Protocol

Orthopedic Applications of Stem-Cell Therapy

(80152)

Medical Benefit		**Effective Date**: 10/01/13	**Next Review Date**: 07/15
Preauthorization	No	**Review Dates**: 09/10, 07/11, 07/12, 07/13, 07/14	

The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. ***Preauthorization is not required but is recommended if, despite this Protocol position, you feel this service is medically necessary.*** *Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

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

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 three-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 three-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), 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 FDA.

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

- Allostem® (AlloSource): partially demineralized allograft bone seeded with adipose-derived MSCs
- Map3™ (rti surgical) contains cortical cancellous bone chips, DBM, and multipotent adult progenitor cells
- Osteocel Plus® (NuVasive): DBM combined with viable MSCs that have been isolated from allogeneic bone marrow
- Trinity Evolution Matrix™ (Orthofix) DBM combined with viable MSCs that have been isolated from allogeneic bone marrow

Whether these products can be considered minimally manipulated tissue is debated. A product would not meet the criteria for FDA regulation part 1271.10 if it is dependent upon the metabolic activity of living cells for its primary function. Otherwise, a product would be considered a biologic product and would need to demonstrate safety and efficacy for the product's intended use with an investigational new drug and Biologics License Application (BLA).

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.
- Vitoss® (Stryker, developed by Orthovita): composed of beta tricalcium phosphate.
- nanOss® Bioactive (rti surgical, developed by Pioneer Surgical): nanostructured hydroxyapatite and an open structured engineered collagen carrier.

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

In 2008, 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 FDA. (2) To date, no NDA or BLA has been approved by 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.

Related Protocols

Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Conditions

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy (Formerly Corporate Medical Guideline)

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

Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix (DBM) with stem cells, is considered **investigational** for all orthopedic applications.

Policy Guideline

Note: This Protocol does not address unprocessed allograft bone.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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15. Saw KY, Anz A, Siew-Yoke Jee C et al. Articular cartilage regeneration with autologous peripheral blood stem cells versus hyaluronic acid: a randomized controlled trial. Arthroscopy 2013; 29(4):684-94.
16. Rush SM, Hamilton GA, Ackerson LM. Mesenchymal stem cell allograft in revision foot and ankle surgery: a clinical and radiographic analysis. J Foot Ankle Surg 2009; 48(2):163-9.
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