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Cell Therapy for Knee Osteoarthritis: Mesenchymal Stromal Cells

Christopher Kim[a] Armand Keating[a, b]

[a]Krembil Research Institute, Toronto Western Hospital, Toronto, ON, Canada; [b]Cell Therapy Translational Research Laboratory, Princess Margaret Cancer Centre, Toronto, ON, Canada

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Abstract
Osteoarthritis (OA) is designated the 11th highest contributor of 291 diseases of global disability and the most common cause of chronic disability in elderly people. OA has a devastating impact on quality of life and represents an enormous socio-economic burden. Currently, OA is incurable, and no approved medications, biological therapy, or procedure prevents the progressive destruction of the osteoarthritic knee joint. All current treatments provide symptomatic relief rather than preventative or regenerative results. There is an urgent and compelling need to find, validate, and test new biological therapeutics. Cell-based therapies involving the delivery of mesenchymal stromal cells (MSCs) to the osteoarthritic knee joint have emerged as a potential solution to overcome this clinical shortcoming. In this review, we address the clinical evidence, challenges, and recent advances surrounding MSC treatment in knee OA.

Introduction

Osteoarthritis (OA) of the knee is a chronic, degenerative, whole-joint disease characterized by degradation and loss of articular cartilage, osteophyte formation, subchondral bone remodelling, and inflammation of the synovial membrane [1]. A dysregulation of chondrocyte homeostasis results in the progressive degradation of cartilage extracellular matrix and this catabolic process involves pro-inflammatory cytokines and matrix metalloproteinases [1]. People living with knee OA complain of joint pain, loss of joint function, reduced mobility, and decreased quality of life [2].

Currently, knee OA is managed using non-surgical treatments such as weight loss, physiotherapy, bracing, and medications, including acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and intra-articular (IA) knee injections, including corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), and mesenchymal stromal cells (MSCs; Box 1). Cyclooxygenase-2 (COX-2) inhibitor use is associated with adverse side effects, including gastrointestinal complications and increased risk of myocardial infarction [3]. Although effective in the short-term, multiple corticosteroid injections in a joint and prolonged exposure to steroids can

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E-Mail karger@karger.com
www.karger.com/ger

Christopher Kim
Toronto Western Hospital
Room 1 East 449, 399 Bathurst Street
Toronto, ON M5T 2S8 (Canada)
E-Mail ck.kim@mail.utoronto.ca

Box 1. Main IA injections for knee OA

- Corticosteroids
- Hyaluronic acids
- Platelet-rich plasma
- Autologous mesenchymal stromal cells

harm articular cartilage and accelerate progression of OA [4]. In a recent systematic review of overlapping meta-analyses comparing treatment of knee OA with IA HA versus oral NSAIDs, IA injection of corticosteroids, PRP, or placebo, Campbell et al. [5] reported no differences in knee pain and function between HA versus NSAIDs, greater effects of PRP versus HA, and positive effects of HA versus corticosteroids and placebo, with HA providing knee pain relief for 26 weeks compared to corticosteroids. In another systematic review of overlapping meta-analyses, the same authors compared treatment of knee OA with IA PRP versus oral NSAIDs, IA injection of corticosteroids, HA, or placebo [6]. The authors showed that IA injection of PRP significantly improved patient knee pain and function through 6–12 months compared with IA HA or placebo [6]. Most recently, Jevsevar et al. [7] designed a network meta-analysis comparing nonsurgical treatments for knee OA that included acetaminophen, NSAIDs, IA corticosteroids, IA HA, IA PRP, IA placebo, and oral placebo. The cumulative probabilities supported naproxen as the most probable to improve patient knee pain and function, followed by IA corticosteroids, IA PRP, celecoxib, and ibuprofen [7]. When these non-surgical treatments fail, total knee arthroplasty (TKA) is the only remaining option for end-stage knee OA. TKA remains the gold standard for end-stage knee OA, is the most effective intervention for severe OA, and is becoming increasingly relied upon to reduce pain, disability, and restore some patients to near normal function [8]. Despite its effectiveness, TKA is often associated with complications, such as infection, incorrect implant position, instability, postoperative stiffness, and pain which causes increased morbidity and decreased patient satisfaction [8]. The risk of failure of a TKA needing revision surgery 10 years postoperatively is 5% [9]. Pooled data from national joint registries worldwide reported that the most common indications for revision TKA included aseptic loosening (29.8%), infection (14.8%), and pain (9.5%) [10–13]. Other main indications for revision TKA were patellofemoral pain, instability, and stiffness [9]. Unfortunately, the demand for TKA is expected to rise as the baby boomer generation ages and younger and active patients increasingly request TKA [14]. Therefore, a novel regenerative medicine strategy for knee OA is necessary.

The direct injection of MSCs into an osteoarthritic joint may enhance the normally limited repair and reduce destructive processes. The regenerative capacity of MSCs was established using preclinical OA animal models. In a collagenase-induced OA mouse model, 20×10^3 mouse adipose-derived MSCs (ASCs) were injected intra-articularly into mouse knee joints 7 days after induction [15]. Forty-two days after ASC injection, the ASC-treated mice showed decreased synovial thickening, reduced formation of enthesophytes, and inhibited cartilage destruction compared to control-treated mice [15]. In an anterior cruciate ligament transection (ACLT) OA rabbit model, Desando et al. [16] injected 2×10^6 and 6×10^6 rabbit ASCs into the knee 8 weeks after ACLT. At 16 and 24 weeks after cell injection, the 2×10^6 ASC-treated groups showed a significant decrease of Laverty's score and reduced expression of tumour necrosis factor-α and matrix metalloproteinase-1 compared to controls [16]. In a closed tibial plateau fracture mouse model of post-traumatic OA, Diekman et al. [17] injected 10×10^3 mouse C57BL/6-derived or MRL/MpJ-derived MSCs into mouse knee joints immediately after fracture. At 8 weeks after injection, the MSC-treated groups demonstrated significantly reduced modified Mankin OA scores, altered levels of synovial interleukin-1β and serum IL-10, and increased bone volume compared to control knees [17]. Therefore, a promising regenerative medicine therapy may be the IA injection of MSCs into osteoarthritic knees.

OA in Older Adults

The prevalence of OA considerably increases with age [18, 19]. It is estimated that 30–50% of adults 65 years and over suffer from OA and present with significant pain or disability [18, 19]. Greater than 80% of adults over the age of 55 years have at least one joint, either hand, spine, hip, or knee, showing radiographic changes of OA [20].

Age is one of the common risk factors for the development of OA [21]. Other common risk factors include obesity, sex, history of joint injury, race, genetics, anatomical and nutritional factors [21, 22]. Age-related factors that contribute to the development of OA include oxidative stress and damage [23], muscle weakness [24], decreased proprioception [25], damage to meniscus and ligaments [26, 27], thinning of articular cartilage [28], increased subchondral bone remodelling [29], and calcium crystal

deposition within joint tissue [30]. Age-related changes in cells and tissues may alter joint homeostasis leading to an insufficient response to joint stress and injury, and cause cartilage and surrounding joint tissue damage and loss. Therefore, the use of MSCs may alter the destructive age-related changes to the joint by augmenting the normally limited repair, limit degenerative changes, replace lost or damaged cells and tissues, and reduce inflammatory mediators.

MSCs for OA

MSCs are multipotent progenitors derived from non-hematopoietic adult stem cell populations present in numerous tissues, including bone marrow, peripheral blood, adipose tissue, synovium, placenta, and umbilical cord [31]. According to the International Society for Cellular Therapy, human MSCs are defined as plastic adherent, positive for CD105, CD73, and CD90 markers, negative for CD45, CD34, CD14 or CD11b, CD79α or CD19, and HLA-DR, and able to differentiate into osteoblasts, chondroblasts, and adipocytes [32]. In addition, MSCs possess intrinsic immunomodulatory properties and can reduce inflammation and support other cells, thereby enhancing angiogenesis, cell survival and differentiation, and preventing fibrosis [33].

Currently, primary isolated stromal cells represent the best option for treatment of OA. The most common sources of MSCs for clinical use are bone marrow-derived stromal cells (BMSCs) and ASCs. BMSCs are commonly harvested from the posterior superior iliac spine as bone marrow concentrate, which contain MSCs, hematopoietic stem cells, endothelial progenitor cells, and associated cytokine and growth factors [34]. ASCs are isolated from the stromal vascular fraction of homogenized adipose tissue generally harvested from subcutaneous sites and the infrapatellar fat pads [34]. In comparison to BMSCs, ASCs have greater cell yield, proliferative capacity in culture, and differentiation potential [35, 36]. However, there are no clinical trials comparing BMSCs and ASCs in knee OA [34].

Bone Marrow-Derived MSCs

In a small clinical study, Orozco et al. [37] studied the clinical efficacy and safety of direct IA injection of 40×10^6 autologous human BMSCs in 12 patients with knee OA. The BMSC-injected patients reported decreased knee pain, no serious adverse effects, and improved articular cartilage quality on post-treatment MRI scans of the knee [37]. In a double-blinded, randomized controlled trial (RCT), Vangsness et al. [38] investigated the effect and safety of IA injection of allogeneic human BMSCs in human OA knees following partial medial meniscectomy. In the 18 patients who received 50×10^6 BMSCs and another group of 18 patients who received 150×10^6 BMSCs, there was evidence of meniscus regeneration and significant reduction in knee pain compared to control patients who did not receive an injection [38]. In another study, Vega et al. [39] randomized 30 patients with knee OA into 2 groups with 15 patients receiving IA injections of 40×10^6 allogeneic human BMSCs and 15 patients in the control group receiving IA injections of HA. The BMSC-treated patients reported a significant decrease in knee pain and improved knee function, improved cartilage quality in defects on post-treatment MRI, and no adverse events [39]. Recently, Gupta et al. [40] examined the efficacy and safety of IA injection of allogeneic human BMSCs in knee OA. Sixty OA patients were randomized to receive 25×10^6, 50×10^6, 75×10^6, 150×10^6 BMSCs or no BMSCs. The 25×10^6 BMSC dose was found to be most effective for reducing OA knee pain and there were no significant adverse events reported [40].

Adipose-Derived MSCs

In a phase I and II clinical trial, Jo et al. [41] investigated the efficacy and safety of IA injection of autologous human ASCs in patients with knee OA. Phase I consisted of 1×10^7, 5×10^7, and 1×10^8 ASC-injected groups with 3 patients each and phase II included 9 patients receiving the high dose of 1×10^8 ASCs. The patients receiving 1×10^8 ASCs showed reduced OA knee pain, improved knee function, regeneration of articular cartilage defects with hyaline-like cartilage, and no serious adverse events [41]. Furthermore, in a two-centre phase I safety study of 18 consecutive patients with symptomatic and severe knee OA, the European Union consortium Adipose-Derived Stromal Cells for Osteoarthritis (ADIPOA) has shown that IA injection of a single dose of 2×10^6, 10×10^6, or 50×10^6 autologous ASCs to the knee was well tolerated, had no adverse effects, and resulted in an improvement in pain and functional outcome scores at 12 months [42].

Systematic Reviews and Meta-Analyses of MSCs in OA

In a meta-analysis of 11 clinical trials involving a total of 582 patients with knee OA, Yubo et al. [43] evaluated the clinical efficacy and safety of BMSC and ASC treatment for knee OA. The investigators demonstrated that MSC treatment improved pain and functional scores af-

ter a 24-month follow-up compared to controls and were safe with no serious adverse events reported [43]. In a systematic review of 5 RCTs and 1 non-RCT on BMSCs and ASCs in knee OA, Pas et al. [44] reported that the 6 trials included for review showed high risk of bias and, in the absence of high-level evidence, the authors do not recommend MSC therapy in knee OA. Jevotovsky et al. [45] performed a systematic review on MSC therapy for OA with 61 studies identified, treating 2,390 patients with OA. BMSCs and ASCs were used in these included studies. The authors concluded an association between MSC therapy and improvement in pain and functional outcome scores, but stated the need for well-designed RCTs with reproducible cell preparation methods for BMSCs and ASCs and longer follow-up [45]. In summary, cell therapy with direct IA injection of MSCs should be considered a novel regenerative medicine strategy for knee OA. Direct IA injection of MSCs in the knee is safe, simple, does not require a surgical procedure, provides pain relief, improves function, and enhances cartilage quality. However, future RCTs and larger patient cohorts are required to demonstrate the safety and efficacy of MSCs in knee OA. Many studies suffer from a lack of high-level evidence and long-term follow-up. In addition, the diversity of cell preparation methods and lack of reproducibility mean that many clinical trials do not contribute to a high-quality evidence base. Therefore, there is a compelling need for additional high-quality clinical data.

Conclusion

The delivery of MSCs to the osteoarthritic knee joint has emerged as a potential treatment option. Studies that are well designed with sufficient follow-up report positive outcomes. However, the scientific evidence in support of the efficacy of these treatments is limited and recommendations for clinical application remain variable and inconclusive. There are some global efforts to provide the clinical proof of concept in well-controlled, blinded, RCTs, and it will be necessary for high-quality clinical centres to lead this effort. The ultimate objective is to provide a cell therapy that is proven to be safe and effective, enhances repair and regenerates articular cartilage, and prevents or delays the onset of knee pain and OA.

Disclosure Statement

The authors have no disclosures.

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