Protocol

Stem-Cell Therapy for Peripheral Arterial Disease

(80155)

Medical Benefit		**Effective Date**: 10/01/11	**Next Review Date**: 07/15
Preauthorization	No	**Review Dates**: 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

Critical limb ischemia due to peripheral arterial disease (PAD) results in pain at rest, ulcers, and significant risk for limb loss. Injection of hematopoietic stem cells concentrated from bone marrow is being evaluated for the treatment of critical limb ischemia when surgical or endovascular revascularization has failed.

Background

PAD is a common atherosclerotic syndrome that is associated with significant morbidity and mortality. A less common cause of PAD is Buerger disease, also called thromboangiitis obliterans, which is a nonatherosclerotic segmental inflammatory disease that occurs in younger patients and is associated with tobacco use. Development of PAD is characterized by narrowing and occlusion of arterial vessels and eventual reduction in distal perfusion. Critical limb ischemia (CLI) is the end stage of lower extremity PAD in which severe obstruction of blood flow results in ischemic pain at rest, ulcers, and a significant risk for limb loss. The standard therapy for severe, limb-threatening ischemia is revascularization aiming to improve blood flow to the affected extremity. If revascularization has failed or is not possible, amputation is often necessary.

Two endogenous compensating mechanisms may occur with occlusion of arterial vessels, capillary growth (angiogenesis) and development of collateral arterial vessels (arteriogenesis). Capillary growth is mediated by hypoxia-induced release of chemo- and cytokines such as vascular endothelial growth factor, and occurs by sprouting of small endothelial tubes from preexisting capillary beds. The resulting capillaries are small and cannot sufficiently compensate for a large occluded artery. Arteriogenesis with collateral growth is, in contrast, initiated by increasing shear forces against vessel walls when blood flow is redirected from the occluded transport artery to the small collateral branches, leading to an increase in the diameter of preexisting collateral arterioles.

The mechanism underlying arteriogenesis includes the migration of bone marrow-derived monocytes to the perivascular space. The bone marrow-derived monocytes adhere to and invade the collateral vessel wall. It is not known if the expansion of the collateral arteriole is due to the incorporation of stem cells into the wall of the vessel or to cytokines released by monocytic bone marrow cells that induce the proliferation of resident endothelial cells. It has been proposed that bone marrow-derived monocytic cells may be the putative circulating endothelial progenitor cells. Notably, the same risk factors for advanced ischemia (diabetes, smoking, hyperlipidemia, advanced age) are also risk factors for a lower number of circulating progenitor cells.

The rationale of hematopoietic stem-cell/bone marrow-cell therapy in PAD is to induce arteriogenesis by boosting the physiological repair processes. This requires large numbers of functionally active autologous

precursor cells, and subsequently, a large quantity of bone marrow (e.g., 240-500 mL) or other source of stem cells. The SmartPReP2® Bone Marrow Aspirate Concentrate System (Harvest Technologies) has been developed as a single-step point-of-care, bedside centrifugation system for the concentration of stem cells from bone marrow. The system is composed of a portable centrifuge and an accessory pack that contains processing kits including a functionally closed dual-chamber sterile processing disposable container. The SmartPReP2® system is designed to concentrate a buffy coat of 20 mL from whole bone marrow aspirate of 120 mL.

The concentrate of bone marrow aspirate contains a mix of cell types, including lymphocytoid cells, erythroblasts, monocytoid cells, and granulocytes. Following isolation and concentration, the hematopoietic stem-cell/bone marrow concentrate is administered either intra-arterially or through multiple injections (20 to 60) into the muscle, typically in the gastrocnemius. Other methods of concentrating stem cells include the in vitro expansion of bone marrow-derived stem cells or use of granulocyte colony-stimulating factor (GM-CSF) to mobilize peripheral blood mononuclear cells. There is some discrepancy in the literature regarding the nomenclature of cell types. Studies addressed in this Protocol include the use of mononuclear cells/monocytes and/or mesenchymal stem cells.

The primary outcome in stem-cell therapy trials regulated by the U.S. Food and Drug Administration (FDA) is amputation-free survival. Other outcomes for CLI include the Rutherford criteria for limb status, healing of ulcers, the Ankle-Brachial Index (ABI), transcutaneous oxygen pressure (Tco_2), and pain-free walking. The Rutherford criteria include ankle and toe pressure, the level of claudication, ischemic rest pain, tissue loss, nonhealing ulcer, and gangrene. The ABI measures arterial segmental pressures on the ankle and brachium, and indexes ankle systolic pressure against brachial systolic pressure (normative range, 0.95-1.2). An increase greater than 0.1 is considered to be clinically significant. Tco_2 is measured with an oxymonitor; the normal value is 70 to 90 mm Hg. Pain-free walking may be measured by time on a treadmill, or more frequently, by distance in a 400-meter walk.

Regulatory Status

Two devices have been identified that provide point-of-care concentration of bone marrow aspirate:

- The SmartPReP2® Bone Marrow Aspirate Concentrate System is a microprocessor-controlled dedicated centrifuge with decanting capability and an accessory BMAC IDE PAD Pack for processing a patient's bone marrow aspirate. The system is in a phase 3 trial; expected completion of the trial is in 2014. FDA product Code: JQC.
- The MarrowStim P.A.D. kit™ (Biomet Biologics) is in a phase 3 trial for the treatment of PAD with completion expected May 2014. FDA product Code: JQC.

Ixmyelocel-T (Aastrom) is an expanded stem-cell product where bone marrow aspirate is sent to a processing facility to be cultured in a bioreactor and expanded over a two-week period. The expanded cell population is enriched with mesenchymal precursors and alternatively activated macrophages. This product is currently being evaluated in a pivotal phase 3 trial regulated by FDA's Center of Biologic Evaluation and Research.

Pluristem is developing allogeneic cell therapy derived from full-term placenta (PLX-PAD cells). This product has been tested in a phase 1 trial in patients with critical limb ischemia.

Related Protocols

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

Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

Orthopedic Applications of Stem-Cell Therapy

Policy (Formerly Corporate Medical Guideline)

Treatment of peripheral arterial disease, including critical limb ischemia, with injection or infusion of cells concentrated from bone marrow aspirate is considered **investigational**.

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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