

(80155)

Medical Benefit		Effective Date: 10/01/18	Next Review Date: 07/19
Preauthorization	No	Review Dates: 07/11, 07/12, 07/13, 07/14, 07/15, 07/16, 07/17, 07/18	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. 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.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With peripheral arterial disease 	Interventions of interest are: <ul style="list-style-type: none"> Stem cell therapy 	Comparators of interest are: <ul style="list-style-type: none"> Conservative management 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Symptoms Change in disease status Morbid events Functional outcomes Quality of life Treatment-related morbidity

DESCRIPTION

Critical limb ischemia due to peripheral arterial disease results in pain at rest, ulcers, and significant risk for limb loss. Injection or infusion of stem cells, either concentrated from bone marrow, expanded in vitro, stimulated from peripheral blood, or from an allogeneic source, is being evaluated for the treatment of critical limb ischemia.

SUMMARY OF EVIDENCE

For individuals who have peripheral arterial disease (PAD) who receive stem cell therapy, the evidence includes small randomized trials, systematic reviews, and case series. Relevant outcomes are overall survival, symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related morbidity. The current literature on stem cells as a treatment for critical limb ischemia due to PAD consists primarily of phase 2 studies using various cell preparation methods and methods of administration. A meta-analysis of the trials with the lowest risk of bias has shown no significant benefit of stem cell therapy for overall survival, amputation-free survival, or amputation rates. Well-designed randomized controlled trials with a larger number of subjects and low risk of bias are needed to evaluate the health outcomes of these various procedures. Several are in progress, including multicenter randomized, double-blind, placebo-controlled trials. More data on the safety and durability of these treatments are also needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Treatment of peripheral arterial disease, including critical limb ischemia, with injection or infusion of stem cells from concentrated bone marrow, expanded in vitro, stimulated from peripheral blood, or from an allogeneic source, is considered **investigational**.

BACKGROUND

PERIPHERAL ARTERIAL DISEASE

PAD is a common atherosclerotic syndrome 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 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.

Physiology

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 chemokines 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.

Treatment

The standard therapy for severe, limb-threatening ischemia is revascularization aiming to improve blood flow to the affected extremity. If revascularization fails or is not possible, amputation is often necessary.

The rationale for hematopoietic cell or bone marrow–cell therapy in PAD is to induce arteriogenesis by boosting the physiologic 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 another 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 cell or 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 a granulocyte-macrophage colony-stimulating factor to mobilize peripheral blood mononuclear cells. There is some discrepancy in the literature regarding the nomenclature of cell types. Studies addressed in this evidence review 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 critical limb ischemia include the Rutherford criteria for limb status, healing of ulcers, the Ankle-Brachial Index, transcutaneous oxygen pressure, and pain-free walking. The Rutherford criteria include ankle and toe pressure, level of claudication, ischemic rest pain, tissue loss, nonhealing ulcer, and gangrene. The Ankle-Brachial Index measures arterial segmental pressures on the ankle and brachium and indexes ankle systolic pressure against brachial systolic pressure (normative range, 0.95-1.2 mm Hg). An increase more than 0.1 mm Hg is considered clinically significant. Transcutaneous oxygen pressure is measured with an oxymonitor; a normal range 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

At least two devices that provide a point-of-care concentration of bone marrow aspirate have been cleared for marketing by the FDA through the 510(k) process:

- The SmartPREP2® Bone Marrow Aspirate Concentrate System, SmartPREP Platelet Concentration System (Harvest Technologies)
- The MarrowStim™ Concentration Kit and Marrow Stim™ Mini Concentration Kit (Biomet Biologics).

FDA product code: JQC.

Ixmyelocel-T (Aastrom Biosciences now Vericel Corp.) 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 precursor cells and alternatively activated macrophages. This product is currently being evaluated in a pivotal phase 3 trial regulated by the FDA.

Pluristem Therapeutics 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 for Wound Healing and Other Non-Orthopedic Conditions

Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

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

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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