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A Review of Mesenchymal Stem Cell Injections for Osteoarthritis

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A review of mesenchymal stem cell injections for osteoarthritis

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Abstract

Mesenchymal stem cell (MSC) injections for osteoarthritis is reviewed.

Methods

PubMed search was conducted to identify articles in English from 2003-2018 that used intra-articular injection (IA), cartilage repair, cartilage regeneration, chondral injury, adipose stem cells, bone marrow stem cells, mesenchymal stem cells, or autologous stem cells.

Results

388 patients receiving IA MSC injections are discussed with data obtained from 10 case reports or case series, 4 randomized clinical trials (RCT), 1 cohort study, and 3 case controlled therapeutic studies.

Conclusions

MSC injections may be an effective adjunct in the management of osteoarthritis and a variety of cartilage related pathologies.

Keywords

stem cells, osteoarthritis, review

Introduction

Osteoarthritis (OA) is a degenerative disease of diarthrodial joints characterized by loss of articular cartilage, deformity, and pain. The two greatest risk factors for OA are obesity and joint injury.^{1,2} Symptomatic OA is reported in 12% of American adults, with as many as 37% of adults demonstrating radiographic evidence of OA.³ OA is a growing problem due to aging population, obesity epidemic, and low intrinsic capacity for cartilage damage repair. Mesenchymal stem cells (MSCs) can present a novel paradigm to deal with the problem of tissue regeneration, cartilage damage, and OA. Their paracrine effect on surrounding tissue reduces inflammatory responses with MSCs providing regenerative cells to repair damaged cartilage.⁴ The goal of this article is to provide a review of the use of MSCs delivered directly to diarthrodial joints by intra-articular injections for orthopedic cartilage repair and symptom relief.

Numerous non-pharmacologic and pharmacologic options are used for symptom management in OA, but none of these strategies can improve the structural damage that occurs with OA.^{5,6} Current OA treatment recommendations by the American Association of Orthopedic Surgeons (AAOS) emphasize educational and physical therapy, the use of acetaminophen and NSAID drugs, and intra-articular corticosteroid injections.⁷ Their recommendations regarding the use of growth factor injections and/or platelet rich plasma (PRP) remain inconclusive.⁷

Surgical management of OA involves different degrees of invasive procedures with total joint replacement being the most common and the most invasive. Less invasive methods such as autologous chondrocyte implantation (ACI) have data proven benefit but an inability to correct large osteochondral defects.⁸ Microfracture and arthroscopic debridement of tissue also offer

symptomatic benefit with success rates similar to other less invasive techniques like autologous matrix induced chondrogenesis (AMIC); however, microfracture and arthroscopic debridement may result in the formation of biomechanically inferior fibrocartilage.⁹ One main goal of newer treatment of OA is the delivery or induction of stem cells to produce true hyaline cartilage.

The success seen using mesenchymal stem cell therapy is rooted in the ability of MSCs to differentiate into all mesodermal tissues, specifically cartilage, bone, ligament, and tendon. They are also capable of modulating functions of T and B cells and secreting a variety of growth factors and cytokines like IL-10 and IL-12p40, which are anti-inflammatory in function.¹⁰⁻¹² This paracrine mechanism is thought to be a major directing force to accelerate and direct tissue repair by host derived cells.¹³ MSCs are thought to suppress local immune response by producing cytokines and prostaglandin E2, inhibiting fibrosis, and further stimulating differentiation of stem cells.^{14,15} MSCs have also demonstrated homing ability, specifically incorporating into injured tissue and assisting the healing of native tissues.¹⁶ Preclinical evidence has shown that MSCs injected into animal models of naturally occurring OA, enzyme-induced OA, and post-traumatic OA may help to regenerate cartilage lesions.^{17,18} The research using animal models and comparisons of scaffold vs non-scaffold stem cell application has also been well reviewed and detailed previously.^{17, 19-21} These features make MSCs an attractive strategy for OA management with MSC isolation and delivery being critical to clinical success.

Traditionally, MSCs have been isolated from bone marrow, typically from the iliac crest.²² Wakitani et al. were the first to demonstrate the regenerative use of MSCs for articular cartilage repair in humans by surgically implanting culture-expanded bone marrow MSCs.²³ Bone marrow- mesenchymal stem cells (BM-MSCs) have been widely studied but carry the morbidity associated with donor site pain and infection. However, in the past decade, multiple sources including adipose tissue, synovium, periosteum, umbilical cord blood, and peripheral blood have also been studied. Key components in selection of an appropriate MSC source include the accessibility of the harvest tissue, stem cell population density, and ease of cell differentiation, making adipose-derived stem cells (ADSCs) very attractive.²⁴⁻²⁶ ADSCs have been demonstrated to have similar differentiation capacity and morphology to bone marrow derived cells.²⁴ Although the most chondrogenic and osteogenic source of MSCs is synovium, ADSCs have chondrogenic and osteogenic activity requiring minimal stimulation by growth factors and cytokines.²⁷⁻²⁹ Augmentation, especially with a co-injection of PRP, may be beneficial.³⁰

PRP is novel biologic scaffold that has been widely used as a MSC carrier. PRP is non-immunogenic, readily bio-absorbable, and easily prepared in a perioperative setting, and thus meets the major criteria as a MSC carrier.³⁰ A double blind prospective multi-center trial by Mishra et al. in 2013 demonstrated clinically meaningful improvement in refractory tennis elbow treated with PRP.³¹

Bone marrow culture expanded mesenchymal stem cells

Bone marrow mesenchymal stem cells (BM-MSCs) are the best characterized MSCs and have osteogenic and chondrogenic potential that is greater than that of ADSCs.²⁷ These MSCs are a reliable source for intra-articular injections and have not been shown to increase risk of

malignancy.³² The earliest reports of successful BM-MSc injection therapy came in 2006 when Centeno et al. described a case report of a male patient with a twenty year history of hip pain and a diagnosis of OA. The patient was treated with two intra-articular hip injections of augmented BM-MSc one month apart. BM-MSc concentrate was added to hyaluronic acid and a thrombin activated platelet scaffold. The first injection was estimated to contain < 100,000 BM-MSc and the second 300-400,000 BM-MSc. At the time of the second injection, the patient had no MRI evidence of improvement but reported clinical improvement. At eight weeks post-injection, evidence of increased joint space and neocortex formation over the area of previous subchondral cysts was reported. Walking distances and sitting tolerances improved two levels as compared with pre-injection scores.³³ Additional case reports and case studies have been reported (Table 1).

Table 1. Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs)

| Author/ Journal | Study Type | Outcomes | Pathology | Treatment | Additional Treatment | # Patients | Follow-Up | Significant Results |
|---------------------------------------|-------------|------------------------------|-------------------------------------|---|---|------------|-------------|---|
| Centeno et al. 2006 Pain Physician | Case report | Harris Hip Score | Hip OA | Two injections of BMSC: 1-3x10 ⁵ cells | HA and thrombin – activated platelet scaffold | 1 | 4 & 8 weeks | MRI showed new neo-cortex at 8 weeks |
| Centeno et al. 2008 Pain Physician | Case report | VAS functional rating index | Knee OA | Cultured BMSC: 22.5 x 10 ⁵ cells | Platelet lysate injections | 1 | 24 weeks | Decreased VAS, and increased cartilage & meniscus volume on MRI at 3 months |
| Emadedin et al. 2012 Arch Iran Med | Case series | VAS, WOMAC, walking distance | Knee OA | Cultured BMSC: 24x10 ⁸ cells | | 6 | 1 year | MRI with cartilage thickening at 6 months |
| Orozco et al. 2013 Transplantation | Case series | VAS, WOMAC | Knee: Kellgren & Lawrence Grade 3,4 | Cultured BMSC: ~40x10 ⁸ injected | | 12 | 1 year | Significant improvement in VAS scores |
| Lee et | Case | ICRS | Knee: | Injected | HA | 35 | 24 | Improvement in |

| | | | | | | | | |
|---|-------------|---------------------------------------|----------------------------------|---|---------------------------------------|---------------------------|---------------|--|
| al. 2012 Ann Acad Med Singapore | series | evaluation package, MRI | full thickness cartilage lesions | vs. open-implanted | injection at weeks 2, 4 | injected 35 open | months | IKDC, Lysholm, VAS, and SF36 in all treatment groups |
| Davatchi et al. 2011 Int J Rheum Dis | Case series | Walking time, VAS | Knee OA | Cultured BMSC: 8×10^7 injected | | 4 | 6 months | Increased walking time, improvement in VAS |
| Varam et al. 2013 J Indian Med Assoc | RCT | ADL evaluation, OA outcome score, VAS | Knee OA | BMSC injections following debridement | | 25 in each group | 6 months | Improved OAOS and VAS |
| Wong et al. 2013 Arthroscopy | RCT | MOCART, Lysholm, Tegner, IKDC | Knee OA | BM- MSC | Micro-fracture, high tibial osteotomy | 28 in each group | 1 year | Improved MOCART, Lysholm, Tegner, and IKDC |
| Vangness et al. 2014 JBJS | RCT | MRI findings, VAS | Knee OA | BM- MSC | Medial meniscectomy | 55 patients in each group | 1 and 2 years | Improved meniscal volume, improved VAS |
| BMSC- Bone Marrow-Derived Stem Cells; OA- osteoarthritis; HA- hyaluronic acid; WOMAC- Western Ontario and McMaster University Osteoarthritis Index; ICRS- International Cartilage Repair Society; ADL- Activities of Daily Living; VAS- Visual Analog Scale; SF-36- Short Form Health Survey; MOCART- Magnetic Resonance Observation of Cartilage Repair Tissue | | | | | | | | |

In 2008, Centeno et al. published a case of knee OA treated with a single injection of cultured BM-MSCs (22.4 million) and a platelet lysate preparation. The patient had follow-up injections of platelet lysate one and two weeks after the first injection. Excellent outcomes were reported with a decrease in visual analog score (VAS) by 95% and magnetic resonance imaging (MRI) evidence of increased cartilage volume at three months post injection.³⁴ In 2011, a study by Davatchi et al. reported the results of four patients with knee OA who were injected with 8×10^6 BM-MSCs and were evaluated one week after the injection and then monthly for one year.³⁵ Functional assessments were made by walking time to pain, stair climb number, and VAS. Three

of the four subjects reported an improvement in walking time and stair climb capacity, and a 24-50% improvement in VAS. No improvement was seen on x-ray at follow-up. In another study by Emadenin et al., 6 patients with knee OA were injected with 24 million cultured BM-MSCs with 12-month follow-up. Optimal results were seen at 6 months as evaluated by VAS, Western Ontario and McMaster University Osteoarthritis Index (WOMAC), and walking distances. Importantly, pain reduction and improvement in joint function were also noted but decreased at one year. Three of the six demonstrated increased thickening of the meniscus on MRI at six months follow-up.³⁶

In 2012, a study by Lee et al. examined the effects of injecting BM-MSCs for seventy non-randomized patients less than 55 years of age with full thickness chondral lesions in a single compartment of the knee. Thirty-five patients received previously established treatment using arthroscopic microfracture and arthroscopic surgical implantation of MSC with periosteal flap coverage. The other thirty-five received the same arthroscopic microfracture followed by injection of 10 million BM-MSCs then 2ml hyaluronic acid (HA) in an outpatient clinic after surgery. Follow-up injections of HA (2ml) at two and four weeks were also administered. Subjects were followed for twenty-four months and evaluated using International Cartilage Repair Society (ICRS) injury evaluation package, Short Form Health Survey (SF-36), International Knee Documentation Committee (IKDC) subjective evaluation form, the Lysholm knee scale, and the Tegner activity level scale. A post-op MRI was also obtained. MRI results at one year showed neocartilage with good filling and significant reduction in underlying marrow edema. Improvement was seen in all patients, but the injected group was reported to have superior results according to the IKDC and Lysholm scores. No difference was noted between the VAS and the SF-36 score between the groups. As a result of the excellent clinical outcomes, no second look arthroscopies were performed.³⁷

Varma et al. conducted a randomized controlled trial (RCT) utilizing BM-MSC with fifty patients with mild to moderate knee OA. Half were treated by injection of buffy coated BM-MSC concentrate following arthroscopic debridement and compared to debridement alone. VAS and osteoarthritis outcome scores (OAOS) were evaluated at one, two, three, and six months follow-up. Significant improvement was seen at six months for the stem cell group in VAS (5.24 vs 2.12) and OAOS scores (56.57 vs 79.28).³⁸

Wong et al. also conducted an RCT using BM-MSC injections at the time of microfracture and high tibial osteotomy (HTO) for twenty-eight patients, and compared these results to twenty-eight patients randomized to receive no MSC injection.³⁹ At one year follow-up, patients' magnetic resonance observation of cartilage repair tissue (MOCART) scores were improved in the group receiving MSCs. Patients in this group also reported statistically significant improvement in Lysholm, Tegner, and IKDC scores.

In 2013, a cohort of twelve patients with Kellgren and Lawrence grade II-IV knee OA was injected with 40 million cultured BM-MSCs and followed for twelve months. Evaluation by MRI T2 showed improvement in cartilage, as well as significant clinical improvement in functional scores and VAS.⁴⁰ These studies clearly demonstrate that optimal dosing of MSC is not known with ranges from 100,000 to 40 million BM-MSCs used in the studies presented.

In 2014, Vangsness et al. published their results from an RCT using BM-MSCs versus placebo injections administered to fifty-five patients seven to ten days after a partial medial meniscectomy.⁴¹ Patients received injections of either 50×10^6 allogeneic BM-MSCs, 150×10^6 MSCs, or a hyaluronic acid control. The authors found increased meniscal volume on MRI in both groups receiving MSCs, and significantly increased VAS score improvement at one and two years in the MSC groups compared to the control group.

Adipose-Derived Mesenchymal Stem Cells (ADSCs)

A critical difference in studies using ADSCs versus BM-MSCs is the near immediate injection of stem cells following harvest; readily available reservoirs include the buttock, abdominal, and infrapatellar fat pads.^{26,30,42-45} Thus, adipose tissue is ideal for same day harvest and injection, making it attractive for traumatic injury cases. Recent studies using ADSCs have covered a wider spectrum of chondral related pathologies, including OA of the hip and knee, osteonecrosis of the femoral head, and osteochondral lesions of the talus (Table 2).

Table 2. Adipose-Derived Mesenchymal Stem Cells (ADSCs)

| Author/ Journal | Study Type | Outcomes | Pathology | Treatment | Additional Treatment | # Patients | Follow-Up | Significant Results |
|---|--------------|-----------------------------------|-------------------------------|---|-------------------------------|------------------------|-----------|---|
| Pak et al. 2013 <i>PLOS ONE</i> | Case series | Pain scale/ MRI evaluation | Chondromalacia | Concentrated ADSCs: $\sim 16 \times 10^6$ | HA, PRP | 3 | 18 months | Improvement in subjective pain scores, and MRI with evidence of cartilage restoration |
| Pak et al. 2011 <i>J Med Case Reports</i> | Case series | MRI, VAS, functional rating index | Hip osteonecrosis and knee OA | Concentrated ADSCs | PRP, HA, CaCl ₂ | 4 | 12 weeks | MRI with evidence of increased cartilage thickness |
| Koh et al. 2012 <i>Knee</i> | Case Control | Lysholm score, Tegner, VAS | Knee OA | Concentrated ADSCs | PRP, arthroscopic debridement | 25 cases in each group | 12 months | No difference from control |
| Koh et al. 2013 <i>Arthroscopy</i> | Case Control | MRI, VAS, WOMAC | Knee OA | Concentrated ADSCs | Arthroscopic debridement, PRP | 18 | 2 years | Decrease in WOMAC at 2 years, with improvement correlation with cell count injected |
| Kim et | Coh | VAS | Osteoc | Concent | Arthros | 30 | 22 | Improved mean |

| | | | | | | | | |
|--|--------------------|--|----------------------------|--------------------------------------|------------------------------------|-------------------------------|------------------|------------------------------------|
| al. 2013 Am J Sports Med | ort Stud y | AOFAS, Ankle- Hindfoot scale, Roles & Maudsley, Tegner | hondral talar lesion | rated ADSCs | copic marrow stimulat ion | ADS C 35 contr ol | mont hs | VAS and AOFAS in ADSC group. |
| Spasov ski et al. J Gene Med | Case serie s | VAS, KSS, radiogra phs | Knee OA | 0.5- 1.0x10 ⁷ ADSCs | | 9 patien ts | 18 mont hs | Improved VAS and KSS |
| ADSC- Adipose-Derived Stem Cells; OA- osteoarthritis; PRP- platelet rich plasma; HA- hyaluronic acid; WOMAC- Western Ontario and McMaster University Osteoarthritis Index; VAS- Visual Analog Scale; AOFAS- American Orthopaedic Foot and Ankle Society; KSS- Knee Society Score | | | | | | | | |

A case series published by Pak et al. in 2011 evaluated the safety and efficacy of concentrated ADSCs in four patients.⁴³ Two patients had stage IV osteonecrosis of the femoral head and were given intra-articular injections of ADSC concentrate mixed with PRP, HA, and CaCl₂. Subjects returned every week for follow-up injection of PRP and CaCl₂ for a total of four injections. Two other subjects with OA of the knee were injected with ADSC, PRP, and CaCl₂. They also had weekly injections of PRP and low dose dexamethasone for four weeks. Patients were seen in follow-up at three weeks and twelve weeks. Pre-procedure evaluations included VAS, MRI, and functional rating index. Repeat MRI at twelve weeks showed bone regeneration of the femoral heads and regeneration of the meniscus in the OA patients. This study suggests that ADSCs may be partially responsible for patients' improvement. In 2013, the same group published another case series using ADSC intra-articular injections to treat chondromalacia patellae in three patients.⁴² Each was evaluated pre-procedurally with MRI and VAS pain assessment. Low abdominal liposuction was used to collect ADSC and cells were concentrated the same day as injection. Sixteen million concentrated ADSCs were injected into the retropatellar joint space with PRP and HA. All patients returned on day three, seven, fourteen, and twenty-eight for repeat injections of PRP and HA with the day fourteen injection including low dose dexamethasone. Patients were seen for follow-up at three months, when MRI demonstrated cartilage-like tissue regeneration, and subjects reported 80-90% pain improvement. However, it should be noted that despite these positive outcomes, there were discrepancies in the authors' reported protocol that limit interpretation of this study.

In 2012, Koh et al. published a therapeutic case series of twenty-five subjects to evaluate whether percutaneous injection of ADSCs from the infra-patellar fat pad could improve clinical outcomes for knee OA.³⁰ Intra-articular injections of ADSCs (mean 1.9 million) in concert with PRP and arthroscopic debridement were compared to a matched control group without injections of stem cells. All patients had follow-up injections of PRP on day seven and fourteen. Pre- and

post-operative evaluations were performed using VAS, Lysholm, and Tegner scores, and all revealed greater total improvement when compared to the control group. Overall outcomes were similar for pain relief and functional improvement. Patients in this study were further evaluated at two years by MRI, VAS, and scores for WOMAC and WOMMS. Interestingly, an improvement of WOMAC scores, from 49.9 at 0-1 years to 30.3 at 1-2 years was observed. Possibly the most important finding from the group was the correlation between cell count at injection and patient outcomes. Notably, there was also a positive correlation between the dosage of ADSCs and improvement of pain, function, and MRI findings.⁴⁴

Another study assessing the effect of ADSCs included thirty study patients and thirty-five control patients with osteochondral (OCD) lesions of the talus. All patients were over fifty years of age. This study assessed the role of ADSCs in treating talar OCD lesions in conjunction with marrow stimulation vs. marrow stimulation alone. ADSCs were harvested from the butt pad the day prior to treatment. Outcomes were assessed using VAS, AOFAS score, Roles and Maudsley score, and Tegner activity scale over a mean of twenty-two months. Patient outcome scores improved in both groups, and the authors noted that patients with lesions larger than 109 mm² or with subchondral cysts were likely to have superior outcomes when treated with ADSCs.⁴⁵

Recently, Spasovski et al. evaluated the clinical and radiographic outcomes of a single injection of ADSCs in nine patients with knee osteoarthritis. The authors used a concentration of 0.5-1.0 x 10⁷ cells. After eighteen months of follow-up, patients reported improvement in VAS and knee society score (KSS). Radiographs showed neither improvement nor progression of degenerative changes.⁴⁶

Peripheral Blood Stem Cells

Peripheral blood progenitor cells (PBPCs) are easily obtained with both central and peripheral intravenous access and have been successfully used to treat international cartilage repair society (ICRS) grade III-IV chondral knee lesions. The case series by Saw et al. describes five subjects who were treated with arthroscopic subchondral drilling followed by five weekly injections of PBPCs mixed with HA.⁴⁷ Second look arthroscopy demonstrated articular cartilage regeneration with histologic sections showing hyaline cartilage regeneration as the major component of the repaired tissue. The success of the case series prompted Saw et. al. to evaluate the treatment process of five weekly injections of PBPCs mixed with HA in an RCT of fifty patients with ICRS grade III-IV lesions randomized to either 1) those treated with subchondral drilling and HA alone, and 2) those treated with drilling followed by PBPCs and HA (Table 3). Subjective IKDC scores and MRI evaluations were made pre- and post-operatively on all patients, and second look arthroscopy and biopsy at eighteen months were taken from sixteen patients in each group. There were no statistically significant differences in IKDC scores. However, statistically significant improvement was seen in both MRI findings and ICRS II scores in the control group. Furthermore, more type 2 collagen was identified in the intervention group, as compared to “limited to no” type 2 collagen in the control.⁴⁸

In another case study of five patients who failed conservative therapy for knee OA, arthroscopic micro drilling was performed in all patients with two subsequent IA injections of PBPCs with

growth factors and HA, repeated at days seven and fourteen. Outcomes evaluated WOMAC and knee injury and osteoarthritis outcome scores (KOO) at baseline, one, and six months along with biopsy. Significant improvements in WOMAC and KOO scores were noted in all patients at one and six months. Biopsy showed increased proteoglycan and glycosaminoglycan content which suggested hyaline cartilage formation (Table 3).⁴⁹ PBPCs presents a less invasive alternative to traditional BM-MSC and ADSC harvest protocols.

Table 3. Peripheral Blood Mesenchymal Stem Cells (PBSCs)

| Author/ Journal | Study Type | Outcomes | Pathology | Additional Treatment | # Patients | Follow-Up | Significant Results |
|---|-------------|--|----------------------------|--|------------------|--------------|--|
| Saw et al. 2013 Arthroscopy | RCT | IKDC scores, MRI, biopsy | Knee chondral lesion | HA, subchondral drilling | 25 in each group | 18 months | Increased amounts of Type II collagen in stem cell group |
| Saw et al. 2011 Arthroscopy | Case series | Second look arthroscopy, tissue biopsy | ICRS grade 3-4 knee lesion | Arthroscopic subchondral drilling, HA | 5 | 10-26 months | Biopsy evidence of hyaline cartilage formation |
| Turajane et al 2013. J Med Assoc Thai | Case series | WOMAC, KOO, biopsy | Knee OA | Arthroscopic subchondral drilling, HA, growth factor | 5 | 6 months | Biopsy with increased proteoglycans and glycosaminoglycans suggestive of hyaline cartilage |
| PBSC- Peripheral blood stem cells; ; OA- osteoarthritis; HA- hyaluronic acid; WOMAC- Western Ontario and McMaster University Osteoarthritis Index; ICRS- International Cartilage Repair Society; IKDC- International Knee Documentation Committee; KOO- Knee Injury and Osteoarthritis Outcome Scores | | | | | | | |

Discussion

Review of current research involving IA injection of MSCs for various chondral-related pathologies is promising. The rising interest in cartilage regeneration is predictable considering the impact that a successful regenerative treatment would have on the field of orthopedics. However, our knowledge of the process is still in the preliminary stages. The vast majority of the publications on stem cell injection therapy are preclinical, but have shown great promise in animal models and RCTs.^{8,15,17,18,21} Studies included in this review demonstrate the diversity and limitations of current research, especially relatively short patient follow-up and the variability in dosing regimens and use of concomitant therapies. However, symptomatic benefit and evidence of improvement on advanced imaging were noted in many studies.

MSCs can be harvested from bone marrow, adipose tissue, synovium, peripheral blood, umbilical cord blood, muscle, skin, and periosteum; each donor has a variable capacity to produce cartilage and bone. Each of these sources also differs in the relative ease or morbidity associated with harvesting MSCs. Furthermore, the optimal number of stem cells injected is far from certain. Although the dose-dependent nature of cartilage regeneration is still unknown, there is some evidence of a dose-dependent effect.^{41,42} Of the groups reviewed, dosing varied significantly with upwards of 40 million to as few as 100,000 cells being used, making any comparison between study outcomes difficult. The proper dose for injection therapy is a key point that needs to be clarified with future research. Finally, although outside the scope of this paper, allogeneic BM-MSCs avoid the expensive and slow cell expansion process used in autologous harvest, but theoretically may cause host immune rejection; no adverse reactions were identified in an RCT by Vega et al. in 2015 examining 30 IA injections for knee OA.⁵⁰

Cellular and biochemical factors related to chondrogenesis are other key developing areas of research. Extensive *in vitro* work has been done showing the growing characteristics and behavior of ADSCs in recombinant BMP-2, TGF- β , PDGF and in various biologic scaffolds like PRP.^{28,51-53} New discoveries and better understanding of MSC processes will continue to fuel advancements in the field of chondral regeneration.

Limitations of MSCs for the treatment of OA must also be considered. Long-term safety and efficacy of these therapies has not been proven. In a review by Peeters et al. of 844 injections with a mean follow-up of twenty-one months, the authors concluded that applications of cultured stem cells in joints appears safe.⁵⁴ A follow-up study by Jo et al. in 2017 examined the two year outcomes of their eighteen patients with knee OA who had received AD-MSC injections, and found that the clinical outcomes for low- and medium-dose groups deteriorated one year after injections, while the high-dose group results plateaued.⁵⁵ Furthermore, patients with severe OA have decreased proliferative capacity of patient-derived MSCs which, in addition to the burden of their advanced degeneration and deformity, limits the utility of these therapies in many patients.⁵⁶ With longer follow-up and further studies, we will continue to gather data and identify potential complications regarding MSC therapies.

Conclusion

MSCs have potential to be a widely used modality in the next decade. New RCTs, case reports, and cohort studies demonstrate the potential use of MSCs in a variety of cartilage-related pathologies and therapies. Larger RCTs are needed to identify optimal cell sources, required cell counts for injection, cell processing methods, and ideal supplemental ingredients such as PRP, HA, and growth factors.

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