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, expanded in vitro, stimulated from peripheral blood, or from an allogeneic source, is being evaluated for the treatment of critical limb ischemia when surgical or endovascular revascularization has failed.

**Background**

Peripheral arterial disease (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 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 (VEGF), and occurs by sprouting of small endothelial tubes from pre-existing 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 pre-existing 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 and advanced age) are also risk factors for a lower number of circulating progenitor cells.
Stem-cell Therapy for Peripheral Arterial Disease

The rationale of hematopoietic stem-cell/bone marrow 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 auffy 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, monocyotid 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-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 policy 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 (TcO2), 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 (normal range 0.95 – 1.2). An increase greater than 0.1 is considered to be clinically significant. TcO2 is measured with an oxymonitor; the normal value is 70-90 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 (Harvest Technologies)
- The MarrowStim P.A.D. kit™ (Biomet Biologics)

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 2-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 the U.S. Food and Drug Administration’s Center of Biologic Evaluation and Research.

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 Policies:**

- Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia
- Orthopedic Applications of Stem Cell Therapy
- Growth Factors in Wound Healing
Stem-cell Therapy for Peripheral Arterial Disease

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Stem-cell therapy for the treatment of peripheral arterial disease is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Stem-cell Therapy for Peripheral Arterial Disease is covered

Not applicable

When Stem-cell Therapy for Peripheral Arterial Disease is not covered

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.

Policy Guidelines

The evidence for stem cell therapy in individuals who have peripheral arterial disease (PAD) includes small randomized trials and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, morbid events, 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. Meta-analysis of these trials shows 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. A number of trials are in progress, including several large randomized, double-blind, placebo-controlled trials. Further information on the safety and durability of these treatments are also needed. The evidence is insufficient to determine the effects of the technology on health outcome.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina website at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0263T, 0264T, 0265T

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.
Stem-cell Therapy for Peripheral Arterial Disease

**Scientific Background and Reference Sources**


Medical Director review 7/2011

Specialty Matched Consultant Advisory Panel review 10/2011


Specialty Matched Consultant Advisory Panel review 10/2012


Specialty Matched Consultant Advisory Panel review 10/2013


Bartel RL, Booth E, Cramer C et al. From bench to bedside: review of gene and cell-based therapies
Stem-cell Therapy for Peripheral Arterial Disease

and the slow advancement into phase 3 clinical trials, with a focus on Aastrom's Ixmyelocel-T. Stem Cell Rev 2013; 9(3):373-83.


Senior Medical Director review 11/2014


Specialty Matched Consultant Advisory Panel review 10/2015

Senior Medical Director review 10/2015


Medical Director review 10/2016


Medical Director review 7/2017

Policy Implementation/Update Information

7/19/11 New policy implemented. Treatment of peripheral arterial disease, including critical limb ischemia, with injection or infusion of cells concentrated from bone marrow aspirate is considered investigational. Medical Director review 7/2011. (mco)


6/29/12 References updated. No changes to Policy Statement. (mco)

11/13/12 Specialty Matched Consultant Advisory Panel review 10/2012. No changes to Policy Statements. (mco)


11/12/13 Specialty Matched Consultant Advisory Panel review 10/2013. No changes to Policy Statements. (mco)

7/15/14 References updated. No changes to Policy Statements. (mco)


7/1/15 References updated. Policy Statements remain unchanged. (td)

Stem-cell Therapy for Peripheral Arterial Disease

4/29/16  Policy Guidelines section updated. References updated. (td)


7/28/17  Policy revised with updated language clarification under the “When Not Covered” section, to include “stem cells from concentrated bone marrow, expanded in vitro, stimulated from peripheral blood, or from an allogeneic source is considered investigational.” No change to policy intent. Medical Director review 7/2017. (jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.