[Primary Care]

Cell Therapy in Joint Disorders

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Context: Articular cartilage possesses poor natural healing mechanisms, and a variety of non-cell-based and cell-based treatments aim to promote regeneration of hyaline cartilage.

Data Sources: A review of the literature to December 2013 using PubMed with search criteria including the keywords *stem cell, cell therapy, cell transplantation, cartilage, chondral*, and *chondrogenic*.

Study Selection: Forty-five articles were identified that employed local mesenchymal stem cell (MSC) therapy for joint disorders in humans. Nine comparative studies were identified, consisting of 3 randomized trials, 5 cohort studies, and 1 case-control study.

Study Type: Clinical review.

Level of Evidence: Level 4.

Data Extraction: Studies were assessed for stem cell source, method of implantation, comparison groups, and concurrent surgical techniques.

Results: Two studies comparing MSC treatment to autologous chondrocyte implantation found similar efficacy. Three studies reported clinical benefits with intra-articular MSC injection over non-MSC controls for cases undergoing debridement with or without marrow stimulation, although a randomized study found no significant clinical difference at 2-year follow-up but reported better 18-month magnetic resonance imaging and histologic scores in the MSC group. No human studies have compared intra-articular MSC therapy to non-MSC techniques for osteoarthritis in the absence of surgery.

Conclusion: Mesenchymal stem cell–based therapies appear safe and effective for joint disorders in large animal preclinical models. Evidence for use in humans, particularly, comparison with more established treatments such as autologous chondrocyte implantation and microfracture, is limited.

Keywords: stem cells; cell therapy; cartilage; osteoarthritis; cell transplantation

Articular surface injury is a frequent problem, with recovery limited by incomplete natural healing mechanisms complicated by progression to osteoarthritis (OA), which leads to further pain and dysfunction.

This lack of effective healing of chondral defects has led to a need to develop therapies to restore the articular surface to near normal. Broadly, these may be considered as non-cell-based and cell-based.[55,63] Cell-based therapies may be further subdivided into non–stem cell therapy or stem cell therapy.

For non–stem cells, the most frequently employed technique is autologous chondrocyte implantation (ACI), with further advancements employing a collagen rather than periosteal cover and third generation approaches utilizing cells seeded within bioscaffolds rather than injection as a cell suspension.[11]

The isolation of mesenchymal stem cells (MSCs) from a variety of tissues and their promise in in vitro and in animal models has led to their relatively recent implementation in humans.[119] This review will focus on localized joint abnormalities such as chondral injury and OA.[95]

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METHODS

A search was conducted through PubMed using various combinations of the terms *stem cell, cell therapy, cell transplantation, cartilage, chondral*, and *chondrogenic* to December 2013 with no earlier limit. Only 9 comparative studies (Table 1) were identified among a total of 45 human reports of local stem cell therapy for joint disorders (see the Appendix, available at http://sph.sagepub.com/content/suppl).

Three randomized trials,[102,117,119] 3 nonrandomized cohort studies,[39,61,84] and 1 case-control study[64] compared stem cell with non–stem cell procedures. A further 2 cohort studies compared different stem cells or implantation methods.[69,105] Statistical analysis was not performed because of differences in study populations and methods.

NON-CELL-BASED TREATMENT OF CHONDRAL INJURY

Non-cell-based surgical treatment includes debridement, marrow stimulation by microfracture, abrasion or drilling of the subchondral bone plate, and osteochondral grafting (mosaicplasty).[55,63,83]

Abnormal cartilage in defects produces detrimental effects on adjacent and opposing cartilage, and debridement can improve symptoms and potentially minimize further chondral loss.[28,55] Activation of the innate repair mechanism by injuries involving the subchondral bone plate, as opposed to partial-thickness chondral injury, provides the rationale for marrow stimulation techniques where multiple small holes are placed in the subchondral bone of the defect.[55] The mechanism of action is thought to be due to the influx of chondroprogenitor cells.[63]

CELL-BASED THERAPY

The first report describing ACI in humans was by Brittberg et al[10] in 1994, involving debridement, covering of the defect with a periosteal flap from the proximal medial tibia sutured to surrounding normal cartilage, and cultured chondrocyte injection beneath the periosteal flap.

Autologous chondrocyte implantation utilizes cultured, mature, autologous chondrocytes suspended in an injectable medium with newer variants using a collagen type I/III membrane (ACI-C, CACI, second generation) rather than periosteal cover (ACI-P, first generation).[11] Third generation techniques such as matrix-induced autologous chondrocyte implantation (MACI) use cells seeded onto the rough side of a collagen type I/III membrane with a smoother side facing the articular cavity, usually fixed with fibrin glue and sometimes sutures.[11]

Characterized chondrocyte implantation (CCI) maximizes chondrogenic capacity through a controlled ex vivo process that produces clinically significant improvement with up to 4 years follow-up.[115] Comparing CCI with microfracture in a randomized trial, Saris et al[98,99] found improved tissue regeneration, although similar clinical outcomes, at 1 year but improved clinical outcome for CCI at 3 years.

These procedures can result in improved clinical, arthroscopic, and histologic features, with hyaline-like cartilage or fibrocartilage present in 43.9% of ACI-C and 36.4% of MACI grafts in 1 prospective, randomized study by Bartlett et al.[4] In a randomized trial comparing ACI-P to MACI, Zeifang et al[128] found better Lysholm and Gillquist scores at 12 and 24 months in the ACI-P group but no significant difference in International Knee Documentation Committee (IKDC), Tegner Activity Score, or Short Form–36 scores.

In a systematic review of cell-based therapy for chondral lesions from 1994 to 2009, Nakamura et al[83] concluded that there was insufficient evidence to indicate superiority of cell-based therapy to non-cell-based treatments with relatively short-term follow-up and most studies demonstrating no convincing differences. Variable results have been obtained comparing ACI with microfracture, with some studies showing no significant difference and others suggesting superiority of ACI.[83] Second and third generation techniques offer potential advantages, but longer term follow-up is required.[11,83]

Basad et al[5] demonstrated significantly improved Lysholm, Tegner, patient ICRS (International Cartilage Repair Society), and surgeon ICRS scores with MACI compared with microfracture at 2 years in a randomized study. For patients undergoing ACI after failed microfracture, significantly higher failure rates were observed.[91]

The chondral defect site as well as level of sports activity and physical training may influence outcome.[83] Surgical technique and experience also play a role. Disadvantages of ACI/MACI include healthy cartilage damage at the donor site and lack of suitable donor cartilage in elderly patients with degenerative changes.[11,83]

STEM CELL THERAPY

Sources of Stem Cells

The stem cells with the greatest capacity for differentiation are embryonic stem cells (ESCs). In addition to ethical concerns, questions of safety have arisen because of the risk of teratoma formation.[51] These concerns have prompted the search for alternative stem cell sources including adult cells and, more recently, induced pluripotential stem cells (iPSCs), although the teratoma risk currently persists with iPSCs.[51,108] IPSCs from osteoarthritic cartilage undergo chondrogenic differentiation in vitro and show chondrogenesis after subcutaneous implantation in mice, but have not yet been used in in vivo articular surface repair.[126]

Mesenchymal stem cells are multipotential cells originally isolated from bone marrow but naturally existing in many tissues, often around blood vessels. They are defined by the expression of various cell surface molecules (eg, CD73, CD90, CD105), the capacity for self-renewal, and the ability to differentiate into osteogenic, chondrogenic, or adipogenic lineages.[48,93] While this capacity already signifies their applicability to musculoskeletal conditions, they also possess potent anti-inflammatory/immunosuppressive properties,[79] which may predict efficacy in OA.[48,71]

Table 1. Comparative human studies involving the use of MSCs for cartilage repair[ab]

Study	Cell Type	Level/ Design	Number of Patients	Comparison/ Controls	Disorder/ Grade	Surgical Approach/Method of Stem Cell Implantation	Follow-up	Outcomes
Giannini et al (2010),[39] Italy	BMC	Level 3 (cohort)	25 MSC	10 open ACI, 46 arthroscopic ACI	Talar osteochondral lesions, average 2.18 ± 0.5 cm^2	Arthroscopic: Debridement, platelet gel + collagen powder or HA membrane	36 months	• In all groups AOFAS improved at 12 and 36 months • No significant difference between groups • Intact cartilage in all cases at arthroscopy • One-step BMC technique less than half the cost of 2-step arthroscopic ACI and less than one third of open
Kim et al (2013),[61] South Korea	SVF	Level 3 (cohort)	31 MSC injection + surgery	37 only surgery	Talar osteochondral lesions, 118.9 ± 47.9 mm^2 in MSC group, 102.7 ± 31.4 mm^2 surgery only	Intra-articular injection—supplement to arthroscopic debridement and microfracture	Mean 21.8 months (range, 12-44 months)	• Significantly greater improvement in MSC group compared with non-MSC for VAS, AOFAS, Roles and Maudsley score and Tegner activity scale at final follow-up
Koh and Choi (2012),[64] South Korea	Infrapatellar fat SVF	Level 4 (case-control)	25 MSC injection + surgery and PRP	25 surgery and PRP only	OA—knee, ICRS grade 3.7 ± 0.4 MSC and 2.8 ± 0.8 control	Intra-articular injection of MSC and PRP following arthroscopic debridement. Marrow stimulation procedures not performed	1 year	• Suggestion of greater benefit from MSC as groups similar at final follow-up, but preoperative clinical scores (VAS, Tegner, Lysholm) and ICRS grade significantly worse for MSC group
Lee et al (2012),[69] Singapore	BM-MSC (culture expanded)	Level 3 (cohort)	35 group 1 (arthro-scopic surgery + MSC injection)	35 group 2 (open MSC implantation)	Full-thickness chondral defects—knee	1: Arthroscopic debridement and microfracture, outpatient injection BM-MSC and HA 2: Open debridement, cultured MSC sheet implantation beneath sutured periosteal patch, fibrin glue	24.5 months	• Both groups significantly improved IKDC, Lysholm, VAS, and SF-36 scores • Injected group more improvement in IKDC and Lysholm scores than open, while improvement in VAS and SF-36 scores were similar
Nejadnik et al (2010),[84] Singapore	BM-MSC (culture expanded)	Level 3 (cohort)	36 MSC	36 ACI (periosteal cover)	Chondral defects/OA, ICRS grade III-IV, MSC average 4.6 cm^2 (SD 3.53), ACI average 3.6 cm^2 (SD 2.84)	Open surgical: debridement, subchondral bone intact, periosteal patch, cells implanted beneath patch, fibrin glue seal	2 years	• No significant difference in IKDC, Tegner activity, and Lysholm scores • Physical role functioning significantly improved in stem cell group

(continued)

Table 1. (continued)

Study	Cell Type	Level/ Design	Number of Patients	Comparison/ Controls	Disorder/ Grade	Surgical Approach/Method of Stem Cell Implantation	Follow-up	Outcomes
Saw et al (2013),[102] Malaysia	PBSC	Level 2 (RCT)	25 PBPC + HA	25 HA only	Knee—chondral defects, ICRS grade III-IV	Intra-articular injection of PBPC + HA (group 1) or HA alone (group 2) × 8 injections following arthroscopic subchondral drilling	24 months	• Biopsy at 18 months, 16 patients from each group, better histology PBSC (1066 vs 957) • MRI scores better at 18 months (9.9 vs 8.5) • No significant clinical difference with IKDC scores at 24 months
Skowroński and Rutka (2013),[105] Poland	BMC/PBSC	Level 3 (cohort)	21 BMC	25 PBSC	Osteochondral defects medial femoral condyle, >4 cm^2, >6 mm deep	Open surgical: BMC or PBSC suspension injected under collagen membrane + fibrin glue following debridement and autologous iliac graft of osseous defect	5 years	• KOOS, Lysholm, and VAS scales significantly better in PBSC group at 6 months and 1 year • Slight decrease in clinical scores at 5 years in both groups
Varma et al (2010),[117] India	BMC	Level 2 (RCT)	25 MSC + surgery	25 surgery only	OA—knee	Intra-articular injection following arthroscopic debridement	6 months	• Significant improvements in ADLs, sports and recreational activity, and quality of life scores at 6 months MSC compared with controls
Wakitani et al (2002, 2008),[119,122] Japan	BM-MSC (culture expanded)	Level 2 (RCT)	12 MSC	12 non-MSC controls	OA—knee, Outerbridge IV, mean 14 × 35 mm	Open surgical: subchondral abrasion and drilling, collagen gel-sheet implant and periosteal cover + high tibial osteotomy	64 months	• Arthroscopic and histologic scores better in MSC group at 28-95 weeks • No clinical difference then or at 64-month follow-up

[a]BM-MSC, bone marrow–derived mesenchymal stem cells; ACI, autologous chondrocyte implantation; SVF, stromal vascular fraction; PBSC, peripheral blood stem cells; RCT, randomized controlled trial; BMC, bone marrow concentrate; OA, osteoarthritis; HA, hyaluronic acid; PRP, platelet-rich plasma; SD, standard deviation; ADLs, activities of daily living; ICRS, International Cartilage Repair Society; MFC, medial femoral condyle; VAS, visual analog scale; AOFAS, American Orthopaedic Foot and Ankle Society; KOOS, Knee Injury and Osteoarthritis Outcome Score; IKDC, International Knee Documentation Committee; SF-36, Short Form-36.
[b]All studies utilized autologous cells. BM-MSCs represent culture-expanded cells. Non-BM-MSC studies utilized non–culture expanded cells from a variety of sources. Levels of evidence are as per the Oxford 2011 Levels of Evidence.[85]

Mesenchymal stem cells are being isolated from an increasingly wider variety of human tissues, including bone marrow,[93] adipose tissue,[130] skeletal muscle,[70] synovial membrane[26,47] and synovial fluid,[47] periosteum,[27] peripheral blood,[88] umbilical cord blood,[124] endometrium,[37] amniotic fluid,[53] and placenta.[54] The potential therapeutic value for MSCs in the treatment of joint disorders is multifactorial, including paracrine effects on regenerating native tissue and immunomodulatory effects.[14,48]

The cytokine-based immunosuppressive properties of MSCs potentially induce immune tolerance, prompting investigation in multiple sclerosis, foreign graft rejection, and rheumatoid arthritis.[48,95] These immunomodulatory effects may help slow the progression of OA by targeting the inflammatory processes in its pathogenesis.[79]

So far, in the musculoskeletal system, MSCs derived from autologous bone marrow, subcutaneous adipose tissue, infrapatellar fat, and peripheral blood have been utilized in humans in treating osteochondral injury, OA, and rheumatoid arthritis.[64,88,101,119]

Bone Marrow–Derived Mesenchymal Stem Cells and Bone Marrow Concentrate

Hematopoietic stem cells (HSCs) and bone marrow–MSCs (BM-MSCs) represent different cells lines, with only BM-MSCs used for chondral regeneration. HSCs renew blood elements while MSCs can differentiate into mesenchymal elements, including cartilage.[93] Most animal and human stem cell studies for cartilage repair used BM-MSCs. Initial human reports employed culture-expanded BM-MSCs,[119] but subsequent publications utilized bone marrow concentrate (BMC) without expansion, allowing a same-day procedure.[15,38] BMC contains nucleated cells with a small stem cell component derived from marrow aspirates after removal of most red cells and plasma by centrifugation.[38] Both show benefits compared with controls in small, human studies.[39,84,117,119,123]

Technique-related differences in aspirate yields include site (anterior vs posterior iliac crest) and syringe size.[92] Substantial variability also exists for MSC counts between patients.[92] For these reasons, comparison between studies or patients within a study is difficult unless the sample is analyzed prior to implantation. Although cell numbers may be counted, characterization with surface markers is required to assess true stem cell counts.[18,105] Reported transplanted BM-MSC counts range from 8 million[25] to 45.6 million[17] cells.

Outcome for femoral head osteonecrosis and tibial nonunion is proportionate to the number of transplanted progenitor cells.[49,50] This remains to be shown in humans for cartilage, but the principle of improved healing with greater cell numbers is important. In vitro work shows that increasing initial seeding density of BM-MSC enhances chondrogenesis.[52] Government regulation forms a barrier to using culture-expanded cells in some countries, including the United States, as the degree of ex vivo manipulation classifies the treatment in the same manner as a drug.[20] Geographic locations of human studies are listed (see the Appendix, available at http://sph.sagepub.com/content/suppl). The US Food and Drug Administration has currently not approved any stem cell products for use in the United States other than cord blood–derived hematopoietic stem cells for certain indications.[114] While the use of culture-expanded cells is prohibited, some clinics offer same day procedures using minimally manipulated cells such as BMC, concentrated at the point of care.[20] The issue of stem cell regulation continues to be a subject of active debate.

An apparent disadvantage of BM-MSCs is that cell numbers diminish with age and exhibit reduced proliferative capacity and increased rates of apoptosis compared with BM-MSC from younger patients.[106]

Adipose-Derived Stem Cells and Stromal Vascular Fraction

Mesenchymal stem cells in adipose tissue arise from or form perivascular cells.[13,130,131] Adipose tissue contains proportionally higher numbers of MSCs (approximately 10% of nucleated cells) than bone marrow and is amenable to liposuction without significant morbidity. In contrast to BM-MSCs, numbers do not decline with age but do decline with obesity.[3] Stem cells may differ in numbers from abdominal adipose tissue compared with the hip or thigh, but proliferation and differentiation do not appear influenced by harvest site.[56]

As with bone marrow, adipose stem cells may be utilized in 2 major forms. Stromal vascular fraction (SVF) is a heterogeneous population of cells that may contain MSCs, fibroblasts, endothelial cells, leukocytes (lymphocytes and macrophages), and pericytes.[8] Stem cells from SVF may be separated and expanded in vitro (adipose-derived stem cells [ADSCs]).

An advantage of SVF and BMC is elimination of the time lag between harvest and implantation, minimizing exposure to risks, reducing cost and logistical difficulties.[39,88,95] However, the lack of cellular content identification of SVF is a major problem in evaluating clinical efficacy and patient responses. SVF contains large numbers of T regulatory (Treg) cells that may assist in immunosuppression and tolerance induction.[95]

Intra-articular SVF has been successfully utilized in dogs with elbow or hip OA but with suboptimal results in horses.[8,9,35] Co-administration of non-infrapatellar fat-derived SVF showed superior clinical results at mean 21.8-month follow-up compared with non-MSC controls in a human study.[61]

Improved cartilage repair was seen with culture-expanded ADSCs compared with controls in rabbit full-thickness chondral defects with better integration and more hyaline cartilage formation, but their use in humans has not been reported.[31]

Infrapatellar Fat Pad–Derived Stem Cells

Infrapatellar fat differs in composition to subcutaneous adipose tissue, containing a large amount of collagenous tissue and possibly synoviocytes.[127] While exhibiting characteristics of ADSCs,[57] they have more similarities with fibrous synovium-derived cells than subcutaneous fat–derived cells, and possibly greater chondrogenic potential.[78] In rabbits, cells cultured from

infrapatellar fat showed promising results compared with controls.[110]

Infrapatellar SVF (not culture-expanded) has shown similar clinical findings in humans at 1 year compared with MSC free controls undergoing arthroscopic debridement, implying a potential benefit from MSC because of poorer preoperative clinical scores and ICRS grades.[64]

Peripheral Blood Mesenchymal Stem Cells/Progenitor Cells

Peripheral blood presents another source of MSCs, obtained with relative ease and no significant donor site morbidity.[21] MSCs derived from human peripheral blood cells (PBSCs) exhibit similar in vitro chondrogenic potential to BM-MSCs, although they are far less concentrated in blood than in marrow.[23] Use of granulocyte–colony stimulating factor (G-CSF) increases MSC numbers in peripheral blood.[21,101] While generally well tolerated, rare risks of G-CSF in healthy donors include splenic rupture and adult respiratory distress syndrome, although the theoretical risk of hematologic malignancy remains to be proven in the healthy donor population.[32]

Following an initial pilot report,[101] PBSCs have been assessed in a randomized study augmenting arthroscopic subchondral drilling with postprocedural injections of either PBSC and hyaluronic acid (HA) or HA alone, reporting improved histologic and MRI scores at 18 months but no significant clinical difference at 24 months.[102]

Other stem cell sources trialed in animals, but not humans, include periosteum, synovium, and skeletal muscle.[73,76,90,118]

METHODS OF STEM CELL TRANSPLANTATION

Open Surgical Implantation of MSCs

Surgical implantation may be similar to ACI, with MSCs beneath a periosteal[119] or collagen[43] cover instead of cultured chondrocytes.[45,60,67,74,84,103,104,109,119-123] A cell-seeded construct (analogous to MACI) may be used rather than suspended cells.[11] An ideal scaffold is nontoxic, absorbable, mechanically sound, and promotes cell growth.[46]

Wakitani et al[118] found that osteochondral progenitor cells from bone marrow or periosteum in type I collagen gel produced superior repair of full-thickness rabbit medial femoral condylar defects compared with empty defects or a cell-free collagen gel with hyaline cartilage formation and mechanically superior repair tissue. Macroscopic appearance at 24 weeks and histologic appearance at 12 and 24 weeks was less favorable than at 4 weeks postimplantation.[118]

Wakitani et al[119] used culture-expanded BM-MSCs in collagen gel in medial femoral condylar defects of humans with OA at the time of high tibial osteotomy, with 12 patients randomized to each group. Subchondral abrasion was performed to facilitate bleeding. A BM-MSC–collagen gel sheet composite was applied to the defect and covered with autologous periosteum. The control group received the same treatment without BM-MSCs. BM-MSC patients demonstrated improved arthroscopic and histologic scores 28 to 95 weeks following treatment, with no clinical difference, including on repeat assessment at 64 months.[119,123]

Gobbi et al[43] applied a 1-step open approach with BMC (nonexpanded) following debridement of knee chondral lesions in 15 patients using a collagen membrane cover. Most underwent associated procedures. Significant clinical improvement was noted at 6, 12, and 24 months (visual analog scale [VAS], Knee Injury and Osteoarthritis Outcome Score [KOOS], IKDC, SF-36, Tegner, Marx, Lysholm). Defect filling at MRI was complete in 12 cases and incomplete in 3 cases. Arthroscopic evaluation in 4 knees was normal to nearly normal, and histology in 3 patients showed hyaline-like features.[43]

Skowroński and Rutka[105] showed significantly better KOOS, Lysholm, and VAS scores for PBSC over nonexpanded BMC in conjunction with autologous iliac bone grafting of medial femoral condylar osteochondral lesions at 6 months and 1 year, but commented that it could reflect double the transplanted cell numbers compared with the BMC group, with possible contribution from more stem cells provided by marrow stimulation in the G-CSF–treated PBSC group.

Regarding open foot and ankle chondral defect repairs, implantation of nonexpanded BMC-impregnated collagen matrix was reported by Richter and Zech[94] in 25 patients who were followed up with at 2 years with significant improvements in VAS foot and ankle scores.

Arthroscopic Implantation of Stem Cells

Giannini et al[38,40] followed 49 patients, aged 14 to 50 years, for 4 years after 1-step arthroscopic implantation of nonexpanded BMC for talar osteochondral lesions, with either collagen powder/platelet gel or HA membrane/platelet gel scaffolds. American Orthopaedic Foot and Ankle Society (AOFAS) scores improved, with best results at 24 months, but deteriorating at 36 and 48 months.

Stem Cell Versus Autologous Chondrocyte Implantation

Few studies directly compare stem cell treatment to ACI. Adachi et al[1] showed similar results of B-galactosidase gene–transfected muscle-derived stem cells (MDSCs) with similarly transfected chondrocytes in rabbits. Testing a gellan gum hydrogel in rabbits, Oliveira et al[86] noted improved hyaline cartilage formation with chondrogenically predifferentiated ADSCs compared with chondrocytes, but similar results between undifferentiated ADSCs and chondrocytes.

Autologous, cultured BM-MSCs were compared with matrix-associated autologous chondrocyte transplantation in sheep, both suspended in collagen gel, with superior results for BM-MSCs at 1 year, particularly regarding integration with adjacent native cartilage.[72]

Arthroscopic, nonexpanded BMC implantation was retrospectively compared with open field and arthroscopic

ACI.[39] Significant clinical improvement was found in all 3 groups at 36 months, with no significant difference between them. Second-look arthroscopies demonstrated intact cartilage in all cases, with components of hyaline cartilage at biopsy. The 1-step arthroscopic BMC technique was less than half the cost of the 2-step arthroscopic ACI technique.[39]

Nejadnik et al[84] matched 36 patients undergoing ACI-P with 36 patients receiving autologous, culture-expanded BM-MSCs, with cultured chondrocytes or BM-MSCs implanted beneath a sutured periosteal patch in similar techniques. No significant difference was shown between the 2 groups in terms of clinical outcome up to 24 months except for physical role functioning, which was better improved for the BM-MSC group. The BM-MSC therapy required only 1 surgery, reduced costs, and caused less donor site morbidity. In contrast to the ACI group, an age-related response was not evident with BM-MSCs.[84]

Intra-Articular Injection of MSCs

Rationale

Intra-articular injection holds several potential advantages, including reduced recovery time and less cost.[15,25,33,58,64,101] Same day intra-articular administration of cells surgically obtained from the infrapatellar fat pad has been used to augment arthroscopic debridement.[64] From a therapeutic perspective, intra-articular injection may be better matched to the pathogenesis of OA,[79,100] although it may increase the risk of synovial proliferation.[63]

Cartilage Defects

In animal studies involving surgically created injuries to anterior cruciate ligaments, menisci, and articular cartilage, intra-articularly administered labeled BM-MSCs migrated to sites of injury.[68,80,81] To enhance migration to the desired location, Kobayashi et al[62] utilized an external magnetic force to direct magnetically labeled, intra-articularly injected BM-MSCs to experimentally created osteochondral defects in rabbit and swine patellae. In a further laboratory study, the magnetic force improved cell adhesion with no deleterious effects on cell proliferation for up to 3 weeks.[82]

Osteoarthritis

The anti-inflammatory and immunomodulatory effects of MSCs may retard the progression of OA. Intra-articular injections of stem cells slowed progression of surgically induced OA in goats following a single intra-articular dose of cultured BM-MSCs,[81] in rabbits using infrapatellar fat pad–derived MSCs,[110] and in rats using MDSCs with transduced genes.[73] BM-MSCs may also prevent the onset of posttraumatic OA in mice when injected at the same time as experimentally created closed tibial plateau fracture.[30]

Studies of animals with spontaneous OA, as well as experimental OA, have also reported improvement following MSC injection.[8,9,44,100] Cell labeling shows incorporation into damaged cartilage and partial cartilage regeneration in guinea pigs using cultured human BM-MSCs.[100] Black et al[8] reported significant clinical improvement in dogs with spontaneous OA of the coxofemoral joint following intra-articular SVF compared with placebo in a randomized, double-blinded, placebo-controlled trial. Improvements were also noted following a single humeroradial SVF injection for dogs with elbow OA, although with no control group in this study.[9] Guercio et al[44] found improved clinical benefit following ADSC injection in 4 dogs with lameness due humeroradial OA that had previously failed to respond to anti-inflammatory drugs. While most investigations appear to focus on restoration of articular cartilage, stem cell therapy may also benefit meniscal defects in animals and humans.[17,81]

Orozco et al[87] followed 12 patients receiving intra-articular, autologous-expanded BM-MSCs (40×10^6 cells) for 1 year, demonstrating significantly improved VAS, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Lequesne scores, with no significant difference in SF-36 and reduction in pain occurring within 3 months. Decreased poor quality cartilage on T2 mapping was seen in 11 patients. No human studies have yet compared MSC injection with other treatments in the absence of concurrent surgery.

Augmenting Surgery

Mesenchymal stem cell injection has been utilized as an adjunct to surgical techniques in humans[64,69,101] and animals.[75,107] In goats, BM-MSCs in alginate applied between osteochondral plugs during mosaicplasty was superior at 24 weeks compared with mosaicplasty alone, and better still using transforming growth factor-β1–transduced BM-MSCs.[107] Comparing intra-articular BM-MSCs and HA to intra-articular HA alone following microfracture of full-thickness chondral defects in horses, McIlwraith et al[75] noted significantly increased firmness and a non-significant trend for better overall repair quality with BM-MSCs.

The location of the infrapatellar fat pad makes it an attractive harvest target. Koh and Choi[64] utilized intra-articular injection of nonexpanded infrapatellar fat cells combined with arthroscopic debridement and PRP in humans with knee OA, with similar 1-year clinical findings compared with controls receiving only PRP post-debridement but significantly worse preoperative clinical (Tegner, Lysholm, and VAS) scores and ICRS grades in the MSC group, favoring a benefit from MSC injection. Of the 25 MSC patients, 18 were reassessed at 2 years, with significantly improved clinical features (WOMAC, Lysholm, and VAS scores) as well as MRI scores compared with preoperative, including significant clinical improvement in patients with grade 3 compared with grade 4 OA.[65] The fat pad was acquired at surgery, but the 3- to 4-hour processing necessitated a separate procedure that day.[64]

Kim et al[61] used non-expanded buttock adipose cells (SVF) as an intra-articular supplement to arthroscopic debridement and microfracture of talar osteochondral lesions. Significantly better clinical scores were obtained with MSC (31 ankles) compared with arthroscopic surgery alone (37 ankles).

In a randomized trial, Varma et al[117] compared 25 patients with mild to moderate knee OA undergoing arthroscopic

debridement alone with 25 patients undergoing arthroscopic debridement followed by intra-articular, nonexpanded BMC injection. Significant improvements in activities of daily living, sports and recreational activity, and quality of life scores were seen at 6 months.[117]

Saw et al[102] randomized 50 patients with ICRS grade 3-4 chondral defects undergoing arthroscopic debridement and subchondral drilling to a series of 8 injections of either non-expanded PBSC and HA or HA alone. Significantly better histologic scores (1066 vs 957) and MRI scores (9.9 vs 8.5) were reported at 18 months, with blinding of the reporting radiologist and pathologist, although no significant difference in IKDC scores at 24 months (74.8 vs 71.1).[102]

Lee et al[69] compared 35 knee full-thickness chondral defects undergoing arthroscopic debridement and microfracture, followed by outpatient injection of culture-expanded BM-MSC and HA, with 35 matched patients receiving open implantation of BM-MSC sheets beneath a sutured periosteal cover. Both groups showed significantly improved IKDC, Lysholm, VAS, and SF-36 scores at up to 2 years. The arthroscopic-injected group experienced more improvement in IKDC and Lysholm scores compared with the open group but similar improvement in VAS and SF-36 scores. MRI at 1 year showed good defect filling and integration.[69]

GROWTH FACTORS, PLATELET-RICH PLASMA, GENE THERAPY, AND HYALURONIC ACID

Platelet-rich plasma (PRP) is a source of autologous growth factors and an effective treatment for elbow tendinopathy.[24] A systematic review of intra-articular PRP injection for cartilage repair has shown safety in humans with potential pain reduction and improved function.[36] Longer term follow-up is required before it can be recommended for OA therapy.[36] After chemical induction of OA in rat knee joints, Mifune et al[76] compared MDSCs expressing bone morphogenetic protein 4 (BMP-4) and sFlt-1 with and without PRP. Improved articular cartilage repair was seen at 4 and 12 weeks with the addition of PRP.

Hyaluronic acid, a glycosaminoglycan extracellular matrix constituent, has been used for human OA with MRI evaluation up to 24 months showing beneficial effects on cartilage preservation.[125] Multiple animal studies have shown the combined use of stem cells and HA to produce better results than HA alone.[68,75,79,81]

Following in vitro expansion, stem cells may be induced via transforming growth factor-β1 or BMP-2 to undergo chondrogenic differentiation[22,72] or can be uninduced.[93,129] Encouraging results have been achieved with both approaches compared with controls.[22,129] Comparing induced with uninduced cells in animal studies shows mixed results.[22,72]

SAFETY OF MESENCHYMAL STEM CELL–RELATED PROCEDURES

In vitro manipulation creates the opportunity for infection, necessitating antibiotic administration above the minimum inhibitory concentration for relevant organisms while not impeding MSC proliferation and differentiation.[59]

Malignancy has been flagged as a potential risk of MSC implantation but has not yet been shown in clinical practice.[18,19,123] Miura et al[77] found that fibrosarcoma developed from murine BM-MSCs after numerous in vitro passages. Tolar et al[111] also identified sarcomatous transformation from mouse BM-MSCs expanded in vitro.

In 2005, Rubio et al[97] reported that after long-term in vitro culture of 4 to 5 months, human ADSCs exhibited malignant transformation. The group retracted this article in 2010, unable to reproduce the findings, proposing potential cross-contamination.[29] Another group described spontaneous transformation of BM-MSCs due to cross-contamination by immortalized cell lines, emphasizing the need for DNA fingerprinting.[96,112]

Bernardo et al[7] found that human BM-MSCs did not demonstrate malignant transformation after long-term culture, showing telomeric shortening with progressive decline in proliferation until reaching senescence.

DISCUSSION

Cell therapy represents promising treatment for many conditions, including joint disorders. The most widely practiced form, ACI and its newer variants, is capable of promoting cartilage repair and providing clinical benefit, although there is insufficient evidence to recommend these procedures over marrow stimulation techniques and osteochondral grafting.[83] Only limited human data exist for use of MSCs, but both surgical implantation and intra-articular injection appear to be safe and exhibit reasonable efficacy. There is currently a paucity of randomized human trials.

Cell sources that do not require in vitro expansion, such as BMC or SVF, provide the opportunity for same day therapy by reducing the turnaround time from cell harvest to treatment.[38,64] Intra-articular injection offers a reduction in postoperative recovery time.[8,64,117] For chondral injury, MSC therapy may improve symptom control through anti-inflammatory and immunomodulatory effects.[19]

CONCLUSION

At present, there is no conclusive evidence to recommend cell therapy over non-cell-based procedures, but both treatments appear to offer beneficial results. Non–stem cell therapy such as ACI, mosaicplasty, and microfracture at present possesses more clinical evidence than MSC treatments.

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