

Medical Policy



Title: Orthopedic Applications of Stem-Cell Therapy

Professional

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DESCRIPTION

Mesenchymal stem cells (MSCs) have the capability to differentiate into a variety of tissue types, including various musculoskeletal tissues. Potential uses of MSCs for orthopedic applications include treatment of damaged bone, cartilage, ligaments, tendons and intervertebral discs.

Background

Mesenchymal stem cells (MSCs) are multipotent cells (also called "stromal multipotent cells") that possess the ability to differentiate into various tissues including organs, trabecular bone, tendon, articular cartilage, ligaments, muscle, and fat. MSCs are associated with the blood vessels within bone marrow, synovium, fat, and muscle, where they can be mobilized for endogenous repair as occurs with healing of bone fractures. Bone-marrow aspirate is considered to be the most accessible source and, thus, the most common place to isolate MSCs for treatment of musculoskeletal disease. However,

harvesting MSCs from bone marrow requires an additional procedure that may result in donor-site morbidity. In addition, the number of MSCs in bone marrow is low, and the number and differentiation capacity of bone marrow-derived MSCs decreases with age, limiting their efficiency when isolated from older patients.

Tissues such as muscle, cartilage, tendon, ligaments, and vertebral discs show limited capacity for endogenous repair. Therefore, tissue engineering techniques are being developed to improve the efficiency of repair or regeneration of damaged musculoskeletal tissues. Tissue engineering focuses on the integration of biomaterials with MSCs and/or bioactive molecules such as growth factors. In vivo, the fate of stem cells is regulated by signals in the local 3-dimensional microenvironment from the extracellular matrix and neighboring cells. It is believed that the success of tissue engineering with MSCs will also require an appropriate 3-dimensional scaffold or matrix, culture conditions for tissue-specific induction, and implantation techniques that provide appropriate biomechanical forces and mechanical stimulation. The ability to induce cell division and differentiation without adverse effects, such as the formation of neoplasms, remains a significant concern. Given that each tissue type requires different culture conditions, induction factors (signaling proteins, cytokines, growth factors, etc.), and implantation techniques, each preparation must be individually examined.

The U.S. Food and Drug Administration (FDA) has stated:

“A major challenge posed by SC [stem-cell] therapy is the need to ensure their efficacy and safety. Cells manufactured in large quantities outside their natural environment in the human body can become ineffective or dangerous and produce significant adverse effects, such as tumors, severe immune reactions, or growth of unwanted tissue.” (1)

Regulatory Status

Concentrated autologous MSCs do not require approval by the U.S. Food and Drug Administration (FDA).

Demineralized bone matrix (DBM), which is processed allograft bone, is considered minimally processed tissue and does not require FDA approval. At least 2 commercially available DBM products are reported to contain viable stem cells:

- Osteocell Plus® (NuVasive): an allograft cellular bone matrix containing native MSCs.
- Trinity Evolution Matrix™ (Orthofix): an allograft that is processed and cryopreserved to maintain viable MSCs and osteoprogenitor cells.

Other products contain DBM and are designed to be mixed with bone marrow aspirate. Some of the products that are currently available are:

- Fusion Flex™ (Wright Medical): a dehydrated moldable DBM scaffold that will absorb autologous bone marrow aspirate.
- Ignite® (Wright Medical): an injectable graft with DBM that can be combined with autologous bone marrow aspirate.

Other commercially available products are intended to be mixed with bone marrow aspirate and have received 510(k) clearance, such as:

- Collage™ Putty (Orthofix): Composed of type-1 bovine collagen and beta tricalcium phosphate.

No products using engineered or expanded MSCs have been approved by the FDA for orthopedic applications.

In 2008, the FDA determined that the mesenchymal stem cells sold by Regenerative Sciences for use in the Regenexx™ procedure would be considered drugs or biological products and thus require submission of a New Drug Application (NDA) or Biologics Licensing Application (BLA) to the FDA. (2) To date, no NDA or BLA has been approved by the FDA for this product. As of 2013, the expanded stem-cell procedure is only offered in the Cayman Islands. Regenexx™ network facilities in the U.S. provide same-day stem-cell and blood platelet procedures, which do not require FDA approval. Available online at [http://www.regenexx.com/common-questions/regenexx-fda-clarification\](http://www.regenexx.com/common-questions/regenexx-fda-clarification)

POLICY

- A. Mesenchymal stem-cell therapy is considered **experimental / investigational** for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.
- B. Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix (DBM) with stem cells, is considered **experimental / investigational** for all orthopedic applications.

Policy Guidelines

Note: This policy does not address unprocessed allograft bone.

RATIONALE

The most recent literature update using the MEDLINE database was performed through March 5, 2013.

In 2010 the literature consisted almost entirely of review articles describing the potential of stem-cell therapy for orthopedic applications in humans, along with basic science experiments on sources of mesenchymal stem cells (MSCs), regulation of cell growth and differentiation, and development of scaffolds. (3) Authors of these reviews indicated that the technology was in an early stage of development. In literature searches of the MEDLINE database, use of cultured MSCs in humans was identified in only a few centers in the U.S., Europe, and Asia. The evidence base has been steadily increasing, although nearly all of the studies to date have been performed outside of the U.S. and are retrospective comparisons.

Cartilage Defects

In 2013, Filardo et al. conducted a systematic review of mesenchymal stem cells for the treatment of cartilage lesions. (4) They identified 72 preclinical papers and 18 clinical reports. Of the 18 clinical reports, none were randomized, 5 were comparative, 6 were case series, and 7 were case reports. In 2 clinical studies, the source of MSCs was adipose tissue, in 5, bone marrow concentrate, and in 11, the source was bone marrow-derived. Following is a summary of the key literature to date, focusing on comparative studies.

Cartilage Defects: MSCs Expanded from Bone Marrow

Wakitani and colleagues first reported use of expanded MSCs for repair of cartilage defects in 2002. (5) Cells from bone marrow aspirate of 12 patients with osteoarthritic knees were culture expanded, embedded in collagen gel, transplanted into the articular cartilage defect, and covered with autologous periosteum at the time of high tibial osteotomy. Clinical improvement was not found to be different between the experimental group and a group of 12 control patients who underwent high tibial osteotomy alone. Wakitani et al. have since published several cases of patients treated for isolated cartilage defects, with clinical improvement reported at up to 27 months. (6) However, most of the defects appear to have been filled with fibrocartilage. A 2011 report from Wakitani et al. was a follow-up safety study of 31 of the 41 patients (3 patients had died and 5 had undergone total knee arthroplasty) who had received MSCs for articular cartilage repair in their clinics between 1998 and 2008. (7) At a mean of 75 months (range, 5 to 137) since the index procedure, no tumors or infections were identified. Function was not reported.

Another study from Asia evaluated the efficacy of bone marrow-derived MSCs compared with autologous chondrocyte implantation (ACI) in 36 matched patient pairs. (8) Thirty-six consecutive patients with at least 1 symptomatic chondral lesion on the femoral condyle, trochlea, or patella were matched with 36 cases of ACI performed earlier, based on lesion sites and 10-year age intervals. Autologous MSCs were cultured from 30 mL of bone marrow from the iliac crest, tested to confirm that the cultured cells were MSCs, and implanted beneath a periosteal patch. Concomitant procedures included patella realignment, high-tibial osteotomy, partial meniscectomy, and anterior cruciate ligament reconstruction. Clinical outcomes, measured pre-operatively and at 3, 6, 12, 18, and 24 months' after operation using the International Cartilage Repair Society (ICRS) Cartilage Injury Evaluation Package, showed improvement in patients' scores over the 2-year follow-up in both groups, with no significant difference between groups for any of the outcome measures except for Physical Role Functioning on the Short Form (SF)-36, which showed a greater improvement over time in the MSC group.

A 2010 publication from Centeno et al. of Regenerative Sciences describes the use of percutaneously injected culture-expanded MSCs from the iliac spine in 226 patients. (9) Following harvesting, cells were cultured with autologous platelet lysate and re-injected under fluoroscopic guidance into peripheral joints (n=213) or intervertebral discs (n=13). Follow-up for adverse events at a mean of 10.6 months showed 10 cases of probable procedure-related complications (injections or stem-cell related), all of which were considered to be self-limited or treated with simple therapeutic measures. Serial magnetic resonance imaging (MRIs) from a subset of patients showed no evidence of tumor formation at a median follow-up of 15 months. The efficacy of these procedures was not reported. This procedure is no longer offered in the U.S.

Cartilage Defects: MSCs Concentrated from Bone Marrow

In 2009, Giannini et al. reported a one-step procedure for transplanting bone marrow-derived cells for type II (>1.5 cm², <5 mm deep) osteochondral lesions of the talus in 48 patients. (10) A total of 60 mL-bone marrow aspirate was collected from the iliac crest. The bone marrow-derived cells were concentrated in the operating room and implanted with a scaffold (collagen powder or hyaluronic acid membrane) and platelet gel. In a 2010 publication, Giannini et al. reported results of a retrospective analysis based on the evolution of the investigator's technique at the time of treatment. Outcomes following arthroscopic application of the MSC concentrate (n=25) were similar to open (n=10) or arthroscopic (n=46) ACI. (11) ACI with a biodegradable scaffold is not commercially available in the U.S.

Cartilage Defects: Adipose-derived MSCs

In 2012, Koh et al. reported a retrospective analysis of the injection of adipose-derived MSCs and platelet-rich plasma (PRP) into arthroscopically-debrided knees of 25 patients with osteoarthritis. (12) Results were compared with a randomly selected group of patients who had previously undergone arthroscopic debridement and PRP injections without stem cells. Although there was a trend for greater improvement in the MSC group, at final follow-up there was no significant difference between the MSC and control groups in clinical outcomes (Lysholm, Tegner, visual analog score).

Cartilage Defects: MSCs from Peripheral Blood

A 2013 report from Asia described a small randomized controlled trial with autologous peripheral blood MSCs for focal articular cartilage lesions. (13) Fifty patients with grade 3 and 4 lesions of the knee joint underwent arthroscopic subchondral drilling followed by 5 weekly injections of hyaluronic acid. Half of the patients were randomly allocated to receive injections of peripheral blood stem cells or no further treatment. There were baseline differences in age between the groups, with a mean age of 38 years for the treatment group compared to 42 for the control group. The peripheral blood stem cells were harvested after stimulation with recombinant human granulocyte colony-stimulating factor, divided in vials, and cryopreserved. At 6 months after surgery, hyaluronic acid and MSC were re-administered over 3 weekly injections. At 18 months after surgery, second look arthroscopy on 16 patients in each group showed significantly higher histological scores (by about 10%) for the MSC group (1,066 vs. 957 by independent observers) while blinded evaluation of magnetic resonance imaging (MRI) showed a higher morphologic score (9.9 vs. 8.5). There was no difference in International Knee Documentation Committee (IKDC) scores between the 2 groups at 24 months after surgery. It is uncertain how differences in patient age at baseline may have affected the response to subchondral drilling.

Cartilage Defects: Conclusions

The evidence base on MSCs for cartilage repair is increasing, although as of March 2013 only one study was identified that was randomized. This small randomized study, which is limited by group differences in age at baseline, is also the only comparative study to show an improvement in histological and morphologic outcomes. No study to date has shown an improvement in functional outcomes following treatment with MSCs for cartilage repair.

Fusion and Non-union

There is limited evidence on the use of allografts with stem cells for fusion of the extremities or spine or for the treatment of non-union. One retrospective series from 2009 was identified on the use of Trinity Evolution Matrix MSC bone allograft for revision surgery of the foot and ankle. (14)

Twenty-three patients were included who had undergone revision foot and/or ankle surgery for residual malunion, non-union, or significant segmental bone loss. Patients were followed to the point of radiographic and clinical union, which occurred at a median of 72.5 days for 21 of the 23 patients (91.3%).

Osteonecrosis

Two randomized comparative trials from Asia have been identified that evaluated the use of MSCs for osteonecrosis of the femoral head.

Osteonecrosis: MSCs Expanded from Bone Marrow

In 2012, Zhao et al. reported a randomized trial that included 100 patients (104 hips) with early stage femoral head osteonecrosis treated with core decompression and expanded bone marrow MSCs versus core decompression alone. (15) At 60 months after surgery, 2 of the 53 hips (3.7%) treated with MSCs progressed and underwent vascularized bone grafting, compared with 10 of 44 hips (23%) in the decompression group who progressed and underwent either vascularized bone grafting (n=5) or total hip replacement (n=5). The MSC group also had improved Harris Hip Scores compared with the control group on independent evaluation (data presented graphically). The volume of the lesion was also reduced by treatment with MSCs.

Osteonecrosis: MSCs Concentrated from Bone Marrow

Another small trial randomized 40 patients (51 hips) with early stage femoral head osteonecrosis to core decompression plus concentrated bone marrow MSCs or core decompression alone. (16) Blinding of assessments in this small trial was not described. Harris Hip Score was significantly improved in the MSC group (scores of 83.65 and 82.42) compared with core decompression (scores of 76.68 and 77.39). Kaplan-Meier analysis showed improved hip survival in the MSC group (mean of 51.9 weeks) compared to the core decompression group (mean of 46.7 weeks). There were no significant differences between the groups in the radiographic assessment or MRI results.

Osteonecrosis: Conclusions

Two small studies from Asia have compared core decompression alone versus core decompression with MSCs in patients with osteonecrosis of the femoral head. Both studies reported improvement in the Harris Hip Score in patients treated with MSCs, although it was not reported whether the patients or investigators were blinded to the treatment group. Hip survival was significantly improved following treatment with either expanded or concentrated MSCs. The effect appears to be larger with expanded MSCs compared to concentrated MSCs. Additional studies with a larger number of patients are needed to permit greater certainty regarding the effect of this treatment on health outcomes.

Ongoing Clinical Trials

A search of online site: ClinicalTrials.gov in March 2013 identified a number of trials on use of MSCs for orthopedic indications from both within and outside the U.S. The following is a sample of some of the larger studies:

- A Phase I/II randomized, placebo controlled, double blind study of 2 doses of Chondrogen™ (Osiris Therapeutics) or a placebo intra-articular injection following meniscectomy in 60 patients is listed as completed in 2008 (NCT00225095). Chondrogen™ is a preparation of adult MSCs in a solution containing hyaluronic acid. Three-year follow-up of Chondrogen™

versus placebo injections is listed as a separate study (NCT00702741). The status of this trial is unknown.

- Medipost is sponsoring a randomized, open-label, multicenter Phase III clinical trial to compare the efficacy and safety of Cartistem® and microfracture in patients with knee articular cartilage injury or defect (NCT01041001). MSCs will be isolated from umbilical cord blood and cultured, mixed with semi-solid polymer, and administered in the cartilage tissue lesion by orthopedic surgery. The study is listed as completed as of April 2012 with an enrollment of 104 patients. Preliminary results of this study were presented at the annual meeting of the American Academy of Orthopaedic Surgeons in February 2012. As of March 2013, no peer-reviewed publications from this trial have been identified.
- Medipost is sponsoring a 60-month follow-up study (NCT01626677) of the patients who participated in the Phase III trial of Cartistem® (NCT01041001). The study has an estimated enrollment of 103 patients with completion in May 2015.
- NCT00885729 is a Phase I randomized, single-blind, active control trial of MSCs compared with chondrocytes to heal articular cartilage defects in 50 patients. The study is sponsored by an academic medical center in Norway. Both MSCs and chondrocytes will be delivered in a commercially available scaffold (not described). The estimated study completion date is 2018.
- The National University of Malaysia is sponsoring a randomized controlled trial of intra-articular MSC injection versus hyaluronic acid in patients with osteoarthritis (NCT01459640). The study has an estimated enrollment of 50 patients with completion in 2014.
- Three series are listed with Trinity Evolution Matrix for foot and ankle surgery, anterior cervical discectomy and fusion (ACDF), and posterior or transforaminal lumbar interbody fusion (PLIF or TLIF). All 3 studies are listed as ongoing but not recruiting subjects.

Summary

Overall, the literature suggests a technology that is at an early stage of development, with the vast majority of studies focused on development of methods for tissue engineering along with preliminary testing in animal models. Despite this research into the methods of treatment, there are uncertainties regarding the optimal source of cells and the delivery method. Current available evidence on procedures using autologous bone-marrow-derived mesenchymal stem cells (MSCs) for orthopedic indications in humans consists primarily of case series and small non-randomized comparative trials with insufficient data to evaluate health outcomes. In addition, expanded MSCs for orthopedic applications are not FDA approved (concentrated autologous MSCs do not require FDA approval). Due the lack of evidence that clinical outcomes are improved, use of stem cells for orthopedic applications is considered investigational.

Practice Guidelines and Position Statements

The American Association of Orthopaedic Surgeons (AAOS) states that stem-cell procedures in orthopedics are still at an experimental stage; most musculoskeletal treatments using stem cells are performed at research centers as part of controlled, clinical trials, and results of studies in animal models provide proof-of-concept that in the future, similar methods could be used to treat osteoarthritis, nonunion of fractures, and bone defects in humans. (17)

In 2006, the Mesenchymal and Tissue Stem-Cell Committee of the International Society for Cellular Therapy proposed a minimal set of criteria to standardize the characterization of multipotent mesenchymal stem cells. (18) The proposed criteria for human MSCs included plastic-adherence when maintained in standard culture conditions; a phenotype of expression of CD105, CD73, and CD90 with a lack surface expression of CD45, CD34, CD14 or CD11b, CD79

alpha or CD19, and HLA-DR surface molecules; and the capability of differentiating into osteoblasts, adipocytes, and chondrocytes using standard *in vitro* tissue culture-differentiating conditions.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

38206 Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230 Bone marrow harvesting for transplantation; allogeneic
38241 Hematopoietic progenitor cell (HPC); autologous transplantation

Diagnoses

Experimental / investigational for all diagnoses related to this policy.

REVISIONS

09-19-2013	Policy added to the bcbsks.com web site on 08-20-2013 for an effective date of 09-19-2013 for professional and institutional.
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