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Orthopedic Applications of Stem-Cell Therapy

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Origination: 3/2013
Last Review: 3/2014
Next Review: 3/2015

Policy

BCBSKC will not provide coverage for orthopedic applications of stem-cell therapy. This is considered investigational.

When Policy Topic is covered

Not Applicable

When Policy Topic is not covered

Mesenchymal stem-cell therapy is considered **investigational** for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.

Description of Procedure or Service

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. Stimulation of endogenous MSCs is the basis of procedures such as bone marrow stimulation (e.g., microfracture) and harvesting/grafting of autologous bone for fusion. 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
No products using engineered MSCs have been approved by the FDA for orthopedic applications.

The FDA has 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.

Rationale

This policy was created in 2010 and updated periodically using the MEDLINE database. The most recent literature update was for the period of February 2011 through February 2012.

Literature Review
At this time, the literature consists 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 indicate that the technology is 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.

Wakitani and colleagues first reported use of expanded MSCs for repair of cartilage defects in 2002. (4) 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. (5) 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. (6) Patients who could not return to clinic were interviewed by telephone to determine if there were any abnormalities in the operated joints. At a mean of 75 months (range, 5 to 137) since the index procedure, no tumors or infections were identified. Function was not reported. In the absence of controlled studies, the benefit of this procedure in comparison with established alternatives such as microfracture is unclear.

Another study from Asia compared the efficacy of bone marrow-derived MSCs and autologous chondrocyte implantation (ACI) in 36 matched patient pairs. (7) 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. At baseline, the MSC group had a slightly (non-significantly) greater lesion size (4.6 cm2 vs. 3.6 cm2, respectively). The grade of the lesion was comparable for the 2 groups (30-33% grade 4). Autologous MSCs were cultured from 30 mL of bone marrow from the iliac crest and tested to confirm that the cultured cells were MSCs. The cultured chondrocytes or MSCs were implanted beneath a periosteal patch. Concomitant procedures included patella realignment, high-tibial osteotomy, partial meniscectomy, and anterior cruciate ligament reconstruction. Clinical outcomes were 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. The Evaluation Package included questions from the Short-Form-36 (SF-36) Health Survey, International Knee Documentation Committee (IKDC) subjective knee evaluation

form, Lysholm knee scale, and Tegner activity level scale. Both treatments improved patients' scores over the 2-year follow-up by mixed effect models. There was no significant difference between groups for any of the measures except for Physical Role Functioning on the SF-36, which showed a greater improvement over time in the MSC group. Although scatter plots were provided, neither the absolute improvement nor the proportion of patients with clinically significant improvement was reported. This study is also limited by the small number of patients.

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. (8) The mean age of the patients was 29 years. Fifteen of the patients had been previously treated by microfracture (n=8), debridement (n=5), or autologous chondrocyte transplantation (n=2). 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. Twenty-two patients underwent associated surgical procedures (osteophytectomy, synovectomy, loose body extraction, or calcaneal osteotomy). Active and passive ankle motions were advised beginning the day after surgery; no weight bearing was recommended for 6 weeks. Patients were evaluated at 6, 12, 18, and 24 months after surgery with standard radiographs and magnetic resonance imaging (MRI). At 24-month follow-up, the mean American Orthopaedic Foot and Ankle Society (AOFAS) score had changed from 64.4 to 91.4, representing a meaningful improvement. The AOFAS score at follow-up was affected by the area of the lesion and previous surgeries. MRI showed newly formed tissue at the lesion site in all patients. Histologic evaluation in the first 3 patients (asymptomatic) showed regenerated tissue in various degrees of remodeling, although none showed entirely hyaline cartilage. Two additional patients were reoperated due to hypertrophic regenerated tissue. Integration with the healthy cartilage was reported to be complete in all 5 patients with a smooth transition zone.

A 2010 publication from Centeno et al. 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 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.

Ongoing Clinical Trials

A search of online site: ClinicalTrials.gov in March 2012 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).
- 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 has an estimated enrollment of 104 patients with completion in 2011. Preliminary results of this study were presented at the annual meeting of the American Academy of Orthopaedic Surgeons in February 2012.
- Orthofix is sponsoring a radiographic and clinical study evaluating a novel allogeneic, cancellous, bone matrix containing viable stem cells (Trinity Evolution Matrix) in subjects undergoing tibiotalar arthrodesis with or without hind-foot fusion (NCT00988338). The study has an estimated enrollment of 100 patients with completion in 2012.

- 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.

Summary

Overall, the literature suggests a technology that is at a very 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. A number of clinical trials are in progress but have not yet been published. Current available evidence on procedures using autologous bone-marrow-derived mesenchymal stem cells for orthopedic indications in humans consists of several case reports/case series and 1 cohort study, with insufficient data to evaluate health outcomes. In addition, MSCs for orthopedic applications are not FDA approved. Therefore, 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. (10)

Medicare National Coverage

There is no national coverage determination.

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Billing Coding/Physician Documentation Information

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

Additional Policy Key Words

8.01.52

Policy Implementation/Update Information

3/1/13 New policy; considered investigational
3/1/14 Literature updated

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