08.01.28 Stem Cell Therapy for Peripheral Arterial Disease

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Original Effective Date: June 2018

Review Date: March 2026

Revised: March 2023

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Related Policies:

- 02.01.32 Platelet-Rich Plasma and Autologous Protein Solution for Orthopedic Applications
- 02.01.18 Prolotherapy
- 08.01.22 Stem Cell Therapy for Orthopedic Indications (Including Allograft Bone Products Used with Stem Cells)*

Summary

Description

Peripheral arterial disease (PAD) is a common atherosclerotic syndrome associated with significant morbidity and mortality. Critical limb ischemia (CLI) is an 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. Injection or infusion of stem cells, either concentrated from bone marrow, expanded in vitro, stimulated from peripheral blood either from an autologous or allogeneic source is being evaluated for the treatment of PAD.

Summary of Evidence

For individuals who have PAD who receive stem cell therapy, the evidence includes small, randomized trials and systematic reviews. 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 CLI 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. Three randomized controlled trials (RCTs) have been published that used granulocyte-macrophage colony-stimulating factor (GM-CSF)-mobilized peripheral blood mononuclear cells (PBMNC). The route of administration of cell therapy and the primary outcomes differed between studies. In the trial that added cell therapy to guideline-based care, there were no significant differences in progression-free survival and frequency of limb amputation at 1 year of follow-up. There was a substantial rate of subsequent surgical intervention in both arms. Well-designed RCTs 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 that the technology results in an improvement in the net health outcomes.

Additional Information

None

OBJECTIVE

The objective of this evidence review is to evaluate whether stem cell therapy improves the net health outcome in individuals with peripheral arterial disease.

PRIOR APPROVAL

Not applicable.

POLICY

Treatment of peripheral arterial disease (PAD) including but not limited to critical limb ischemia (CLI), with an injection or infusion of stem cells from concentrated bone marrow, expanded in vitro, stimulated from peripheral blood (autologous), or from an allogeneic source, is considered **investigational** because the evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

POLICY GUIDELINES

Coding

See the Codes table for details.

BACKGROUND

Peripheral Artery Disease

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

individuals and is associated with tobacco use. The 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 the 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

Use of autologous stem cells freshly harvested and allogeneic stem cells are reported to have a potential role in the treatment of PAD. Stem cells can be administered in a variety of routes, derived from different progenitors, and be grouped with different co-factors, many which are being studied, in order to determine the best clinical option for individuals. The primary outcome in stem cell therapy trials regulated by the U.S. Food and Drug Administration (FDA) is amputation-free survival, defined as time to major amputation and/or death from any cause. Other outcomes for critical limb ischemia include the Rutherford criteria for limb status, healing of ulcers, the Ankle-Branchial Index (ABI), transcutaneous oxygen pressure, and pain free walking. The Ankle-Brachial Index (ABI) measures arterial segmental pressures on the ankle and brachium and indexes ankle systolic pressure against brachial systolic pressure (normative range 0.96 – 1.2 mm Hg).

Regulatory Status

Several point-of-care concentrations of bone marrow aspirate have been cleared for marketing by the FDA through the 510(k) process and are summarized below. Please note this is not intended to be an all-inclusive list:

Table 1. FDA Approved Point-of-Care Concentration of Bone Marrow Aspirate Devices

Device	Manufacturer	Date Cleared	510(k) No.
Arthrex Angel System Kit	Arthrex, Inc.	5/23/2018	BK180180
ART BMC System	SpineSmith Holdings, LLC	Not available	Not available
BioCUE Platelet Concentration Kit (now	Biomet Biologics, Inc.	5/26/2010	BK1000027

Device	Manufacturer	Date Cleared	510(k) No.
BioCUE Blood and Bone Marrow Aspiration (bBMA) Concentration Kit)			
Magellan Autologous Platelet Separator System	(Ateriocyte Medical Systems-Medtronic)	11/09/2004	BK040068
MarrowStim Concentration Kit and Marrow Stim Mini Concentration Kit	Biomet Biologics, Inc	12/18/2009	BK090008
PureBMC SupraPhysiologic Concentrating System	EmCyt Corporation	5/30/2019	K183205
PXP® System (now PXP®-1000)	ThermoGenesis Corp.	07/10/2008	K081345
SmartPReP2 Bone Marrow Aspirate Concentrate System, SmartPReP Platelet Concentration System	Harvest Technologies	12/06/2010	K103340

RATIONALE

This evidence review was created in June 2018 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through February 2026.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), 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 1 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. Randomized controlled trials 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 in Individuals with Peripheral Arterial Disease

Clinical Context and Therapy Purpose

The purpose of stem cell therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with peripheral arterial disease (PAD).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with peripheral arterial disease (PAD).

Interventions

The therapy being considered is stem cell therapy. 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.

Comparators

Comparators of interest include conservative management, rehabilitation protocols or surgical intervention. 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.

Outcomes

The general outcomes of interest are overall survival, symptoms, change in disease status, morbid events, functional outcomes, quality of life (QOL), and treatment related morbidity including amputation rates, improved amputation free survival, improved wound healing, ulcer healing, and pain-free walking distance. Follow-up at 3, 6, and 12 months is of interest for stem cell therapy to monitor relevant outcomes. Longer-term follow-up is also of interest.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Review of Evidence

Systematic Reviews

Several systematic reviews have been published (Table 2). Rigato et al (2017) published a systematic review of autologous cell therapy for PAD. The authors 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. Many studies were 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 low risk of bias (n=3) found no benefit of cell therapy.

In a meta-analysis of RCTs, Xie et al (2018) reviewed published evidence evaluating the safety and efficacy of autologous stem cell therapy in critical limb ischemia (CLI). Cell therapy increased the probability of angiogenesis (relative risk [RR], 5.91; 95% confidence interval [CI], 2.49 to 14.02; p<.0001), increased ulcer healing (RR,1.73; 95% CI, 1.45 to 2.06; p<.00001), and decreased amputation rates (RR, 0.59; 95% CI, 0.46 to 0.76; p<.0001). Compared with the control group, significant improvement in the cell therapy group was also seen in Ankle-Brachial Index (ABI) (mean difference, 0.13; 95% CI, 0.11 to 0.15; p<.00001), transcutaneous oxygen tension (mean difference,12.22; 95% CI, 5.03 to 19.41; p=.0009), and pain-free walking distance (mean difference, 144.84; 95% CI, 53.03 to 236.66; p=.002).

Gao et al. (2019) reviewed 27 RCTs including 1186 patients and 1280 extremities. A majority of studies showed a high risk of bias. Meta-analysis indicated that autologous stem cell therapy was more effective than conventional therapy on the healing rate of ulcers. There was also a significant improvement in ABI, total carbon dioxide, and pain-free walking distance while a significant reduction was shown in amputation rate and rest pain scores. However, the result presented no significant improvement in major limb salvage.

Pu et al. (2022) included 12 RCTs (N=630) in a meta-analysis of patients with atherosclerosis obliterans (the most common type of PAD). Autologous cell implantation was compared with placebo or standard care in all studies. A single injection of cell products was administered in all but 1 study in which injections were repeatedly administered. Follow-up periods ranged from 1 to 12 months. The analysis found improvements in total amputation (RR, 0.64; 95% CI, 0.47 to 0.87; p=.004; I^2, 12%), major amputation (RR, 0.69; 95% CI, 0.50 to 0.94; p=.02; I^2, 12%), and ABI (mean difference, 0.08; 95% CI, 0.02 to 0.13; p=.004; I^2, 84%). Death and ulcer size were not improved with cell therapy. Findings of this analysis are applicable only to patients with no other therapy options. The analysis is limited by the small sample size in each trial (range, 10 to 160 patients) and heterogeneity in cell therapy methods (e.g., dosage, cell type, route of administration).

Moazzami et al. (2022) published a Cochrane review of 4 RCTs (N=176) in individuals with CLI who were treated with autologous bone marrow mononuclear cells (BM-MNCs). It was uncertain if amputations were lower (4 studies; RR, 0.52; 95% CI, 0.27 to 0.99), and mortality was not reduced with BM-MNCs (3 studies; RR, 1.0; 95% CI, 0.15 to 6.63). Data were limited by risk of bias, imprecision, and inconsistency.

Table 2: Systematic Reviews of Trials Assessing Autologous Cell Therapy for PAD

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Moazzami (2022)	Nov 2021	4	Patients with CLI who were treated with local intramuscular transplantation of autologous adult BM-MNCs	176	RCTs	• Pooled analysis of 4 RCTs found very low- to low-certainty evidence and no conclusion regarding BM-MNC for improving clinical outcomes can be drawn.

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Pu (2022)	Mar 2021	12	Patients with atherosclerosis obliterans and "no available treatment" who received autologous cell therapy	630	RCTs	• Pooled analysis of 12 RCTs showed a significant improvement in total amputation, major amputation, and ABI but not all-cause death or ulcer size.
Gao (2019)	May 2019	27	Patients with PAD or CLI who received autologous stem cell therapy	1186	RCTs	• Pooled analysis of 27 RCTs showed a significant improvement in ABI, total carbon dioxide, and pain-free walking distance while significant reduction was shown in amputation rate and rest pain scores.
Rigato (2017)	Jul 2016	67	Patients with severe intractable PAD or CLI who received autologous cell therapy	2352	RCTs, cohort	• Pooled analysis of 19 RCTs showed a reduction in amputation rates, improved amputation-free survival, and improved wound healing.
Xie (2018)	Jan 2018	23	Patients with PAD or CLI who received autologous stem cell therapy	1118	RCTs	• Pooled analysis of 18 studies showed a reduction in amputation rate, ulcer healing, and pain-free walking distance (n=512).

ABI: Ankle-Brachial Index; BM-MNC: bone marrow mononuclear cells; CLI: critical limb ischemia; PAD: peripheral arterial disease; RCT: randomized controlled trial.

Randomized and Nonrandomized Trials

Concentrated Bone Marrow Aspirate (Monocytes and Mesenchymal Stem Cells)

Intramuscular Injection

Prochazka et al. (2010) reported on a randomized study of 96 patients with CLI and foot ulcers. 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 to treatment with bone marrow concentrate (n=42) or standard medical care (n=54). The primary endpoints were major limb amputation during the 120 days posttreatment, and degree of pain and function at 90- and 120-day follow-ups. At baseline, the control group compared with the treatment group had a higher proportion of patients with diabetes (98.2% versus 88.1%), hyperlipidemia (80.0% versus 54.8%), and ischemic heart disease (76.4% versus 57.1%), respectively. Additionally, the control group had a higher proportion of patients (72% versus 40%) with the 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 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 endpoints 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. Food and Drug Administration 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 a 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%) were 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%).

Intramuscular injection with a combination of 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. These measures 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.

Gupta et al (2017) evaluated the efficacy and safety of intramuscular adult human bone marrow-derived, cultured, pooled, allogeneic mesenchymal stromal cells (Stempeutics Research, Bangalore, India) in a phase II prospective, open-label dose-ranging study. Ninety patients were nonrandomly allocated to 3 groups: 1 million cells/kg body weight (n=36), 2 million cells/kg body weight (n=36), and standard of care (SOC; n=18). Compared with the SOC group, greater reduction in rest pain and healing of ulcers were seen in the 2 million cells/kg body weight group (0.3 units per month [standard error (SE), 0.13]; 95% CI, -0.55 to -0.05; p=.0193 and 11.0% decrease in size per month [SE, 0.05%]; 95% CI, 0.80 to 0.99; p=.0253, respectively) and in the 1 million cells/kg body weight group (0.23 per month [SE, 0.13]; 95% CI, -0.49 to 0.03; p=.081 and 2.0% decrease in size per month [SE, 0.06%]; 95% CI, 0.87 to 1.10; p=.6967, respectively). Limitations of this study included the geographically and ethnically homogenous cohort and a lack of clearly defined methods for cohort selection. Additionally, patients in the cell administration groups had lower ABI values and larger ulcers indicating potential investigator bias to allocate more severe patients to the treatment groups.

Dubsky et al. (2022) compared standard therapy with BM-MNC in patients with CLI and diabetic foot. Forty individuals with no-option chronic limb-threatening ischemia and no available treatment options were randomized to no treatment or BM-MNC for 12 weeks. Transcutaneous oxygen pressure (a marker of wound healing) had greater improvement in the BM-MNC group compared with no treatment (difference, 21.8 mm Hg; p=.034). There were more healed ulcers at 12 weeks in the BM-MNC group (31.3% vs. 0%; p=.48). The amputation rate and amputation-free survival was not different between groups. Although short-term improvements in outcomes were seen in this trial, the trial is limited by its small sample size, lack of placebo comparator, and single-center design.

Henderson et al (2024) examined Phase II trial data of ACP-01 (autologous angiogenic cell precursors) in patients with no-option CLI who presented with ulcers before treatment. Sixty-seven patients were randomized 2:1 to ACP-01 (n=46) or placebo (n=21). This analysis focused on 21 treated patients (30 ulcers) and 8 placebo patients (11 ulcers) who presented with wound ulcers before administration of ACP-01. Ulcer size in the ACP-01 group decreased from 1.46 cm² to 0.40 cm² at 3 months (p=.002), while placebo showed no significant change. At 1-year, major amputation occurred in 4.8% (n=1) of treated patients vs. 25% in placebo (n=2; p=.11). Pain scores improved slightly in both groups but without significant difference.

Intra-Arterial Injection

The Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation trial was a randomized, double-blind, placebo-controlled study (2015) from Europe. This foundation-supported trial evaluated the clinical effects of repeated intra-arterial infusion of BM-MNCs in 160 patients with nonrevascularizable CLI. Patients received a 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 QOL, rest pain, ABI score, and transcutaneous oxygen pressure improved to a similar extent in both groups, reinforcing the need for a placebo control in this type of trial. Results from a long-term follow-up analysis of 109 of the participants found that improvements in self-reported QOL persisted for a median of 35 months in both groups, who remained blinded to treatment assignment. 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 Intra-arterial Progenitor Cell Transplantation of Bone Marrow Mononuclear Cells for Induction of Neovascularization in Patients with Peripheral Arterial Occlusive Disease (PROVASA) trial (Walter et. al. 2011) were reported. In this double-blind, phase 2 trial, 40 patients with critical limb ischemia (CLI) who were not candidates or had failed to respond to interventional or surgical procedures were randomized to intra-arterial administration of bone marrow mononuclear cells (BM-MNCs) or placebo. The cell suspension included hematopoietic, mesenchymal, and other progenitor cells. After 3 months, both groups were treated with BM-MNCs 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 not 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 versus 0.05) following intra-arterial BM-MNC administration.

Section Summary: Concentrated Bone Marrow Aspirate (Monocytes and Mesenchymal Stem Cells)

There is preliminary evidence of benefit to the use of intramuscular concentrated bone aspirate injection in CLI patients. Randomized controlled trials and a non-randomized comparative study have been published.

Two RCTs have been published with intra-arterial injection of concentrated bone marrow aspirate. The RCTs did not find support for their respective primary outcome measures; the rate of major amputation after 6 months or a significant increase in the ABI score at 3 months.

Expanded Monocytes and Mesenchymal Stem Cells (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 mesenchymal stem cells (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 40% reduction in any treatment failure 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.

Norgren et al (2024) conducted a phase III study (PACE) to evaluate the efficacy and safety of PLX-PAD, an off-the-shelf placental-derived mesenchymal stromal cell-like therapy, in patients with CLI unsuitable for revascularization. The study included 213 participants randomized to receive PLX-PAD (n=143) or placebo (n=70), with intramuscular injections administered on days 0 and 60. Primary endpoints were amputation-free survival (AFS) and safety outcomes, with follow-up lasting up to 36 months. No significant improvement in AFS was observed when comparing placebo and PLX-PAD (33% and 28.6% respectively; HR 0.93; 95% CI 0.53 to 1.63; p=0.788). Rates of revascularization and complete wound healing were also comparable between the 2 groups. Adverse events were common in both groups and consistent with the CLI population, including skin ulcers and gangrene.

Granulocyte-Macrophage Colony Stimulating Factor Mobilization

Poole et al (2013) reported on the 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=.08). Changes in the physical functioning subscale score of the 36-Item Short-Form Health Survey 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 36-Item Short-Form Health Survey 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 a 100% increase in progenitor cells (60 seconds).

Horie et al (2018) reported results from an RCT (IMPACT: Improvement of Peripheral Arterial Disease by Granulocyte Colony-Stimulating Factor-Mobilized Autologous Peripheral-Blood-Mononuclear Cell Transplantation) of 107 patients with PAD characterized as Buerger disease that evaluated the efficacy and safety of GM-CSF-mobilized peripheral blood mononuclear cell (PBMNC) transplantation compared with SOC (Tables 3 and 4). Participants were randomized to guideline-based SOC or SOC plus intramuscular weight-based PBMNC administration. After disease progression or completion of a 1-year follow-up, 17 patients in the control group underwent cell therapy. Furthermore, 21 patients underwent revascularization after completion of the protocol treatment period or after discontinuation of the study (12 in the cell therapy group, 9 in the control group; 18 patients underwent percutaneous transluminal angioplasty, 2 had bypass surgery, and 1 had thrombectomy). Serious adverse events occurred in 20% of the cell therapy group compared with 11.3% of the control group (p=.28). Leukopenia, alkaline phosphatase elevation, and hyperuricemia were determined to be adverse events related to GM-CSF

administration. This study was limited by a small number of advanced cases (Fontaine stage IV cases 20.4%), a high-risk group of hemodialysis patients, and a high number of patients who did not complete treatment (cell therapy group: 38.5%; control group: 50.9%).

McDermott et al. (2017) reported results from an RCT of 210 patients with PAD that evaluated whether GM-CSF combined with supervised treadmill exercise improves 6-minute walk distance (6MWT) compared with exercise alone and compared with GM-CSF alone and to determine whether GM-CSF alone improves 6MWT more than placebo and whether exercise improves 6MWT more than an attention control intervention. Supervised exercise consisted of treadmill exercise 3 times weekly for 6 months. Participants were randomized to 1 of 4 groups: supervised exercise + GM-CSF (exercise + GM-CSF) (n=53), supervised exercise + placebo (exercise alone) (n=53), attention control + GM-CSF (GM-CSF alone) (n=53), attention control + placebo (n=51). The attention control consisted of weekly educational lectures by clinicians for 6 months. The primary outcome was change in 6MWT distance at a 12-week follow-up, with a minimum clinically important difference of 20 meters. Ninety-three percent of patients completed a 12-week follow-up. At follow-up, exercise + GM-CSF did not significantly improve 6MWT distance more than exercise alone (p=.61) or more than GM-CSF alone (Hochberg-adjusted p=.052). Use of GM-CSF alone did not improve a 6MWT more than attention control + placebo (p=.91). Exercise alone improved a 6MWT compared with attention control + placebo (Hochberg-adjusted p=.02).

Table 3: Key Characteristics of RCT with Intramuscular GM-CSF -Mobilized PBMNCs for PAD

					Treatment	
Study (Year)	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Horie (2018) IMPACT	Japan	17	2009 to 2013	Patients with PAD, Fontaine classification II-IV (n=107)	Intramuscular GM-CSF, single dose of 200 µg/m^2 per day for 4 days (n=52)	Guideline based standard of care[1] (n=55)

GM-CSF: granulocyte-macrophage colony-stimulating factor; PAD: peripheral arterial disease; PBMNC: peripheral blood mononuclear cells; RCT: randomized controlled trial.
[1] Includes the use of lipid, antihypertensive, antidiabetic, antithrombotic drugs, exercise, and prostanoids.

Table 4: Results of RCT with Intramuscular GM-CSF -Mobilized PBMNCs for PAD

Study (Year)	**PFS (95% CI)**	**Frequency of major limb amputation**	**New ulcer or gangrene**	**Serious AE**
Horie (2018) IMPACT				
Cell Therapy group	0.42 (0.13-1.36)	6.0%	18%	20.0%
Control group	0.62 (0.28-1.36)	5.7%	15.1%	11.3%
p-value	.07	1.00	.80	.28

AE: adverse events; CI: confidence intervals; GM-CSF: granulocyte-macrophage colony-stimulating factor; PAD: peripheral arterial disease; PBMNC: peripheral blood mononuclear cells; PFS: progression-free survival; RCT: randomized controlled trial.

The purpose of the limitations tables is to display notable limitations identified in the study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 5: Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Horie (2018) IMPACT		3 - fixed dosing was used (not weight-based)			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 6: Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Horie (2018) IMPACT		1,2,3 - open-label trial				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
b Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Granulocyte-Macrophage Colony-Stimulating Factor Mobilization

Three RCTs have been published. The route of administration of cell therapy and the primary outcomes differed between studies. In the trial that added cell therapy to guideline-based care, there were no significant differences in PFS and frequency of limb amputation at 1 year of follow-up. There was a substantial rate of subsequent surgical intervention in both arms.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Heart Association (AHA) and American College of Cardiology (ACC)

The 2016 guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) provided recommendations on the management of patients with lower-extremity peripheral arterial disease (PAD), including surgical and endovascular revascularization for critical limb ischemia (CLI). Stem cell therapy for PAD was not addressed.

In 2024, the ACC/AHA along with other national organizations published updated guidance for the management of lower extremity PAD. Stem cell therapy for PAD was not addressed.

European Society of Cardiology (ESC)

In 2011, the European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of PAD did not recommend for or against stem cell therapy for PAD. However, in 2017, updated guidelines, published in collaboration with the European Society of Vascular Surgery, stated: "Angiogenic gene and stem cell therapy are still being investigated with insufficient evidence in favor of these treatments." The current recommendation is that stem cell/gene therapy is not indicated in patients with chronic limb-threatening ischemia (class of recommendation: III; Level of evidence: B).In 2024, recommendations for PAD and aortic diseases were updated and consolidated into one guideline. Stem cell therapy was not addressed.

Global Vascular Guidelines

In 2019, a Global Vascular Guideline on the management of chronic limb-threatening ischemia summarized the available literature on therapeutic angiogenesis for various etiologies. The guideline was a joint venture of the Society for Vascular Surgery, the European Society for Vascular Surgery, and the World Federation of Vascular Societies. Based on a moderate level of evidence, the guideline recommended that therapeutic angiogenesis in patients with chronic limb-threatening ischemia should be limited to the context of a clinical trial (strong recommendation). The authors noted that Phase 3 clinical trials are planned or underway so additional data may be forthcoming in the future.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	0263T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest
	0264T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest
	0265T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy
HCPCS		

Codes	Number	Description
	No code(s)	
Type of Service	Therapy	
Place of Service	Outpatient/ Inpatient	

POLICY HISTORY

Date	Reason	Action
March 2026	Annual Review	Policy Renewed
March 2025	Annual Review	Policy Renewed
March 2024	Annual Review	Policy Renewed
March 2023	Annual Review	Policy Revised
June 2022	Annual Review	Policy Renewed
June 2021	Annual Review	Policy Revised
June 2020	Annual Review	Policy Renewed
June 2019	Annual Review	Policy Renewed
June 2018		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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