stem cell research&therapy

REVIEW

Mesenchymal stem cells for cartilage repair in osteoarthritis

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Abstract

Osteoarthritis (OA) is a degenerative disease of the connective tissue and progresses with age in the older population or develops in young athletes following sports-related injury. The articular cartilage is especially vulnerable to damage and has poor potential for regeneration because of the absence of vasculature within the tissue. Normal load-bearing capacity and biomechanical properties of thinning cartilage are severely compromised during the course of disease progression. Although surgical and pharmaceutical interventions are currently available for treating OA, restoration of normal cartilage function has been difficult to achieve. Since the tissue is composed primarily of chondrocytes distributed in a specialized extracellular matrix bed, bone marrow stromal cells (BMSCs), also known as bone marrow-derived 'mesenchymal stem cells' or 'mesenchymal stromal cells', with inherent chondrogenic differentiation potential appear to be ideally suited for therapeutic use in cartilage regeneration. BMSCs can be easily isolated and massively expanded in culture in an undifferentiated state for therapeutic use. Owing to their potential to modulate local microenvironment via anti-inflammatory and immunosuppressive functions, BMSCs have an additional advantage for allogeneic application. Moreover, by secreting various bioactive soluble factors, BMSCs can protect the cartilage from further tissue destruction and facilitate regeneration of the remaining progenitor cells *in situ*. This review broadly describes the advances made during the last several years in BMSCs and their therapeutic potential for repairing cartilage damage in OA.

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Introduction

The knee joint is a marvel of engineering that acts as a conduit for transferring the weight of the body and also enables sophisticated movements that are essential for normal human mobility. Normal joint movements depend upon the anatomical structures of the tissue. This also helps perfoming physiological functions that the joint cartilage and synovial membrane carry out to enable smooth functioning of the tissue. The cartilage is a highly specialized structure that is composed predominantly of extracellular matrix (ECM) and an aggregate-forming proteoglycan, aggrecan, with embedded chondrocytes [1]. The main structural feature contributing to the whitish glassy appearance of the tissue is due to the ECM known as hyaline cartilage [2]. The ECM is composed of a dense framework of collagen fibers of mainly type II with small amounts of other subtypes of collagen. This unique biomechanical and structural composition of cartilage enables the tissue to balance its mechanical sturdiness and flexibility that are essential for normal tissue function.

Osteoarthritis (OA) has a direct effect on the functioning of several joints, of which the knee is the most important clinically. It has been estimated that all individuals above the age of 65 will have some clinical or radiographic evidence of OA. The basic pathophysiological feature of OA is a loss of articular cartilage, although multiple components of the joint, including bone and synovial membrane, may also be affected [3]. The chondrocyte, which is the principal cellular component of the cartilage, is a relatively inert cell and has little regenerative capacity. While some regeneration does take place in childhood, this ability is lost with age and is almost completely absent after 60 years or more. In addition, complex molecular mechanisms, including the secretion of proteolytic enzymes, further degrade the diseased cartilage. These enzymes include aggrecanases and metalloproteineases and are mediated by interleukin 1 as well as by tumor necrosis factor-alpha [4]. Figure 1 describes the major pathological and biochemical features that ultimately lead to OA.

Current treatment for osteoarthritis

Mild cases of OA can be treated with a combination of non-pharmacologic (for example, physiotherapy) and

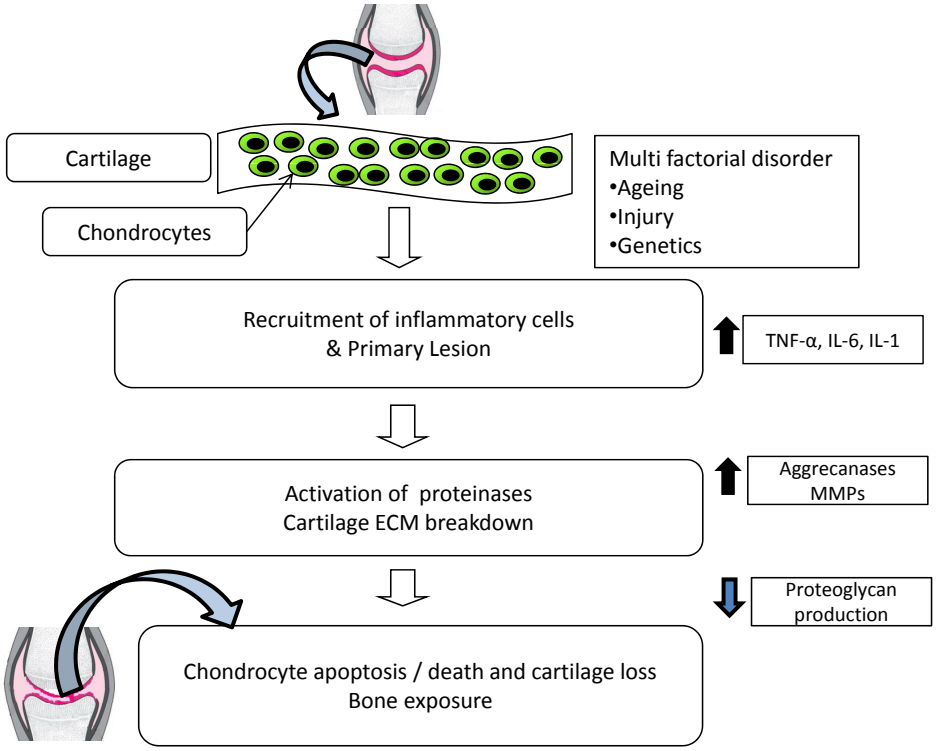

Figure 1. Pathogenesis of osteoarthritis. Osteoarthritis is a progressively degenerative disease of multiple etiology in which injury and aging lead to gradual breakdown of articular cartilage. The pathogenesis is categorized by severe inflammation, recruitment of inflammatory cells, proinflammatory cytokine production, and activation of proteinases that results in extracellular matrix (ECM) degradation and ultimately apoptotic cell death of differentiated chondrocytes. IL, interleukin; MMP, matrix metalloproteinase; TNF-α, tumor necrosis factor-alpha.

pharmacologic agents to reduce pain and inflammation. However, as the disease progresses, additional aggressive treatments are required and these may include the use of intra-articular steroids (Hycort) or hyaluronic acid (Hyalgan) administration [4]. Although some patients experience temporary relief, the efficacy of these interventions is not uniform and there is some debate about their effectiveness. In more advanced or severe cases of OA, knee replacement is the only viable therapeutic option [5].

It has been suggested that many of the mechanisms that cause the symptoms and pathophysiology of OA can be reversed by the application of cell-based therapies [6]. The use of cultured autologous chondrocytes for cartilage regeneration has been used successfully for over a decade [7,8]. However, this technique necessitates cartilage biopsy, which is an invasive procedure, and the early promise of this technique has not been borne out in carefully conducted clinical trials. In addition, chondrocytes obtained from the donor site have been shown to de-differentiate during culture expansion with concomitant downregulation of cartilage-specific genes and limited life span following transplantation [9]. This has left the field open to other therapies and the most promising of these are bone marrow stromal cells (BMSCs) to repair the damaged tissue.

Mesenchymal stem cells and chrondrogenesis

Several varieties of stem cells, including BMSCs in particular, have been shown to differentiate in the presence of appropriate growth stimuli, along specific pathways for producing cartilage tissue. Mesenchymal stem cells (MSCs) have been isolated first from the bone marrow [10] and subsequently from a variety of other tissues such as adipose tissue, placenta, umbilical cord and cord blood, dental pulp, and amnion. However, the ability of MSCs isolated from these tissues to form cartilage is currently being examined rigorously [11]. MSCs or MSC-like cells are believed to replace cells lost due to aging or tissue injury. MSCs are usually isolated by their plastic adherence property and can be expanded in large-scale culture for clinical use. Although no specific marker has been identified to isolate the MSC population, the International Society of Cell Therapy has defined these cells to be positive for stromal cell markers CD73, CD105, and CD90 and negative for hematopoietic

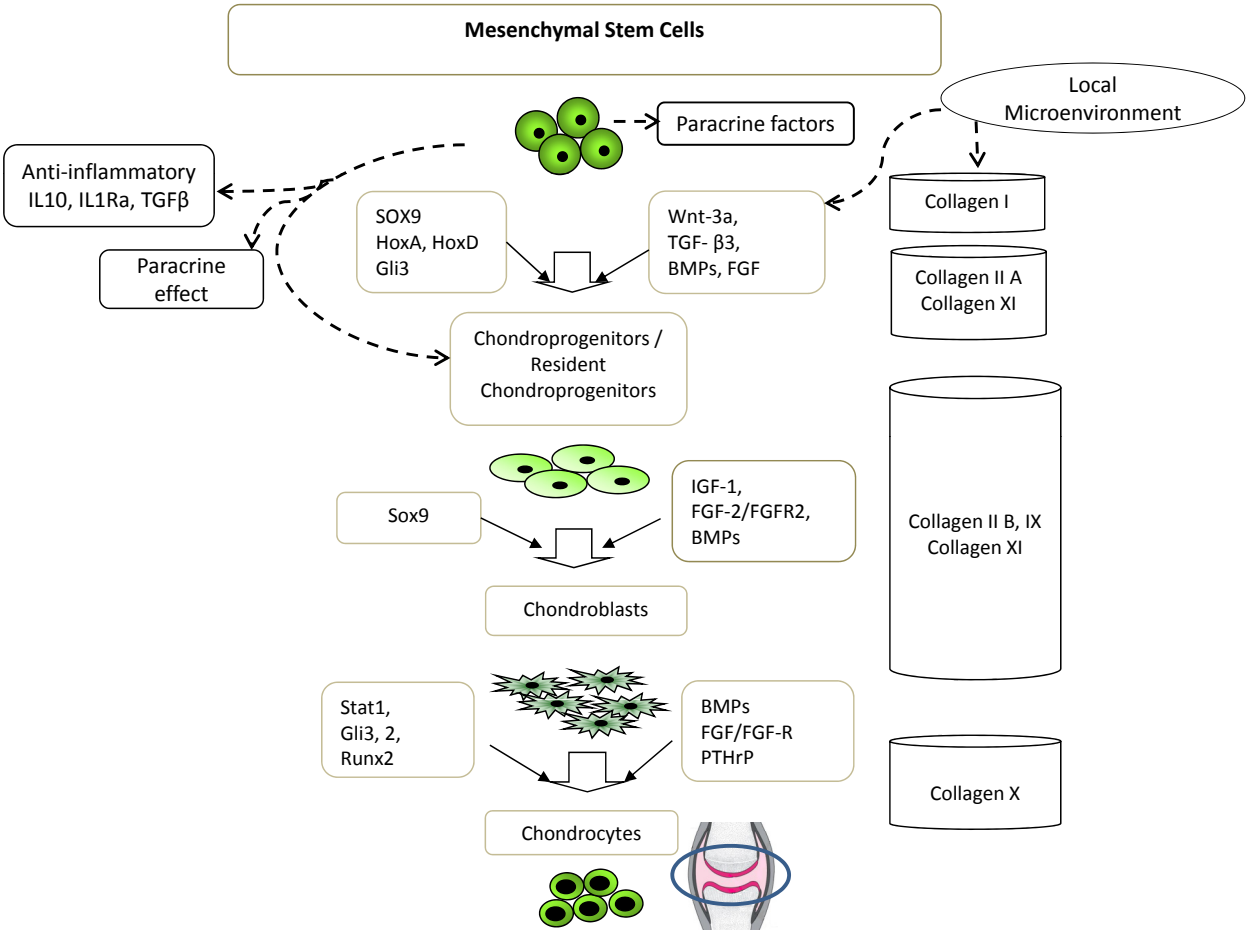

Figure 2. Possible mechanisms operative in cartilage regeneration by mesenchymal stem cells. The anti-inflammatory and immunosuppressive properties of bone marrow stromal cells (BMSCs) ensure that these cells can reduce inflammation in the knee. Concurrently, BMSCs may initiate the repair process by differentiating into chondrocytes or by inducing proliferation and differentiation of the remaining healthy chondroprogenitos into mature chondrocytes or both. A whole host of transcription factors, biological modulators, and extracellular matrix proteins expressed or produced by BMSCs may play a pivotal role in enhancing neocartilage formation. The various factors implicated for cartilage tissue synthesis are depicted in this figure. BMP, bone morphogenic protein; FGF, fibroblast growth factor; Gli3, gliobastoma transcription factor 1; HoxA, homeobox protein A; IGF-1, insulin-like growth factor 1; IL, interleukin; PTHrP, parathyroid hormone-related protein; Runx2, Runt related transcription factor 2; SOX9, SRY (sex determining region Y)-box 9 gene; STAT 1, signal tranducers and activators of transcription factor 1; TGF-β, transforming growth factor-beta.

markers (CD45, CD34, CD14, CD19, CD11b, and HLA-DR) [12]. The lack of a specific marker to identify MSCs has made it difficult to categorically determine the similarities or differences between the biological properties of these cells isolated from various tissue types. Interestingly, BMSCs have been shown to possess several unique biological properties that are potentially beneficial for their use in both autologous and allogeneic cell therapy. Their intrinsic self-renewing ability and differentiation potential into chondrocytes, adipocytes, and osteocytes have been well documented [13,14].

Chondrogenic differentiation of BMSCs is a complex interactive network between transcriptional factors, extracellular growth factors, and signal transduction pathways [15,16] (Figure 2). The intrinsic chondrogenic differentiation potential of BMSCs is believed to be controlled by transcription factors sox-9 and runx-2, whereas transforming growth factor (TGF), like TGF-β3, as well as bone morphogenic proteins are some of the most potent inducers of BMSC chondrogenesis [17,18]. Recently, Weiss and colleagues [19] showed that parathyroid hormone-like peptide and basic fibroblast growth factor play a critical role in regulating terminal differentiation of BMSCs by suppressing collagen X while maintaining the expression of other matrix protein, thus preventing hypertrophic differentiation of BMSCs by *in vitro* pellet cultures. A comparative study using MSCs obtained from various tissue sources reported that

synovium-derived MSCs exhibited maximum chondrogenesis potential followed by bone marrow-derived MSCs [20]. These results suggest that bone marrow-derived MSCs can be used as a cell source for cartilage repair, although the mechanism of hypertrophic differentiation of MSC-derived cartilaginous structures to bone after transplantation remains to be elucidated [19].

MSCs isolated from bone marrow and adipose tissue and loaded on a three-dimensional scaffold under appropriate differentiation cues can acquire chondrogenic phenotype, and the resulting construct can be used as replacement tissue for cartilage repair [21-25]. Several comparative studies have shown that the quality of cartilage produced by using bone marrow-derived stromal cells is substantially lower than that obtained by using chondrocytes. In a recent study, micron-sized fibers, produced by the electro-spinning technique, were shown to provide a structure and properties comparable to those of the cartilage ECM and to enhance chondrogenesis of BMSCs [26]. Researchers are also making efforts to improve scaffolds by combining BMSCs with several biomaterials such as poly-lactic-co-glycolic acid sponge and fibrin gel along with TGF-β1 with satisfactory results [27]. In another study, investigators used human MSCs incubated *in vitro* with TGF-β3-releasing fibronectin-coated pharmacologically active microcarriers (PAMs) in chondrogenic medium, and these cells firmly adhered to the surface of PAMs and rapidly form cell aggregates [28]. After three weeks, strong upregulation of cartilage-specific markers was observed at both the mRNA and protein levels, whereas osteogenic or adipogenic genes could not be detected. These results provide new insight into chondrocyte differentiation of BMSCs in the presence of appropriate biomaterials and chondrogenic factors that require *in vivo* experimentation for cartilage regeneration.

Biology of mesenchymal stem cells

In addition to having multi-lineage differentiation capacity, multi-potent stromal cells obtained from bone marrow and other tissues possess several properties that are unique to these cells in order to bring about tissue regeneration. In particular, BMSCs are known to preferentially home and accumulate to the site of injury and inflammation. The SDF1/CXCR pathway is a key regulator for BMSC migration, and, in the absence of SDF1 signal, migration of these cells to the bone tissue has been found to be impaired [29,30]. These cells are also known to secrete a large number of growth factors, cytokines, and chemokines that carry out different functions. This paracrine activity of MSCs obtained from various sources is thought to be one of the major means by which these cells mediate anti-inflammatory, anti-apoptotic, anti-fibrotic, angiogenic, mitogenic, and wound-healing properties [31]. The complex interplay of some of these biological mediators secreted by MSCs has been shown to be important in regulating regeneration of a variety of damaged or diseased organs of the body, although complete clarity with respect to the secretome profile of MSCs obtained from different tissues and their specific functions still requires extensive investigations [32].

Immunomodulatory properties of mesenchymal stem cells

One of the key characteristics of MSCs, regardless of the organs from which they are isolated, is that these cells are generally hypoimmunogenic and possess immunosuppressive activity, although the mechanism of immunomodulation may not be same between different types of MSCs. As a result, use of MSCs for allogeneic therapy does not require HLA matching [33]. Allogeneic cell therapy often calls for using traditional immunosuppressive medications, but this may not be the case for MSC transplantation. The basis of their hypo- or non-immunogenic nature is that MSCs express low to intermediate levels of HLA class I antigens and are negative for cell surface expression of HLA class II molecules [33]. Upon treatment with interferon-gamma, BMSCs express HLA class II antigens on the surface; however, this expression was not found to alter the immunomodulatory activity of these cells [34]. In addition, BMSCs have been shown to be negative for co-stimulatory molecules that are required for alloreactive T-cell stimulation [33,35]. More importantly, chondrocytes, adipocytes, and osteocytes differentiated from human BMSCs have also been shown to be non-immunogenic in nature [33]. Collectively, these results suggest that BMSCs could be used as off-the-shelf product for allogeneic application for cartilage repair.

Preclinical efficacy of mesenchymal stem cells in cartilage regeneration

The effect of MSC transplantation has also been shown to be effective for cartilage repair in various preclinical models of OA. In an elegant study by Murphy and colleagues [36], autologous BMSCs were suspended in hyaluronan solution and injected intra-articularly in goats in which OA was induced by surgery. Although injected labeled BMSCs were not found in large numbers in the cartilage area, regeneration of the tissue was clearly evident in animals receiving cells in comparison with the control group. Similarly, undifferentiated BMSCs or pre-differentiated BMSCs on scaffolds yielded encouraging results in rabbit [37] and sheep [38] models of OA. From these studies, it appears that BMSCs alone or MSCs embedded on biodegradable scaffold have the potential to be therapeutically effective for degenerative diseases, including OA.

Bone marrow stromal cell-based therapy for cartilage repair

Several clinical investigators from various parts of the world have reported on the safety and therapeutic effect of BMSC administration in patients with OA (Table 1). Nejadnik and colleagues [39] conducted a study to compare the clinical outcome of patients treated with first-generation autologous chondrocyte implantation (n = 36) with that of patients treated with autologous BMSCs (n = 36). The clinical outcome was measured before and at various time points after operation by using the International Cartilage Repair Society Cartilage Injury Evaluation Package. There was significant improvement in the patients' quality of life after cartilage repair in both groups. However, there was no difference between the BMSCs and the autologous chondrocyte implantation groups in terms of clinical outcome except for physical role functioning, and a greater improvement over time in the BMSC group was observed. The improvement in clinical symptoms observed after cartilage repair using BMSCs in the clinical trial by Nejadnik and colleagues [39] is in agreement with clinical outcomes of earlier studies in which clinical symptoms were reported to have improved and repair of cartilage was detected by histopathological evaluation and magnetic resonance imaging (MRI) techniques [40,41]. In fact, Wakitani and colleagues [41] showed that the defect in one patient had been repaired with fibrocartilaginous tissue after 12 months of cell transplantation. The MRI result obtained from another patient after 12 months revealed complete coverage of the defect, although the nature of the cartiliganeous tissue was not determined. In a separate study, Haleem and colleagues [42] reported that autologous BMSCs placed on platelet-rich fibrin glue when administered into the knee of patients with OA resulted in complete defect fill and surface congruity with the native cartilage in one patient whereas the other two patients showed incomplete congruity. Similarly, Kasemkijwattana and colleagues [43] showed improvement in cartilage regrowth in two BMSC-transplanted patients by arthroscopic assessment, which was accompanied with functional recovery. Studies published by other investigators also demonstrated reduction in pain [44] and some improvement in femoral cartilage volume [45], albeit in a smaller number of patients.

In a phase I/II trial conducted by Osiris Therapeutics, Inc. (Columbia, MD, USA), intra-articular administration of allogeneic BMSCs in patients with OA significantly reduced pain in comparison with the placebo group. This effect was observed in patients receiving a low dose (50 million cells) as well as in patients receiving a high dose (150 million cells) [46]. A recent presentation made by the same group demonstrated consistency in the pain score of BMSC-treated patients two years after the cell administration [47]. However, MRI examination of the treated knee revealed wide variability in the meniscus volume between the cell-treated and the control groups of patients. Thus, it is clearly evident that administration of autologous or allogeneic BMSCs into the knee of patients with OA is safe and efficacious as far as the pain reduction is concerned, with improvement in articular cartilage regeneration and physical function. It is noteworthy that a clinical study conducted with adipose tissue-derived stem cells along with a low dose of dexamethasone also showed encouraging results in regard to cartilage regeneration and reduced pain score in patients with OA [48].

In a search of the ClinicalTrials.gov website [49] in which the keywords 'osteoarthritis' and 'mesenchymal stem cells' were used, 16 clinical trials in OA could be shortlisted; 14 of these are using either autologous or allogeneic BMSCs, and the remaining two trials are investigating the effect of adipose tissue-derived and umbilical cord blood-derived MSCs. The various investigative parameters of these clinical trials are also summarized in Table 1.

Recently, we initiated two randomized, double-blinded, multi-center, placebo-controlled, dose-finding studies assessing the safety and efficacy of *ex vivo*-cultured allogeneic BMSCs following intra-articular administration in patients with OA. Our previous clinical data from the same product demonstrated safety of allogeneic BMSCs in patients with critical limb ischemia and acute myocardial infarction (Gupta and colleagues, manuscript in preparation). Considering our safety data and the published clinical trials conducted in OA, we are performing dose-ranging clinical trials in India (NCT01453738) and Malaysia (NCT01448434), where OA is highly prevalent among older men and women. The study in India is being conducted by using four different doses (25, 50, 75, and 150 million) of allogeneic BMSCs, whereas the Malaysia trial involves two doses of cells (25 and 50 million). The patients will be followed up for a total of two years by using different efficacy parameters such as WOMAC (Western Ontario and McMaster Universities) Osteoarthritis Index, ICOAP (Intermittent and Constant Osteoarthritis Pain) score, Visual Analogue Score, and radiological evidence of improvement by both x-ray and MRI of affected knee joints. Results obtained from our study as well as from the clinical trials being conducted elsewhere may conclusively determine the efficacy and safety of using BMSCs for the regeneration of cartilage in patients with OA.

Conclusions

Several important characteristics of BMSCs make them an attractive population of cells for cartilage repair. In particular, BMSCs have been shown to migrate and

Table 1. Summary of clinical studies conducted using bone marrow-derived mesenchymal stem cells in patients with osteoarthritis

Study number	Authors or institution	Number of subjects	Type of study	Cell type and dose used	Efficacy parameters	Outcome	Duration of follow-up	Reference or Clinical-Trials. gov identifier
1	Kuroda *et al.*, 2007 [40]	1	Case report	Autologous BM-MSCs + collagen gel	Arthroscopy and HPE	Defect filled with hyaline-like type of cartilage tissue	1 year	[40]
2	Wakitani *et al.*, 2007 [41]	3	Case series	Autologous BM-MSCs (5 million) + collagen sheet	HPE and MRI	Histology: defect repaired with fibrocartilaginous tissue MRI: complete coverage of defect	1 year	[41]
3	Osiris Therapeutics, Inc. (Columbia, MD, USA), 2007	55	Randomized double-blind	Allogeneic BM-MSCs (50 and 150 million)	VAS pain score and MRI	VAS: Significantly reduced pain MRI: Decreased degenerative bone changes	2 years	[46,47]
4	Centeno *et al.*, 2008 [45]	1	IRB-approved study	Autologous BM-MSCs (22.4 million) + 1 mL of nucleated cells + 1 mL of 10% platelets	VAS pain score and MRI knee joint	Decreased VAS score MRI: increase in meniscus and femoral cartilage volume	24 weeks	[45]
5	Nejadnik *et al.*, 2010 [39]	72	Observational cohort study	Autologous BM-MSCs: n = 36; Chondrocytes: n = 36	ICRS Cartilage Injury Evaluation Package	Improvement in physical role functioning in BM-MSCs	2 years	[39]
6	Davatchi *et al.*, 2011 [44]	4	IRB-approved study	Autologous BM-MSCs (8 to 9 million)	Walking time for the pain to appear and VAS pain score	Walking time for pain improved in 3 patients VAS decreased in all patients	1 year	[44]
7	Haleem *et al.*, 2012 [42]	5	Case series	Autogous BMSCs placed on platelet-rich fibrin glue	RHSSK scores and MRI	Improvement in RHSSK score and subjective symptoms MRI: complete defect fill and complete surface congruity with native cartilage	1 year	[42]
8	Kasemkijwattana *et al.*, 2011 [43]	2	Case report	Autologous BMSCs (12 million)	KOOS, IKDC score, and arthroscopy	Improvements in KOOS and IKDC score Arthroscopy: Good defect fill, stiffness, and incorporation to the adjacent cartilage	30-31 months	[43]
9	National University of Malaysia/ Cytopeutics (Malaysia)	50	Randomized controlled	Autologous BMSCs	VAS, IKDC Subjective Knee Evaluation Form, and x-ray	NA	1 year	NCT01459640
10	Royan Institute (Tehran, Iran)	40	Randomized triple-blinded	Autologous BMSCs	WOMAC, VAS, and MRI	NA	6 months	NCT01504464
11	Red de Terapia Celular (Barcelona, Spain)	12	Non-randomized open-label	Autologous BMSCs (40 million)	VAS, Oswestry disability index, and SF-36 life quality	NA	2 years	NCT01183728

Continued overleaf

Table 1. Continued

Study number	Authors or institution	Number of subjects	Type of study	Cell type and dose used	Efficacy parameters	Outcome	Duration of follow-up	Reference or Clinical-Trials. gov identifier
12	Royan Institute (Tehran, Iran)	6	Non-randomized open-label	BMSCs	WOMAC, VAS, SF-36, and MRI	NA	1 year	NCT01207661
13	Royan Institute (Tehran, Iran)	6	Non-randomized open-label	Autologous BMSCs	VAS, WOMAC, x-ray, and MRI	NA	6 months	NCT01436058
14	Royan Institute (Tehran, Iran)	6	Non-randomized open-label	Autologous BMSCs	VAS, WOMAC, Harris Hip Score questionnaire , x-ray, and MRI	NA	6 months	NCT01500811
15	Stempeutics Research (Bangalore, India)	60	Randomized double-blind	Allogeneic BMSCs (25, 50, 75, and 150 million)	VAS, WOMAC, ICOAP, x-ray, and MRI	NA	2 years	NCT01453738
16	University of Marseille (Marseille, France)	50	Open-label	Autologous BMSCs	IKS and ICRS	NA	1 year	NCT01159899
17	Stempeutics Research Malaysia Sdn. Bhd (Malaysia)	72	Randomized double-blind	Allogeneic BMSCs (25 and 50 million)	VAS, WOMAC, ICOAP, x-ray, and MRI	NA	2 years	NCT01448434
18	Cairo University (Egypt)	25	Open-label	Autologous BMSCs	Clinical scoring, x-ray, and MRI	NA	1 year	NCT00891501
19	Royan Institute	6	Open-label	Autologous BMSCs	Pain, knee cartilage defects	NA	1 year	NCT00850187
20	Banc de Sang i Teixits (Barcelona, Spain)	15	Open-label	Autologous BMSCs (40 million)	VAS, HAQ, SF-36, and MRI	NA	1 year	NCT01227694
21	Mesoblast (Melbourne, Australia)	24	Randomized double-blind	MSB-CAR001	VAS, KOOS, SF-36, x-ray, and MRI	NA	2 years	NCT01088191

BM-MSC, bone marrow-derived mesenchymal stem cell; BMSC, bone marrow stromal cell; HAQ, Health Assessment Questionnaire; HPE, histopathological evaluation; ICOAP, Intermittent and Constant Osteoarthritis Pain; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; IKS, International Knee Score; IRB, institutional review board; KOOS, Knee and Osteoarthritis Outcome Score; MRI, magnetic resonance imaging; NA, not applicable; RHSSK, Lysholm and Revised Hospital for Special Surgery Knee; SF-36, Short Form Health Survey-36; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities (Osteoarthritis Index).

engraft onto multiple musculoskeletal tissues, especially at the site of injury, and undergo tissue-specific differentiation. The anti-inflammatory and immunosuppressive properties of BMSCs ensure that these cells can be used in the context of allogeneic transplantation. Both autologus and allogeneic cell-based therapies using BMSCs for cartilage repair have been shown to produce acceptable clinical results. Although the exact mechanism by which BMSCs are expected to regenerate articular cartilage in patients with OA is not clear, the ability of these cells to induce proliferation and differentiation of resident progenitor cells or their innate differentiation potential to chondrocytes may aid the regeneration of the damaged cartilage. It is also plausible that the combination of paracrine activity and differentiation ability of BMSCs may be operative *in vivo* to bring about the desired changes in neocartilage formation. Carefully planned clinical trials using BMSCs obtained from patients (autologous) and from normal healthy volunteers (allogeneic) may shed valuable insight into the curative properties and long-term sustenance of these cells in the local microenvironment. Undoubtedly, a great deal of progress is required at both basic and clinical research fronts before these cells can be used routinely in the clinic for treating patients with OA.

This article is part of a thematic series on *Clinical applications of stem cells* edited by Mahendra Rao. Other articles in the series can be found online at http://stemcellres.com/series/clinical

Abbreviations

BMSC, bone marrow stromal cell; ECM, extracellular matrix; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; OA, osteoarthritis; PAM, pharmacologically active microcarrier; TGF, transforming growth factor.

Competing interests

All authors are employees of Stempeutics Research, and some hold stock options.

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