plus fibrin, and allogenic chondroprogenitor cells plus fibrin (n = 4 or 12 per treatment). Horses underwent strenuous exercise throughout the 12 months study, and evaluations included lameness (pain) and arthroscopic, radiographic, gross, histologic, and immunohistochemical analyses. It was found that autologous chondroprogenitor cells in fibrin appeared to yield a modest improvement over fibrin alone, with a 128% difference in central osteophyte formation compared with fibrin-only treatment. This cell type may be showed clinical benefit, and comparisons with other cartilage resurfacing techniques should be considered.

Human Studies

In 2012, Varma *et al*. [15] studied 50 patients with mild to moderate knee OA that were divided into two groups (Group A and Group B). Group A received arthroscopic debridement alone and Group B received buffy coat (MSCs concentrate) injection along with the arthroscopic debridement of the knee. On follow-up, patients were assessed on the basis of visual analogue scale (VAS) score and OA outcome score, to compare results in both groups against each other to determine the efficacy of arthroscopic injection of buffy coat in the management of OA. The results suggested that the technique used in the study considerably improved the overall OA outcome score, especially the quality of life within the studied follow-up period, and at the end of the follow-up. This study is the only one included in the Cochrane Library so far.

In 2012 and 2013, Koh and Choi; Koh *et al*. [16,17] in a therapeutic case-control study (Level III) tried to determine if isolated MSCs derived from the infrapatellar fat pad could effectively improve clinical results when percutaneously injected into arthritic knees. Twenty-five stem cell injections combined with arthroscopic debridement were administered to patients with knee OA. A mean of 1.89 × 10(6) stem cells were prepared with approximately 3.0 mL of platelet-rich plasma (PRP) and injected in the selected knees of patients in the study group. The mean Lysholm, Tegner activity scale, and VAS scores of patients in the study group improved significantly by the last follow-up visit. No major adverse events related to the injections were observed during the treatment and follow-up periods. The results were compared between the study and control groups, in which the patients had undergone arthroscopic debridement and PRP injection without stem cells. Although the preoperative mean Lysholm, Tegner activity scale, and VAS scores of the study group were significantly poorer than those of the control group, the clinical results at the last follow-up visit were similar, and not significantly different between the two groups. The short-term results of this study were encouraging and demonstrated that infrapatellar fat pad-derived MSC therapy with intra-articular injections were safe, and provided assistance in reducing pain and improving function in patients with knee OA.

Twelve patients with chronic knee pain unresponsive to conservative treatments and radiologic evidence of OA were treated by Orozco *et al*., in 2013 [18] with autologous expanded BMSCs by intra-articular injection (40×10 cells). Twelve patients with chronic knee pain unresponsive to conservative treatments and radiologic evidence of OA were treated with autologous expanded BMSCs by intra-articular injection (40×10 cells). Clinical outcomes were followed for 1-year and included evaluations of pain, disability, and quality of life. Articular cartilage quality was assessed by quantitative magnetic resonance imaging T2 mapping. Feasibility and safety were confirmed, and strong indications of clinical efficacy were identified. Patients exhibited rapid and progressive improvement of algofunctional indices that approached 65-78% by 1-year. This outcome compares favorably with the results of conventional treatments. In addition, quantification of cartilage quality by T2 relaxation measurements demonstrated a highly significant decrease of poor cartilage areas (on average, 27%), with the improvement of cartilage quality in 11 of the 12 patients. The authors concluded that the intervention was simple, did not require hospitalization or surgery, provided pain relief, and significantly improved cartilage quality.

DISCUSSION

OA, a prevalent chronic condition with a striking impact on quality of life, represents an enormous societal burden. Yet no approved procedure prevents the progressive destruction of the OA joint. Local delivery of *ex vivo* cultures of MSCs has produced promising outcomes in preclinical models of joint disease [1-14].

MSCs have the capacity to differentiate into a variety of connective tissue cells including cartilage. These multipotent cells have been isolated from bone marrow and from other adult tissues including skeletal muscle, fat, and synovium. Delivering MSCs preparations to the injured knee joint we could stimulate regeneration of cartilage and retard the progressive destruction of the joint [1,2].

Only three low-quality clinical studies have been reported so far on the role of MSCs injections in knee OA. Study design weakness prevents effective comparison of the efficacy of MSCs injections with that of other treatments for relief of pain and other outcomes in knee OA. The consistency of evidence of the clinical studies is low because of many uncontrolled variables [19].

CONCLUSION

Sixteen animal experiments suggest that intra-articular injections of autologous MSCs can have the potential to promote cartilage regeneration in knee OA. Taking into account the low quality of the data reported in clinical studies, my conclusion is that intra-articular injections of autologous MSCs in knee OA is a treatment that is still experimental.

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