Stem Cell Therapy for Peripheral Arterial Disease

Policy # 00298
Original Effective Date: 06/15/2011
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the treatment of peripheral arterial disease (PAD), 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 to be **investigational.***

Background/Overview

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 (eg, 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
At least 2 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:

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- 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 2-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 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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

STEM CELL THERAPY

At this time, the literature on stem cell therapy consists primarily of case series, small phase 1/2 studies, and review articles. Systematic reviews, controlled studies, and the larger case series are described next.

Rigato et al (2017) published a systematic review of autologous cell therapy for peripheral arterial disease. They identified 19 RCTs (837 patients), 7 nonrandomized controlled studies (338 patients), and 41 noncontrolled studies (1177 patients). There was heterogeneity across studies in setting, underlying diseases, types and doses of cells, routes of administration, and follow-up durations. The routes of administration were intra-arterial or intramuscular, and the cell types used included bone marrow mononuclear cells (BM-MNCs), mesenchymal stem cells, mobilized peripheral blood, ixmyelocel-T, CD34-positive cells, and CD133-positive cells. Many studies were a pilot or phase 2 trials and were rated as low quality. There was an indication of publication bias. A meta-analysis of all RCTs showed a significant reduction in amputation rates, improved amputation-free survival, and improved wound healing. However, when only the placebo-controlled trials (n=19) were analyzed the effects were no longer statistically significant, and analysis of only RCTs with a low risk of bias (n=3) found no benefit of cell therapy.

The following discussion concerns some RCTs included and not included in the meta-analyses. A number of these RCTs were described as pilot or phase 2 studies.

Concentrated Bone Marrow Aspirate (Monocytes and MSCs)
Intramuscular Injection
Prochazka et al (2010) reported on a randomized study of 96 patients with critical limb ischemia (CLI), and foot ulcer. Patient inclusion criteria were CLI as defined by an Ankle-Brachial Index (ABI) score of 0.4 or less, ankle systolic pressure of 50 mm Hg or less or toe systolic pressure of 30 mm Hg or less, and failure of basic conservative and revascularization treatment (surgical or endovascular). Patients were randomized to treatment with bone marrow concentrate (n=42) or standard medical care (n=54). The primary end points were major limb amputation during 120 days posttreatment and degree of pain and function at 90- and 120-day follow-ups. At baseline, the control group compared with treatment group had a higher proportion of patients with diabetes (98.2% vs 88.1%), hyperlipidemia (80.0% vs 54.8%), and ischemic heart disease (76.4% vs 57.1%), respectively. Additionally, the control group had a higher proportion of patients (72% vs 40%) with University of Texas Wound Classification stage DIII (deep ulcers with osteitis). For the 42 patients in the treatment group, there was a history of 50 revascularization procedures; 46 of 54 patients in the control group had a history of revascularization procedures. All 42 patients in the bone marrow group finished 90 days of follow-up, and 37 of 54 patients in the control group finished 120 days of follow-up. Differences in lengths of follow-up for the primary outcome measure were unexplained. Five patients in the bone marrow group and eight in the control group died of causes unrelated to the therapy during follow-up. At follow-up, the frequency of major limb amputation was 21% in patients treated with bone marrow concentrate and 44% in controls. Secondary end points were assessed only in those treated with bone marrow concentrate. In the treatment group with salvaged limbs, toe pressure and Toe-Brachial Index score increased from 22.66 to 25.63 mm Hg and from 0.14 to 0.17, respectively. Interpretation of results is limited by unequal baseline measures, lack of blinding, differences in lengths of follow-up, differences in losses to follow-up, and differences in follow-up measures for the 2 groups.

Benoit et al (2011) reported on a U.S. FDA–regulated, double-blind pilot RCT of 48 patients with CLI who were randomized 2:1 to bone marrow concentrate using the SmartPReP system or to iliac crest puncture

with an intramuscular injection of diluted peripheral blood. At 6-month follow-up, the differences in the percentages of amputations between the bone marrow concentrate group (29.4%) and diluted peripheral blood group (35.7%) was not statistically significant. In a subgroup analysis of patients with tissue loss at baseline (Rutherford 5), intramuscular injection of bone marrow concentrate resulted in a lower amputation rate (39.1%) than placebo (71.4%). Power analysis indicated that 210 patients were needed to achieve 95% power in a planned pivotal trial.

Intramuscular injection with a combination BM-MNCs and gene therapy with a vascular endothelial growth factor plasmid was tested in a 2015 European RCT assessing 32 patients. Controls in this trial were treated pharmacologically, and therefore the groups were not blinded to treatment. Several objective measures were improved in the BM-MNC group but not in the control group. They included ABI scores, development of collateral vessels measured with angiography, and healing rates of ischemic ulcers. Amputations were performed in 25% of patients in the BM-MNC group and in 50% of patients in the control group.

Intra-Arterial Injection

The Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation (JUVENTAS) trial was a randomized, double-blind, placebo-controlled study (2015) from Europe (NCT00371371). This foundation-supported trial evaluated the clinical effects of repeated intra-arterial infusion of BM-MNCs in 160 patients with nonrevascularizable CLI. Patients received repeated intra-arterial infusion of BM-MNCs or placebo (autologous peripheral blood erythrocytes) into the common femoral artery. The primary outcome measure (rate of major amputation after 6 months) did not differ significantly between groups (19% for BM-MNCs vs 13% controls). Secondary outcomes of quality of life, rest pain, ABI score, and transcutaneous oxygen pressure improved to a similar extent in both groups, reinforcing the need for placebo control in this type of trial. Results from a long-term follow-up analysis of 109 of the participants found improvements in self-reported quality of life persisted for a median of 35 months in both groups, who remained blinded to treatment assignment.[8] The percentages of patients undergoing amputation also remained similar in the 2 groups (25.9% for the BM-MNC group vs 25.3% for the control group).

Results from the multicenter Intraarterial Progenitor Cell Transplantation of Bone Marrow Mononuclear Cells for Induction of Neovascularization in Patients with Peripheral Arterial Occlusive Disease (PROVASA) trial (2011) were reported. In this double-blind, phase 2 trial, 40 patients with CLI who were not candidates or had failed to respond to interventional or surgical procedures were randomized to intra-arterial administration of BM-MNC or placebo. The cell suspension included hematopoietic, mesenchymal and other progenitor cells. After 3 months, both groups were treated with BM-MNC in an open-label phase. Twelve patients received additional treatment with BM-MNC between 6 months and 18 months. The primary outcome measure (a significant increase in the ABI score at 3 months) was not achieved (from 0.66 at baseline to 0.75 at 3 months). Limb salvage and amputation-free survival rates did differ between groups. There was a significant improvement in ulcer healing (ulcer area, 1.89 cm^2 vs 2.89 cm^2) and reduced pain at rest (an improvement on a 10-point visual analog scale score of ≈3 vs 0.05) following intra-arterial BM-MNC administration, respectively.

Adverse Events
Jonsson et al (2012) reported a high incidence of serious adverse events in patients treated with peripheral blood mononuclear cells, causing the investigators to terminate the study. Of 9 patients, two had myocardial infarction believed to be related to the bone marrow stimulation, one of whom died. Another patient had a minor stroke 1 week after stem cell implantation.

Expanded Monocytes and MSCs
Interim and final results from the industry-sponsored phase 2, randomized, double-blind, placebo-controlled RESTORE-CLI trial, which used cultured and expanded monocytes and MSCs derived from bone marrow aspirate (ixmyelocel-T), were reported by Powell et al (2011, 2012). Seventy-two patients with CLI received ixmyelocel-T (n=48) or placebo with sham bone marrow aspiration (n=24) and were followed for 12 months. There was a 40% reduction in any treatment failure (due primarily to differences in doubling of total wound surface area and de novo gangrene), but no significant differences in amputation rates at 12 months.

Granulocyte-Macrophage Colony-Stimulating Factor
Poole et al (2013) reported on results of a phase 2, double-blind, placebo-controlled trial of granulocyte-macrophage colony-stimulating factor (GM-CSF) in 159 patients with intermittent claudication due to PAD. Patients were treated with subcutaneous injections of GM-CSF or placebo 3 times weekly for 4 weeks. The primary outcome (peak treadmill walking time at 3 months) increased by 109 seconds (296 to 405 seconds) in the GM-CSF group and by 68 seconds (308 to 376 seconds) in the placebo group (p=0.08). Changes in the physical functioning subscale score of the 36-Item Short-Form Health Survey (SF-36) and distance score of the Walking Impairment Questionnaire were significantly better in patients treated with GM-CSF. However, there were no significant differences between the groups in ABI score, Walking Impairment Questionnaire distance or speed scores, claudication onset time, or SF-36 Mental Component or Physical Component Summary scores. The post hoc exploratory analysis found that patients with more than a 100% increase in progenitor cells (CD34-positive/CD133-positive) had a significantly greater increase in peak walking times (131 seconds) than patients who had less than 100% increase in progenitor cells (60 seconds).

SUMMARY OF EVIDENCE
For individuals who have peripheral arterial disease 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 peripheral arterial disease 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.

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Policy History

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06/02/2011	Medical Policy Committee review
06/15/2011	Medical Policy Implementation Committee approval. New policy.
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2014	Medical Policy Committee review
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06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. Policy statement updated to describe specific sources of stem cells.

Next Scheduled Review Date: 06/2019

Coding

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Code Type	Code
CPT	0263T, 0264T, 0265T
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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