APPENDIX to Orthopedic Applications of Stem Cell Therapy Policy

Prior Authorization Requirements

This service (or procedure) is considered **investigational** in all instances. If you would like to submit additional information please forward to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

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) in 2012 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.

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 would require submission of a New Drug Application (NDA) or Biologics Licensing Application (BLA) to the FDA. At the time of this policy development (2013), no NDA or BLA has been approved by the FDA for this product.

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 MSCs, regulation of cell growth and differentiation, and development of scaffolds (Deans & Elisseeff, 2009). 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 in 2002 first reported use of expanded MSCs for repair of cartilage defects. 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. in 2007 have since published several cases of patients treated for isolated cartilage defects, with clinical improvement reported at up to 27 months. 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. 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 in 2012 by Nejadnik et al. compared the efficacy of bone marrow-derived MSCs and autologous chondrocyte implantation (ACI) in 36 matched patient pairs. 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. 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. 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.

A number of clinical trials are in progress but no trial results have been posted and some trials are not expected to be completed for several years. In addition, MSCs for orthopedic applications are not approved by the U.S. Food and Drug Administration (FDA). Therefore, use of stem cells for orthopedic applications is considered investigational.

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) 2007 stated that stem-cell procedures in orthopedics were still at an experimental stage; most musculoskeletal treatments using stem cells at that time were performed at research centers as part of controlled, clinical trials, and results of studies in animal models provided proof-of-concept that in the future, similar methods could be used to treat osteoarthritis, nonunion of fractures, and bone defects in humans.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	20999	Unlisted procedure, musculoskeletal system, general
	38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPC	None	
ICD9 Procedure	None	
ICD9 Diagnosis	All Diagnoses	
Place of Service	All Places of Service	

Tables

N/A

Definitions

Mesenchymal stem cells (MSCs) - are a prototypical adult stem cell with capacity for self-renewal and differentiation with a broad tissue distribution. Initially described in bone marrow, MSCs have the capacity to differentiate into mesoderm- and nonmesoderm-derived tissues including osteoblasts (bone cells), chondryocytes (cartilage cells), and adipocytes (fat cells). This phenomenon has been documented in specific cells and tissues in living animals and their counterparts growing in tissue culture.

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

- N/A

Key / Related Searchable Words

N/A

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
3/29/2013	New Policy Adoption	Medical Policy Committee

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

Click here to view the policy statement for this policy

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