

Mesenchymal stem cell therapy for osteoarthritis: current perspectives

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Abstract: Osteoarthritis (OA) is a painful chronic condition with a significant impact on quality of life. The societal burden imposed by OA is increasing in parallel with the aging population; however, no therapies have demonstrated efficacy in preventing the progression of this degenerative joint disease. Current mainstays of therapy include activity modification, conservative pain management strategies, weight loss, and if necessary, replacement of the affected joint. Mesenchymal stem cells (MSCs) are a multipotent endogenous population of progenitors capable of differentiation to musculoskeletal tissues. MSCs have a well-documented immunomodulatory role, managing the inflammatory response primarily through paracrine signaling. Given these properties, MSCs have been proposed as a potential regenerative cell therapy source for patients with OA. Research efforts are focused on determining the ideal source for derivation, as MSCs are native to several tissues. Furthermore, optimizing the mode of delivery remains a challenge both for appropriate localization of MSCs and for directed guidance toward stemming the local inflammatory process and initiating a regenerative response. Scaffolds and matrices with growth factor adjuvants may prove critical in this effort. The purpose of this review is to summarize the current state of MSC-based therapeutics for OA and discuss potential barriers that must be overcome for successful implementation of cell-based therapy as a routine treatment strategy in orthopedics.

Keywords: mesenchymal stem cell, osteoarthritis, treatment, regenerative medicine, cell therapy

Introduction

Among the various forms of degenerative joint disease, osteoarthritis (OA) is by far the most common and represents a painful chronic condition that can affect any synovial joint.¹ Disease prevalence is increasing in parallel with an aging population and will impose significant socioeconomic burden over the coming decades.²⁻⁴ Arthritis is the most common source of disability among adults in the United States; in 2003, the disease afflicted 50 million Americans and this number is expected to increase to 67 million by 2030.^{5,6} The cost attributable to arthritis in the United States in 2003 was \$128 billion, a figure that will certainly increase in conjunction with health care cost inflation and the number of patients projected to be afflicted with degenerative joint disease.⁶ Complicating this reality are the limited treatment options for OA. No pharmaceutical or non-operative therapies have demonstrated unequivocal efficacy in reversing or halting disease progression, restricting therapy to long-term management of exacerbating factors and pain control.⁷ Surgical options such as osteotomies exist for improving alignment and decreasing risk of OA when mechanical deformity

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is present; however, these procedures have limited benefit once significant degenerative changes have taken place.⁸ Surgical intervention can also be pursued for focal articular cartilage lesions with techniques such as microfracture, osteochondral grafts, or chondrocyte implantation that may be accompanied by scaffolds or matrices.^{9–15} Despite advances in these procedures, they cannot be applied to more extensive damage in the joint secondary to OA. In the absence of effective strategies, the search for disease-modifying treatments continues.

Mesenchymal stem cells (MSCs) have been proposed as an optimal regenerative cellular therapeutic for degenerative musculoskeletal conditions like OA.¹⁶ These cells are found in a variety of tissues and have the ability to rapidly proliferate and differentiate to musculoskeletal lineages including bone and cartilage.¹⁷ A significant body of research has also demonstrated that these cells orchestrate important immunologic functions through modulation of the local inflammatory response.¹⁸ Taken together, these factors support the theoretical ability of MSCs to deter degenerative joint disease. Research efforts have focused on defining the ideal source for MSC derivation, as this cytotype exists in a broad array of tissues.¹⁹ Optimizing appropriate localization of MSCs in tandem with the use of scaffolds and matrices to maximize regenerative potency and local immunomodulatory impact are critical challenges in this effort.

The purpose of this review is to summarize the current state-of-the-art in MSC-based therapeutic efforts to treat OA with a look ahead toward obstacles impeding successful implementation as a routine treatment strategy.

Current treatment approach to patients with OA – an unmet need

Treating patients with OA presents a significant challenge for physicians as no therapies to date have demonstrated efficacy in curing or even halting disease progression. Therefore, most approaches initially target pain management and factors that may be exacerbating stress on the joint. Conservatively, this involves weight loss, modifying painful activities, initiating a program of low-impact exercise and stretching, the use of braces or gait aids, and over the counter analgesic medications or creams.⁷ Modalities from alternative and complementary medicine are often pursued by many patients as well.²⁰

When these first-line strategies fail, a trial of corticosteroid injections may be pursued. Current guidelines suggest a maximum of four injections per joint per year.²¹ Efficacy of these agents is highly variable between patients and the period

of relief afforded by corticosteroids tends to shorten with each subsequent administration.²² Furthermore, injected corticosteroids have known toxicity to both chondrocytes and MSCs, thus potentiating OA progression in exchange for temporary pain relief.^{23–25} However, the degree of toxicity differs with respect to the specific formulation.²⁵ Elective surgery on the joint receiving a corticosteroid injection is recommended to be delayed at least 8–12 weeks as wound healing is temporarily impaired.²¹ If corticosteroid injections fail to provide relief, then injectable hyaluronic acid preparations may be pursued, although there is conflicting evidence as to patient improvements with regard to pain or function.²⁶

The ultimate solution for OA refractory to all other modalities is total joint replacement with artificial prosthetics. These procedures are most commonly and successfully applied to the hip, knee, and shoulder joints; however, options are expanding in many other joints including the elbow, ankle, and at multiple locations in the hand.^{27–29} Total joint replacement represents some of the most successful procedures ever devised in modern medicine. Despite these advances, complications still exist, prosthetic joints cannot match the functionality of a native joint, and access to these procedures falls well short of demand.^{3,4} Clearly, there is a substantial unmet need for this chronic disease that would benefit greatly from disease-modifying therapy.

MSC tissue sources, physiology, and function

MSCs have been proposed by many as an optimal regenerative cellular therapeutic for musculoskeletal regeneration, especially in the setting of degenerative pathology like OA.^{30,31} Defining characteristics include the ability to rapidly proliferate and differentiate to tissues of mesenchymal lineage including bone, cartilage, and adipose in conjunction with the presence of typical surface markers.¹⁷ The proliferative capacity, differentiation potential, and surface marker profile differ based on the tissue of origin.^{17–19,32–37} MSCs have been isolated from a variety of tissues, with primary interest for treating OA being generated from either the bone marrow or adipose tissue (Figure 1).^{16,37–39}

MSCs seem to provide critical advantages over chondrocytes when considering treatment of degenerative conditions like OA. First, they are much easier to culture and expand *ex vivo*.¹⁷ Proliferation is more rapid and they maintain their phenotype to a greater degree during this process. Furthermore, chondrocytes are terminally differentiated, whereas MSCs can specialize to all tissues within the joint. Theoretically, this enables them to repair lesions restricted

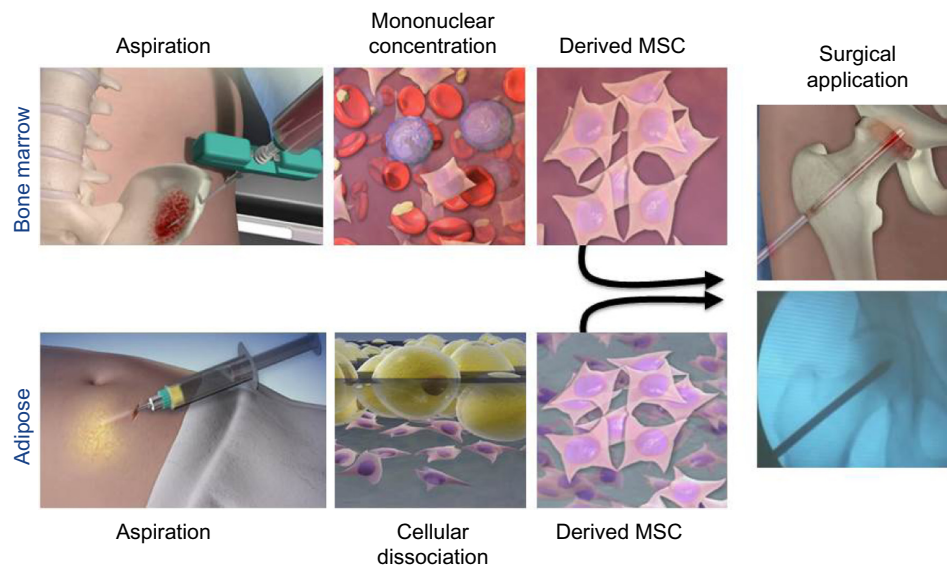


Figure 1 Techniques for derivation and surgical application of bone marrow- and adipose-derived MSCs. Following extraction of either bone marrow (top row) or adipose tissue (bottom row), MSCs can be isolated and subsequently transplanted (black arrows) to musculoskeletal tissues in need of regeneration.

Abbreviation: MSCs, mesenchymal stem cells.

to articular cartilage or more complex osteochondral lesions and even tendons or ligaments.¹⁸

Although MSCs provide an ideal source for direct regeneration of joint surfaces, a recent and increasing body of research is beginning to suggest that the primary benefit of these cells is derived from their paracrine activities.³⁰ Regeneration of joint tissues has been documented after injection of MSCs; however, some studies have found that reconstitution of tissue is primarily from native cells and relatively few transplanted cells.⁴⁰ Other studies have shown that the cell signaling milieu is altered after administration of MSCs with subsequent increase in Type II collagen production by the host.⁴¹ Together, these factors suggest that MSCs may be orchestrating the reparative response rather than directly replacing damaged areas. This is in line with the well-documented anti-inflammatory and immunomodulatory role of MSCs.¹⁸

MSC derangements in OA and related conditions

Select findings raise suspicion that systemic depletion and derangement of MSCs may contribute to OA pathophysiology. MSCs from patients with OA can be decreased in number with concomitant impairment of proliferation and differentiation capacity.⁴² Specifically, depressed chondrogenesis and adipogenesis with increased osteogenesis are typical in OA patients. The majority of this work has been performed in bone marrow-derived MSCs, yet similar results have been documented from a variety of tissue sources suggesting a systemic nature to the changes.⁴²

MSC alterations seem to be involved in disease-specific pathology. Decreased chondrogenesis and increased osteogenesis in OA could be potentiating loss and/or lack of replacement of articular cartilage with subsequent production of osteophytes. Functional MSC changes have also been documented in osteoporosis and osteonecrosis.^{43–46} For osteonecrosis, the differentiation profile demonstrates maintained MSC chondrogenesis and adipogenesis with decreased osteogenesis, the inverse of what has been observed in OA (unpublished data). Decreased osteogenesis in osteonecrosis could represent a failure to reconstitute the failing tissue, in this case bone. Thus in both OA and osteonecrosis, a plausible explanation can be made for disease pathophysiology through correlation with specific alterations present in MSC capability. Although MSC dysfunction appears to be systemic in these degenerative musculoskeletal conditions, bone marrow may be impacted to the greatest degree. Studies from OA and osteonecrosis patients have shown the most prominent impact on bone marrow-derived MSCs, with adipose-derived MSCs maintaining a greater level of functionality.⁴⁷ This observation may be secondary to the intense physiologic stress of the bone marrow microenvironment relative to comparatively quiescent adipose tissue. Differential dysfunction of MSCs by disease and tissue source has important implications for therapeutic implementation of cell transplantation therapies.

Evidence from preclinical models

Foundational work was performed by Murphy et al in a goat model of post-traumatic OA.⁴⁰ They resected the anterior

cruciate ligament and medial meniscus, leading to articular degeneration and osteophyte formation. Joints that received subsequent injection of autologous MSCs showed improvement compared with control joints via meniscal and cartilage regeneration. Interestingly, transplanted MSCs were primarily localized to synovial and meniscal surfaces, suggesting that they served an orchestrative role as opposed to supplying the direct building blocks of regeneration. Similar outcomes with injected MSCs preserving joint integrity have been demonstrated in a variety of knee OA models including horse, sheep, rat, mouse, rabbit, and guinea pig.^{41,48–53} Specifically in the rat model documented by Horie et al, MSCs demonstrated upregulated expression of bone morphogenetic protein 2, parathyroid hormone-like hormone, and Indian hedgehog, which subsequently increased Type II collagen production in the native joint tissue.⁴¹ This gives further credence to the theory of MSC governance of regeneration through paracrine stimulation of the local microenvironment.

Evidence from human trials

Proof-of-concept evidence from preclinical studies has led to the genesis of multiple clinical trials.⁵⁴ Much of this work remains in nascent stages; however, in 2015, clinicaltrials.gov documents 14 open clinical trials addressing OA with MSCs (Table 1).^{55–68} Most studies utilize autologous bone marrow- or adipose-derived MSCs. Some incorporate same-day harvesting and transplantation procedures with autologous bone marrow concentrate or stromal vascular fraction, the latter being a known source of adipose-derived MSCs.⁶⁹ Others employ a two-stage process with harvesting followed by ex vivo expansion prior to transplantation. Approaches with allogenic MSC sources include umbilical cord blood or bone marrow.

Additional key differentiating factors between these ongoing studies are cell dose and vehicle of administration. The number of cells in a single dose is highly variable as indicated in Table 1. Optimal titration will likely be a finding of more advanced-phase clinical trials after initial safety and efficacy are established. Most ongoing clinical trials are delivering the MSCs through direct injection in the absence of a scaffold or matrix; nevertheless, some are using adjuvants such as hyaluronic acid. The reasons for this are primarily twofold – regulatory and philosophical. MSCs, like any cell therapy, are a complex therapeutic. Regulatory barriers to implementation of these biologics are quite stringent, which is only further complicated by multi-component interventions such as MSCs embedded in a biomatrix. Philosophical reasons for scaffold-free injection are rooted in preclinical

evidence suggesting that the more powerful role of MSCs in treating OA rests with orchestration of regeneration as opposed to providing the direct building blocks.

Modes of derivation and delivery for MSCs

Despite preponderance of scaffold-free autologous MSCs in ongoing clinical trials, intense preclinical efforts are being directed toward optimizing derivation and delivery of MSCs. This bears further discussion as development in these areas may shift future trends.³¹ The first issue to consider is donor source. Proponents of autologous products value safety and predictability from the lack of immunogenicity, whereas those on the side of allogenic MSCs argue that young and healthy donors overcome issues related to MSC suppression that may have potentiated disease in the first place.⁷⁰ No clear winner has been determined, yet autologous products are more common likely due to the less cumbersome regulatory issues. MSC tissue source is another area of investigation. Bone marrow, adipose, and umbilical cord blood have been used most commonly, but the wide distribution of these cells has generated interest in other locations such as synovium and periosteum.^{71,72} Bone marrow has been the historic leader and is the most well studied. Some authors have found a trophic advantage with bone marrow-derived MSCs; however, newer evidence stands in contrast to this dogma by suggesting that bone marrow-derived MSCs may be less potent in comparison to MSCs that reside in adipose tissue.^{19,33–35,37,38,50,73–75} Perhaps this is secondary to the physiologic stress and high turnover present in bone marrow compared with adipose, but the exact mechanism is yet to be elucidated.

Regardless of MSC source, physicians and scientists must determine whether single procedure cell transplantation or staged procedure cell transplantation after ex vivo expansion is more desirable. Single procedure techniques are more feasible with bone marrow and adipose. Bone marrow can be aspirated and centrifuged in the operative suite to derive a mononuclear cell concentrate prior to transplantation.⁷⁶ Adipose tissue can similarly be fractionated in the operative suite to derive the stromal vascular fraction prior to transplantation.⁶⁹ Both approaches allow the patient to receive complete treatment in one sitting, with delivery of MSCs admixed with other stromal and parenchymal cellular components from the native tissue bed. By contrast, ex vivo expansion allows for purification and standardization of the cell product.⁷⁷ Quality control is easier to perform with this approach and an exact number of MSCs can be transplanted. However, this technique requires two procedures, and is more

Table 1 Ongoing clinical trials using MSCs for the treatment of osteoarthritis^a

Trial	Sponsor	Phase; stage	Indication	Intervention	Comparator
NCT02365142; ⁵⁵ Treatment of Osteoarthritis by Intraarticular Injection of Bone Marrow Mesenchymal Stem Cells With Platelet Rich Plasma (CMM-PRGF/ART)	Clinica Universidad de Navarra	Phase I/II; recruiting	Knee OA	Intraarticular injection of 100 million ex vivo expanded autologous bmMSCs + three intraarticular injections of autologous PRP	Intraarticular injection of autologous PRP
NCT02237846; ⁵⁶ Clinical Study of Umbilical Cord Tissue Mesenchymal Stem Cells (UC-MSC) for Treatment of Osteoarthritis	Translational Biosciences	Phase I/II; recruiting	Knee OA	Intraarticular injection of allogenic cbMSCs	Three intravenous injections of allogenic cbMSCs
NCT01985633; ⁵⁷ Mesenchymal Stem Cells Enhanced with PRP Versus PRP in OA Knee (MSCPRPOAK)	Postgraduate Institute of Medical Education and Research	Phase I/II; recruiting	Knee OA	Intraarticular injection of 1×10 ⁷ ex vivo expanded autologous bmMSCs + 8–12 mL PRP	Intraarticular injection of 8–12 mL PRP
NCT02291926; ⁵⁸ Human Umbilical Cord Mesenchymal Stem Cell Transplantation in Articular Cartilage Defect	Shenzhen Hornetcorn Biotechnology Company, LTD	Phase I; recruiting	Knee OA	Four monthly intraarticular injections of 2×10 ⁷ ex vivo expanded allogenic cbMSCs	None
NCT01895413; ⁵⁹ Autologous Bone Marrow Mesenchymal Stem Cells Transplantation for Articular Cartilage Defects Repair	Pontificia Universidade Católica do Paraná	Phase I/II; recruiting	Knee OA	Single arthroscopic administration of autologous bmMSCs	None
NCT01739504; ⁶⁰ Autologous Adipose-Derived Stromal Cells Delivered Intracellularly in Patients With Osteoarthritis	Ageless Regenerative Institute	Phase I/II; recruiting	OA	Intraarticular injection of aMSCs + autologous PRP	None
NCT02241408; ⁶¹ Outcomes Data of Adipose Stem Cells to Treat Osteoarthritis	StemGenex	Prospective cohort; recruiting	Knee or Hip OA	Intraarticular and intravenous injection of autologous SVF	None
NCT02118519; ⁶² Mesenchymal Stem Cells in Knee Cartilage Injuries	University of Jordan	Phase II; recruiting	Knee OA	Intraarticular injection of autologous bmMSCs pre-treated with platelet lysate	Intraarticular injection of autologous bmMSCs
NCT01947348; ⁶³ Safety and Clinical Effectiveness of A3 SVF in Osteoarthritis	Institute of Regenerative and Cellular Medicine	Phase I/II; recruiting	OA	Intraarticular and intravenous injection of autologous SVF + autologous PRP	None
NCT01978639; ⁶⁴ Injections of FloGraft Therapy, Autologous Stem Cells, or Platelet Rich Plasma for the Treatment of Degenerative Joint Pain	Arizona Pain Specialists	Prospective cohort; recruiting	OA	Intraarticular injection of autologous bmMSCs	Intraarticular FLOGRAFT [®] injection or intraarticular autologous PRP injection
NCT02351011; ⁶⁵ Human Autologous MSCs for the Treatment of Mid to Late Stage Knee OA	University Health Network, Toronto	Phase I/II; recruiting	Knee OA	Intraarticular injection of ex vivo expanded autologous bmMSCs. Three dose levels: 1×10 ⁶ , 10×10 ⁶ , 50×10 ⁶	None
NCT01953523; ⁶⁶ Safety and Clinical Outcomes Study: SVF Deployment for Orthopedic, Neurologic, Urologic, and Cardio-pulmonary Conditions	Cell Surgical Network Inc.	Phase I; recruiting	OA	Intraarticular injection of autologous SVF	None
NCT02370823; ⁶⁷ A Controlled Surveillance of the Osteoarthritic Knee Microenvironment With Regenexx [®] SD Treatment	Regenerative Sciences, LLC	Prospective cohort; recruiting	Knee OA	Intraarticular injection of autologous BMC	None
NCT01733186; ⁶⁸ Evaluation of Safety and Exploratory Efficacy of CARTISTEM [®] , a Cell Therapy Product for Articular Cartilage Defects	Medipost Co Ltd	Phase I/II; recruiting	Knee OA or focal knee cartilage defect	Intraarticular injection of ex vivo expanded allogenic cbMSCs	None

Note: ^aCurrent as of May 2015.

Abbreviations: OA, osteoarthritis; MSCs, mesenchymal stem cells; aMSCs, adipose-derived MSCs; bmMSCs, bone marrow-derived MSCs; cbMSCs, cord blood-derived MSCs; SVF, stromal vascular fraction; BMC, bone marrow concentrate; PRP, platelet-rich plasma; FLOGRAFT[®], cryopreserved, liquid, injectable amniotic fluid-derived allograft; CARTISTEM[®], allogeneic-unrelated, umbilical cord blood-derived mesenchymal stem cells, ex vivo cultured, combined with sodium hyaluronate.

labor intensive and costly. Furthermore, it carries added concern that hyperproliferation prior to transplantation may alter cell potency and phenotype.⁷⁸

Interest has also been directed toward biocompatible MSC carriers. Myriad scaffolds and biomatrices have been developed to provide a structured vehicle for delivery.⁷⁹ As mentioned previously, regulatory issues have prevented co-administration with MSCs from being more common in clinical studies, but the preclinical literature is rich with biologics in development. Matrices used to date in vivo have combined hydrogels impregnated with MSCs for regeneration of osteochondral defects; however, these studies have been relatively small and have short-term follow-up.^{80,81} Scaffolds offer the potential to more precisely localize MSC delivery and direct their proliferation and differentiation. The ideal carrier would have a variety of properties including, but not limited to the following: biocompatibility and biodegradability timed with tissue healing, gas and nutrient permeability, porous structure to support cell migration, malleability and strength to maintain mechanical integrity in the joint, and be inductive and conductive of osteochondral tissue.³¹ Unfortunately, this combination has remained elusive, but options demonstrating promise include synthetic scaffolds constructed from polymers and hydrogels primarily derived from components native to the joint such as collagen, hyaluronic acid, alginate, and chitosan.³¹ Matrices are also being designed with impregnation of growth factors to optimize the trophic microenvironment. How these biologics are tailored for specific purposes moving forward will largely depend on whether the focus is to potentiate the ability of MSCs to orchestrate regeneration or directly differentiate and replace damaged tissue.

Conclusion

OA is a prevalent chronic degenerative joint disease that will continue to impose an increasing burden on the aging population unless disease-modifying therapies are developed. The current standard of care with risk factor modification, pain management, and joint replacement will be inadequate to meet the needs of society moving forward. MSCs offer a potential regenerative solution given their ability to differentiate to all tissues within a joint and modulate the local inflammatory response. Although these characteristics suggest they provide ideal building blocks to restore damaged joints, a strong body of evidence supports MSC-guided regeneration through paracrine stimulation of native tissue. Further preclinical work will be mandatory to establish the mechanism by which MSCs have demonstrated a proof-of-concept

to heal OA lesions as this will have critical implications for clinical implementation strategies.

Determining the ideal MSC source, processing, and delivery vehicle are further challenges that must be addressed to optimize biologics-based treatment of OA. Bone marrow, adipose, and cord blood offer different advantages as does derivation and application in a single procedure versus staged transplantation after ex vivo expansion. Although scaffold-free injection of MSCs predominates ongoing clinical trials, biomatrices may prove a critical adjuvant as these therapies evolve. In 2015, the translation of MSCs to clinical therapy for OA has been slow; however, signs of progress are evident and ongoing trials may show efficacy to indicate these products can serve as the disease-modifying therapy necessary to stem the tide of OA.

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