Stem-cell Therapy for Peripheral Arterial Disease

Policy # 00298
Original Effective Date: 06/15/2011
Current Effective Date: 06/21/2017

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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 cells concentrated from bone marrow aspirate to be investigational.*

Background/Overview
Peripheral arterial disease 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 monocyctic bone marrow cells that induce the proliferation of resident endothelial cells. It has been proposed that bone marrow–derived monocyctic 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
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precursor cells and, subsequently, a large quantity of bone marrow (eg, 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, monocyteid 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 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 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, 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 clinically significant. Tco₂ is measured with an oxymonitor; a 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Two devices have been identified that provide point-of-care concentration of bone marrow aspirate:
- The SmartPREP Bone Marrow Aspirate Concentrate System (Harvest Technologies)
- The MarrowStim P.A.D. kit™ (Biomet Biologics).

FDA product code: JQC.

Ixmyelocel-T (Astrom 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 FDA’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.
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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
This evidence review was created 2011 and has been updated periodically with searches of the MEDLINE database. The most recent review was performed through November 17, 2015. At this time, the literature 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.

A 2014 Cochrane review identified 2 small studies (total N=57 patients) that met the review’s inclusion criteria for local intramuscular transplantation of autologous mononuclear cells (monocytes) for CLI. Studies were excluded that used mesenchymal stem cells (MSCs) or bone marrow aspirate. In one of the studies, intramuscular injection of bone marrow–derived mononuclear cells (BM-MNCs) was compared with standard conservative treatment. In the second study, peripheral blood–derived mononuclear cells were collected following injections of granulocyte-macrophage colony-stimulating factor (GM-CSF) and transplanted by intramuscular injections. Both studies showed a significant reduction in amputations with treatment with monocytes, but larger randomized controlled trials (RCTs) are needed to adequately evaluate the effect of treatment with greater certainty.

In 2015, Peeters Weem et al reported a meta-analysis of 10 double-blind placebo-controlled RCTs on bone marrow–derived cell therapy in CLI. A total of 499 patients were included in the meta-analysis (range, 10-160 patients per study). The studies varied in routes of administration (2 intra-arterial, 8 intramuscular) and in cell types used (BM-MNCs, MSCs, Ipmyocel-T, CD34+ cells, CD133+ cells). Many of the studies were pilot or phase 2 trials and were rated as low study quality. Meta-analysis found no significant differences between the experimental and the control groups for the primary outcomes of major amputation rate (relative risk [RR], 0.91), survival (RR=1.00), or amputation-free survival (RR=1.03). There were modest improvements compared with placebo in the Ankle-Brachial Index score, transcutaneous oxygen pressure (TcO_2), and pain score, with a mean decrease in the pain score of 1.3 in the cell therapy group and 0.6 in the controls. There was no difference between percentages of healed ulcers.

Following is a description of some RCTs not included in the meta-analyses and some of the RCTs included in the meta-analyses. A number of these studies are described as either pilot or phase 2 studies.

Concentrated Bone Marrow Aspirate (Monocytes and MSCs)
Intramuscular Injection
Prochazka et al reported a randomized study of 96 patients with CLI and foot ulcer in 2010. Patient inclusion criteria were CLI as defined by an 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 into treatment with bone marrow concentrate (n=42) or standard medical care (n=54). The primary end points were major limb amputation during 120 days and degree of pain and function at 90- and 120-day follow-ups. At baseline, the control group had a higher proportion of patients with diabetes (98.2% vs 88.1%), hyperlipidemia (80.0% vs...
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54.8%), and ischemic heart disease (76.4% vs 57.1%), all respectively. In addition, the control group had a higher proportion of patients with stage DIII (deep ulcers with osteitis) University of Texas Wound Classification (72% vs 40%, respectively). 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. The reason for differences in length of follow-up for the primary outcome measure is unclear. Five patients in the bone marrow group and 8 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 performed only in the group treated with bone marrow concentrate. In the treatment group with salvaged limbs, toe pressure and Toe-Brachial Index increased from 22.66 to 25.63 mm Hg and from 0.14 to 0.17, respectively. Interpretation of this study is limited by unequal baseline measures, lack of blinding, different lengths of follow-up, different losses to follow-up, and different measures at follow-up for the 2 groups.

In 2011, Benoit et al reported 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 iliac crest puncture with intramuscular injection of diluted peripheral blood. At 6-month follow-up, the difference in the percentage of amputations between the cell therapy group and controls (29.4% vs 35.7%, respectively) 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 than placebo (39.1% vs 71.4%, respectively). Power analysis indicated that 210 patients would be 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 (VEGF) plasmid was tested in a European RCT with 32 patients. Controls in this study 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 the ABI score, development of collateral vessels measured with angiography, and healing of ischemic ulcers. Amputations were performed in 25% of patients in the BM-MNC group and 50% of patients in the control group.

Intra-Arterial Injection
JUVENTAS (Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation) is a randomized, double-blind, placebo-controlled trial 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 TcPO2 improved to a similar extent in both groups, reinforcing the need for a placebo control in this type of trial. The improvement in self-reported quality of life persisted for a median of 35 months in both the BM-MNC and the placebo groups, who remained blinded to treatment. The percentage of patients undergoing amputation was also similar in the 2 groups (25.9% for the BM-MNC group, 25.3% for the control group).

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Results from the multicenter PROVASA trial (Intraarterial Progenitor Cell Transplantation of Bone Marrow Mononuclear Cells for Induction of Neovascularization in Patients with Peripheral Arterial Occlusive Disease) were reported in 2011. 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 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 the 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 (improvement of ≈3 vs 0.05) following intra-arterial BM-MNC administration.

**Adverse Events**
In 2012, Jonsson et al 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, 2 had myocardial infarction believed to be related to the bone marrow stimulation, and 1 of the 2 patients died. Another patient had a minor stroke 1 week after stem cell implantation.

**Expanded Monocytess 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 in 2011 and 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 amputations at 12 months.

**Granulocyte-Macrophage Colony-Stimulating Factor**
In 2013, Poole et al reported results of a phase 2, double-blind, placebo-controlled study of GM-CSF in 159 patients with intermittent claudication due to PAD. Patients were treated with subcutaneous injections of GM-CSF or placebo 3 times a week 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 subscore of the 36-Item Short-Form Health Survey (SF-36) and distance score of the Walking Impairment Questionnaire (WIQ) were significantly better in patients treated with GM-CSF. However, there were no significant differences between the groups in ABI score, WIQ distance or speed scores, claudication onset time, or SF-36 Mental Component or Physical Component Summary scores. Post hoc exploratory analysis found that patients with more than a 100% increase in progenitor cells (CD34+/CD133+) had a significantly greater increase in peak walking time than patients who had less than a 100% increase in progenitor cells (131 seconds vs 60 seconds, respectively).

**Comparative Studies**
A 2011 study by Lu et al was a randomized, double-blind safety and feasibility study of 41 patients with bilateral diabetic CLI and foot ulcer who were injected intramuscularly with expanded bone marrow MSCs or
bone marrow–derived monocytes in 1 limb and normal saline in the other limb. At 24 weeks after treatment, outcomes (painless walking time, ABI score, TcO₂, magnetic resonance angiography) were significantly improved in both experimental groups compared with injection with normal saline. Outcomes on some outcome measures were modestly improved for treatment with MSCs compared with mononuclear cells. Ulcer healing at 24 weeks occurred in 100% of experimental limbs, with a faster rate of healing in the MSC-treated limbs. No cell-treated limbs underwent amputation, compared with 6 of 37 control limbs.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1. A search of ClinicalTrials.gov in December 2015 and reviews by Powell in 2012 and Bartel et al in 2013 identified a number of ongoing trials with concentrated or expanded stem cells for PAD (see Table 1).

The 2012 review by Powel of clinical trials evaluating the effect of biologic therapy in patients with CLI described several products in phase 2 or 3 trials. FDA recommended that the primary efficacy end point in a phase 3 CLI trial should be amputation-free survival. When the probability of this outcome is combined with the comorbid burden of CLI patients and variable natural history, large numbers of patients (≈500) may be needed to evaluate clinical outcomes.

Table 1. Summary of Key Trials

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<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT01245335&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pivotal Study of the Safety and Effectiveness of Autologous Bone Marrow Aspirate Concentrate (BMAC) for the Treatment of Critical Limb Ischemia Due to Peripheral Arterial Disease</td>
<td>210</td>
<td>Nov 2016</td>
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<tr>
<td>NCT01049919&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MarrowStim PAD Kit for the Treatment of Critical Limb Ischemia (CLI) in Subjects With Severe Peripheral Arterial Disease (PAD)</td>
<td>152</td>
<td>May 2020</td>
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<tr>
<td>Unpublished</td>
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<td>NCT00434616</td>
<td>Security and Effectiveness of Autologous Bone Marrow Stem Cell Transplantation to Avoid Amputations in Patients With Limb-threatening Ischemia: A Multicentric Randomized Placebo-controlled Double-blind Study (BONMOT-CLI)</td>
<td>90</td>
<td>Apr 2011</td>
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<tr>
<td>NCT01483898&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate The Efficacy, Safety, And Tolerability of Ixmyelocel-T in Subjects With Critical Limb Ischemia and No Options for Revascularization</td>
<td>41</td>
<td>Mar 2015</td>
</tr>
<tr>
<td>NCT01679990</td>
<td>A Phase II, Randomized, Double-Blind, Multicenter, Multinational, Placebo-Controlled, Parallel-Groups Study to Evaluate the Safety and Efficacy of Intramuscular Injections of Allogeneic PLX-PAD Cells for the Treatment of Subjects With Intermittent Claudication (IC)</td>
<td>150</td>
<td>Dec 2015</td>
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NCT: national clinical trial.
<sup>a</sup> Denotes industry-sponsored or cosponsored trial.
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Summary
The evidence for stem cell therapy in individuals who have 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.

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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
06/05/2014 Medical Policy Committee review
06/18/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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.

Next Scheduled Review Date: 06/2018

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<td>ICD-10 Diagnosis</td>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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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:

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