Stem Cell Therapy for Peripheral Arterial Disease

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DESCRIPTION

Peripheral arterial disease (PAD) is a common atherosclerotic syndrome associated with significant morbidity and mortality. Critical limb ischemia 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.

The development of PAD is characterized by narrowing and occlusion of arterial vessels and eventual reduction in distal perfusion. 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.

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.

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 use of stem cells autologous or allogeneic are reported to have a role in the treatment of peripheral arterial disease (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. 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 Rutherford criteria include ankle and toe pressure, level of claudication, ischemic rest pain, tissue loss, non-healing ulcer and gangrene. 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). 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.

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).

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

Interventions
The therapy being considered is stem cell therapy. The rationale for stem 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 (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.

Review of Evidence
Currently the literature on stem cell therapy consists primarily of small randomized controlled trials (RCTs), case series, controlled studies, and systematic reviews and meta-analyses.

In 2021, Liu et. al., performed a randomized single-blinded noninferiority trial (NCT02089828) specifically designed to evaluate the therapeutic efficacies of the transplantation of purified $CD34^+$ cells (PCCs) versus those of peripheral blood mononuclear cells (PBMNCs) for the treatment of angiitis-induced critical limb ischemia (AICLI). This study aimed to compare the mid-term safety and efficacy between the two groups and determine their respective advantages. From April 2014 to September 2019, 50 patients with AICLI were equally allocated to the two groups, except for 1 lost patient, 1 amputee, and 1 patient who died of heart disease. The other 47 patients completed the 36-month follow-up. The endpoints were as follows: major amputation-free survival and total amputation-free survival at 6 months, which were 96.0% and 84.0% in the PBMNCs

group and 96.0% and 72.0% in the PCCs group, respectively. These rates remained stable at 12, 24, and 36 months. The PCCs group had a significant higher probability of rest pain relief than the PBMNCs group, whereas earlier significant improvements in the Rutherford classification were observed in the PBMNCs group. Accordingly, PCCs would be preferred for patients with significant pain, whereas PBMNCs may be a good option for patients with two or more critically ischemic limbs. Concerning cost-effectiveness, PCCs are not more cost-effective than PBMNCs. These outcomes require verification from long-term trials involving larger numbers of patients.

In 2019, Gao et. al. completed a systematic review and meta-analysis to evaluate the efficacy and safety of autologous implantation of stem cells in patients with peripheral arterial disease (PAD) critically, compared with active controls and placebo. Randomized controlled trials (RCTs) of autologous implantation of stem cells compared with placebo and control for PAD were included. Electronic medical databases including MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), the Chinese Biomedical Literature Database, China National Knowledge Infrastructure (CNKI), and ClinicalTrials.gov were searched from initial period to September 2018. Independently, two reviewers screened citations, extracted data, and assessed the risk of bias according to the criteria of the Cochrane handbook. The quality of evidence was evaluated by GRADE evidence profile. The primary outcomes consisted of amputation rate, major amputation rate, ulcer healing rate, and side effects. The second outcomes included ankle-brachial index (ABI), transcutaneous oxygen tension (TcO2), pain-free walking distance (PFWD), and rest pain score. Statistical analysis was conducted via RevMan 5.3 and Stata 12.0. According to the twenty-seven RCTs, 1186 patients and 1280 extremities were included, and the 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 [OR = 4.31 (2.94, 6.30)]. There was also significant improvement in ABI [MD = 0.13 (0.10, 0.17)], TcO2 [MD = 0.13 (0.10, 0.17)], and PFWD [MD = 178.25 (128.18, 228.31)] while significant reduction was showed in amputation rate [OR = 0.50 (0.36, 0.69)] and rest pain scores [MD = - 1.61 (- 2.01, - 1.21)]. But the result presented no significant improvement in major limb salvage [0.66 (0.42, 1.03)]. Besides, stem cell therapy could reduce the amputation rate [OR = 0.50 (0.06, 0.45] and improve the ulcer healing rate [OR = 4.34 (2.96, 6.38] in DM subgroup. Eight trials reported the side effects of autologous stem cell therapy, and no serious side effects related to stem cells were reported. GRADE evidence profile showed all the quality evidence of outcomes were low. The authors concluded, based on the review autologous stem cell therapy may have a positive effect on "no-option" patients with PAD, but presented no significant improvement in major limb salvage. However, the evidence is insufficient to prove the results due to high risk of bias and low-quality evidence of outcomes. Further research of larger, randomized, double-blind, placebo-controlled, and multicenter trials are still in demand.

In 2018, Xie et. al. reviewed published evidence of randomized controlled trials evaluating the safety and efficacy of autologous stem cell therapy in critical limb ischemia (CLI) in a meta-analysis. The meta-analysis showed that cell therapy significantly increased the probability of ulcer healing (RR = 1.73, 95% CI = 1.45-2.06),

angiogenesis (RR = 5.91, 95% CI = 2.49-14.02), and reduced the amputation rates (RR = 0.59, 95% CI = 0.46-0.76). Ankle-brachial index (ABI) (MD = 0.13, 95% CI = 0.11-0.15), TcO2 (MD = 12.22, 95% CI = 5.03-19.41), and pain-free walking distance (MD = 144.84, 95% CI = 53.03-236.66) were significantly better in the cell therapy group than in the control group (P < 0.01). The authors concluded, the results of this meta-analysis indicate that autologous stem cell therapy is safe and effective in CLI. However, higher quality and larger RTCs are required for further investigation to support clinical application of stem cell transplantation.

In 2018, Wahid et. al. compared the efficacy and safety of autologous cells derived from different sources, prepared using different protocols, administered at different doses, and delivered via different routes for the treatment of 'no-option' critical limb ischemia patients (CLI) patients. Revascularization is the gold standard therapy for patients with critical limb ischemia (CLI). In over 30% of patients who are not suitable for or have failed previous revascularization therapy (the 'no-option' CLI patients), limb amputation is eventually unavoidable. Preliminary studies have reported encouraging outcomes with autologous cell-based therapy for the treatment of CLI in these 'no-option' patients. However, studies comparing the angiogenic potency and clinical effects of autologous cells derived from different sources have yielded limited data. Data regarding cell doses and routes of administration are also limited. The Cochrane Vascular Information Specialist (CIS) searched the Cochrane Vascular Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid, Embase Ovid, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED), and trials registries (16 May 2018). Review authors searched PubMed until February 2017. Seven Randomized controlled trials (RCTs) involving 'no-option' CLI patients comparing a particular source or regimen of autologous cell-based therapy against another source or regimen of autologous cell-based therapy were included with at total of 359 participants. These studies compared bone marrow-mononuclear cells (BM-MNCs) versus mobilized peripheral blood stem cells (mPBSCs), BM-MNCs versus bone marrow-mesenchymal stem cells (BM-MSCs), high cell dose versus low cell dose, and intramuscular (IM) versus intra-arterial (IA) routes of cell implantation. No other comparisons were identified in these studies. Most studies were considered to be at low risk of bias in random sequence generation, incomplete outcome data, and selective outcome reporting; at high risk of bias in blinding of patients and personnel; and at unclear risk of bias in allocation concealment and blinding of outcome assessors. The quality of evidence was most often low to very low, with risk of bias, imprecision, and indirectness of outcomes the major downgrading factors. Three RCTs (100 participants) reported a total of nine deaths during the study follow-up period. These studies did not report deaths according to treatment group. Results show no clear difference in amputation rates between IM and IA routes (RR 0.80, 95% CI 0.54 to 1.18; three RCTs, 95 participants; low-quality evidence). Single-study data show no clear difference in amputation rates between BM-MNC- and mPBSC-treated groups (RR 1.54, 95% CI 0.45 to 5.24; 150 participants; low-quality evidence) and between high and low cell dose (RR 3.21, 95% CI 0.87 to 11.90; 16 participants; very low-quality evidence). The study comparing BM-MNCs versus BM-MSCs reported

no amputations. Single-study data with low-quality evidence show similar numbers of participants with healing ulcers between BM-MNCs and mPBSCs (RR 0.89, 95% CI 0.44 to 1.83; 49 participants) and between IM and IA routes (RR 1.13, 95% CI 0.73 to 1.76; 41 participants). In contrast, more participants appeared to have healing ulcers in the BM-MSC group than in the BM-MNC group (RR 2.00, 95% CI 1.02 to 3.92; one RCT, 22 participants; moderate-quality evidence). Researchers comparing high versus low cell doses did not report ulcer healing. Single-study data show similar numbers of participants with reduction in rest pain between BM-MNCs and mPBSCs (RR 0.99, 95% CI 0.93 to 1.06; 104 participants; moderate-quality evidence) and between IM and IA routes (RR 1.22, 95% CI 0.91 to 1.64; 32 participants; low-quality evidence). One study reported no clear difference in rest pain scores between BM-MNC and BM-MSC (MD 0.00, 95% CI -0.61 to 0.61; 37 participants; moderate-quality evidence). Trials comparing high versus low cell doses did not report rest pain. Single-study data show no clear difference in the number of participants with increased ankle-brachial index (ABI; increase of > 0.1 from pretreatment), between BM-MNCs and mPBSCs (RR 1.00, 95% CI 0.71 to 1.40; 104 participants; moderate-quality evidence), and between IM and IA routes (RR 0.93, 95% CI 0.43 to 2.00; 35 participants; very low-quality evidence). In contrast, ABI scores appeared higher in BM-MSC versus BM-MNC groups (MD 0.05, 95% CI 0.01 to 0.09; one RCT, 37 participants; low-quality evidence). ABI was not reported in the high versus low cell dose comparison. Similar numbers of participants had improved transcutaneous oxygen tension (TcO_2) with IM versus IA routes (RR 1.22, 95% CI 0.86 to 1.72; two RCTs, 62 participants; very low-quality evidence). Single-study data with low-quality evidence show a higher TcO_2 reading in BM-MSC versus BM-MNC groups (MD 8.00, 95% CI 3.46 to 12.54; 37 participants) and in mPBSC- versus BM-MNC-treated groups (MD 1.70, 95% CI 0.41 to 2.99; 150 participants). TcO_2 was not reported in the high versus low cell dose comparison. Study authors reported no significant short-term adverse effects attributed to autologous cell implantation. The authors concluded mostly low and very low-quality evidence suggests no clear differences between different stem cell sources and different treatment regimens of autologous cell implantation for outcomes such as all-cause mortality, amputation rate, ulcer healing, and rest pain for 'no-option' CLI patients. Pooled analyses did not show a clear difference in clinical outcomes whether cells were administered via IM or IA routes. High-quality evidence is lacking; therefore, the efficacy and long-term safety of autologous cells derived from different sources, prepared using different protocols, administered at different doses, and delivered via different routes for the treatment of 'no-option' CLI patients, remain to be confirmed. Future randomized controlled trials (RCTs) with larger numbers of participants are needed to determine the efficacy of cell-based therapy for CLI patients, along with the optimal cell source, phenotype, dose, and route of implantation. Longer follow-up is needed to confirm the durability of angiogenic potential and the long-term safety of cell-based therapy.

Rigato et. al. (2017) published a systematic review and meta-analysis of studies evaluating the safety and efficacy of autologous cell therapy for intractable peripheral arterial disease/critical limb ischemia. They identified 19 randomized controlled trials (837 patients), 7 nonrandomized trials (338 patients), and 41 non-controlled 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.

Concentrated Bone Marrow Aspirate (Monocytes and MSCs)

Intramuscular Injection

In 2018, Lindeman et. al. conducted a confirmatory, double-blinded randomized placebo-controlled phase 3 trial for cell-based strategies for end-stage peripheral artery disease (PAD) patients. This randomized controlled trial was registered NCT00539266. Inclusion criteria included stable or progressive disabling end-stage peripheral artery disease (PAD), no imminent need for amputation, absent accepted options for revascularization. Diabetic disease was an exclusion criterion. Bone marrow (500-700 mL) was harvested, and bone marrow-derived mononuclear cells were concentrated to 40 mL. Concentrated cells or placebo (diluted blood) were intramuscularly injected at 40 locations of the calf muscle. Fifty-four patients (mean (sd) age 58.2 (14.2) years, 58% males) were randomized. Twenty-eight patients received BM-MNCs, 26 placebos. Baseline criteria were similar in the 2 groups. No significant differences were observed for the primary (number of amputations, (pain free) walking distance) and secondary outcome parameters (ankle brachial index, pain scores, quality of life (SF-36)). The authors concluded this fully blinded replication trial of autologous BM-MNC fails to confirm a benefit for cell therapy in no-option PAD patients, consequently BM-MNC therapy should not be offered as a clinical treatment. Apparent contrasting conclusions from open and controlled studies underscore the importance of a controlled trial design in evaluating cell-based interventions in PAD.

In 2017, Gupta et. al. conducted a phase II, prospective, nonrandomized, open-label, multicentric study to assess the efficacy and safety of an intramuscular injection of adult human bone marrow-derived, cultured, pooled, allogeneic mesenchymal stromal cells (BMMSCs) in critical limb ischemia (CLI) due to Buerger's disease. Patients were allocated to three groups: 1 and 2 million cells/kg body weight (36 patients each) and standard of care (SOC) (18 patients). BMMSCs were administered as 40-60 injections in the calf muscle and locally, around the ulcer. Most patients were young (age range, 38-42 years) and ex-smokers, and all patients had at least one ulcer. Both the primary endpoints-reduction in rest pain (0.3 units per month [SE, 0.13]) and healing of ulcers (11% decrease in size per month [SE, 0.05])-were significantly better in the group receiving 2 million cells/kg body weight than in the SOC arm. Improvement in secondary

endpoints, such as ankle brachial pressure index (0.03 [SE, 0.01] unit increase per month) and total walking distance (1.03 [SE, 0.02] times higher per month), were also significant in the group receiving 2 million cells/kg as compared with the SOC arm. Adverse events reported were remotely related or unrelated to BMMSCs. In conclusion, intramuscular (i.m.) administration of BMMSC at a dose of 2 million cells/kg showed clinical benefit and may be the best regimen in patients with CLI due to Buerger's disease. The authors concluded, further randomized controlled trials are required to confirm the most appropriate dose.

Skora et. al. (2015) studied the safety and effectiveness of combined autologous bone marrow mononuclear cell (MNC) and gene therapy in comparison to conventional drug therapy in patients with critical limb ischemia (CLI). Thirty-two patients with CLI persisting for 12-48 months (average time 27.5 months) were randomized into 2 groups, each consisting of 16 patients. In the first group, administration of autologous bone marrow MNC and vascular endothelial growth factor (VEGF) plasmid was performed. The patients from the second group were treated pharmacologically with pentoxifylline. Therefore, the groups were not blinded to treatment. The Ankle-Brachial Index (ABI) was measured, and angiography was performed before and 3 months after treatment. The pain was evaluated using the Visual Analog Scale (VAS) before and after 3 months. Several objective measures were improved in the bone marrow mononuclear cell (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 group 1 (bone marrow mononuclear cell (MNC) group) and in 50% of patients in the control group (treated pharmacologically with pentoxifylline).

Intra-Arterial Injection

In 2021, Sharma et. al., evaluated the safety and efficacy of angiogenesis induced by intraarterial autologous bone marrow-derived stem cell (BMSC) injection in patients with severe peripheral arterial disease (PAD). Eighty-one patients with severe PAD (77 men), including 56 with critical limb ischemia (CLI) and 25 with severe claudication, were randomized to receive sham injection (group A) or intraarterial BMSC injection at the site of occlusion (group B). Primary endpoints included improvement in ankle-brachial index (ABI) of > 0.1 and transcutaneous pressure of oxygen ($TcPO_2$) of > 15% at mid- and lower foot at 6 mo. Secondary endpoints included relief from rest pain, > 30% reduction in ulcer size, and reduction in major amputation in patients with CLI and > 50% improvement in pain-free walking distance in patients with severe claudication. Technical success was achieved in all patients, without complications. At 6 months, group B showed more improvements in ABI of > 0.1 (35 of 41 [85.37%] vs 13 of 40 [32.50%]; P < .0001) and $TcPO_2$ of > 15% at the midfoot (35 of 41 [85.37%] vs 17 of 40 [42.50%]; P = .0001] and lower foot (37 of 41 [90.24%] vs 19 of 40 [47.50%]; P < .0001). No patients with CLI underwent major amputation in group B, compared with 4 in group A (P = .0390). No significant difference was observed in relief from rest pain or > 30% reduction in ulcer size among patients with CLI or in > 50% improvement in pain-free walking distance among patients with severe claudication.

The Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation (JUVENTAS) trial was a randomized, double-blind, placebo-controlled study (Terra et. al. 2015) from Europe (NCT00371371). The objective of this trial was to determine whether repetitive intra-arterial infusion of bone marrow mononuclear cells (BM-MNCs) in 160 patients with severe, non-revascularizable critical limb ischemia (CLI) can prevent major amputation. Patients were randomly assigned to repetitive (3 times: 3- week interval) intra-arterial infusion of BM-MNCs or placebo (autologous peripheral blood erythrocytes) into the common femoral artery. No significant differences were observed for the primary outcome, i.e., major amputation at 6 months, with major amputation rates of 19% in the BM-MNC versus 13% in the placebo group (relative risk, 1.46; 95% confidence interval, 0.62-3.42). The safety outcome (all-cause mortality, occurrence of malignancy, or hospitalization due to infection) was not significantly different between the groups (relative risk, 1.46; 95% confidence interval, 0.63-3.38), neither was all-cause mortality at 6 months with 5% versus 6% (relative risk, 0.78; 95% confidence interval, 0.22-2.80). Secondary outcomes quality of life, rest pain, ankle-brachial index, and transcutaneous oxygen pressure improved during follow-up, but there were no significant differences between the groups. The authors concluded, repetitive intra-arterial infusion of autologous BMMNCs into the common femoral artery did not reduce major amputation rates in patients with severe, non-revascularizable limb ischemia in comparison with placebo. The general improvement in secondary outcomes during follow-up in both the BMMNC and the placebo group, as well, underlines the essential role for placebo-controlled design of future trials.

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, respectively. These exploratory findings of this pilot trial need to be confirmed in a larger randomized trial in patients with critical limb ischemia and stable ulcers.

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. (1211, 2012). This study was conducted at 18 centers in the United States in patients with critical limb ischemia (CLI) and no option for revascularization. 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.

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 (median age 64 years; 87% male; 37% with diabetes) with intermittent claudication due to peripheral arterial disease (PAD) to determine if GM-CSF improves exercise capacity in this patient population. Patients were treated with subcutaneous injections of CM-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 Ankle Brachial Index (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). The authors concluded, therapy with GM-CSF 3 times a week did not improve treadmill walking performance at the 3- month follow-up. The improvements in some secondary outcomes with GM-CSF suggest that it may warrant further study in patients with claudication.

In 2018, Horie et. al. reported on a randomized controlled trial (RCT) to evaluate the efficacy and safety of granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood (PB) mononuclear cell (MNC) transplantation (PBMNC) in patients with peripheral arterial disease (PAD), especially in those with mild to moderate severity with primary endpoint of progression-free survival (PFS). In total, 107 subjects were enrolled. At baseline, Fontaine stage was II/III in 82 patients and IV in 21, and 54 patients were on hemodialysis. A total of 50 patients had intramuscular transplantation of PBMNC combined with standard of care (SOC) (cell therapy group), and 53 received SOC only (control group). PFS tended to be improved in the cell therapy group than in the control group (P=0.07). PFS in Fontaine stage II/III subgroup was significantly better in the cell therapy group than in the control group. Cell therapy-related adverse events were transient and not serious. This study was limited a small number of advanced cases (Fontaine stage IV cases (20.4%), a high- risk group of hemodialysis patients and by the high number of patients who did not complete treatment (cell therapy group: 38.5%; control group: 50.9%)

Two randomized controlled trials (RCTs) have been published. The route of administration of the 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 (PFS) and frequency of limb amputation at one year of follow-up. There was a substantial rate of subsequent surgical intervention in both arms.

Summary of Evidence
For individuals who have end-stage peripheral arterial disease (PAD) due to critical limb ischemia (CLI) who receive stem cell therapy, the evidence includes randomized controlled trials (RCTs), systematic reviews, and meta-analysis, retrospective reviews, and case series. The current literature on stem cell as a treatment for critical limb ischemia due to peripheral arterial disease (PAD) consists primarily of studies using various cell preparation methods and methods of administration therapy using bone marrow-mononuclear cells (BM-MNCs), mobilized peripheral blood stem cells (mPBSCs), bone marrow-mesenchymal stem cells (BM-MSCs), high cell dose versus low cell dose, and intramuscular (IM) versus intra-arterial (IA) routes of cell implantation. Based on the review current peer reviewed medical evidence which is mostly low and very low quality of evidence it suggests no clear differences between the stem cell sources and different treatment regimens of autologous cell implantation for outcomes such as all-cause mortality, amputation rate, ulcer healing and rest pain for “no option” CLI individuals. Pooled analyses did not show a clear difference in clinical outcomes whether cells were administered via IM or IA routes. High-quality evidence is lacking; therefore, the efficacy and long-term safety of autologous cells derived from different sources, prepared using different protocols, administered at different doses, and delivered via different routes for the treatment of 'no-option' CLI individuals, remain to be confirmed. Further larger randomized, double-blind, placebo-controlled, and multicenter trials are needed to determine the efficacy of cell-based therapy for CLI individuals, along with the optimal cell source, phenotype, dose, and route of implantation. Longer follow-up is needed to confirm the durability of angiogenic potential and the long-term safety of cell-based therapy. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Practice Guidelines and Position Statements

American Heart Association (AHA) and American College of Cardiology (ACC)
The 2016 guidelines from the American Heart Association and American College of Cardiology 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.

European Society of Cardiology
In 2017, the European Society of Cardiology in collaboration with the European Society for Vascular Surgery updated the guideline on the diagnosis and treatment of peripheral

arterial diseases which states the following: “Angiogenic gene and stem cell therapy are still being investigated with insufficient evidence in favor of these treatments.”

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. This guideline states the following: “Regenerative medicine approaches (e.g., cell, gene therapies) for chronic limb-threatening ischemia (CLTI) should be restricted to rigorously conducted randomized clinical trials.

Regulatory Status
Six point-of-care concentrations of bone marrow aspirate have been cleared for marketing by the FDA through the 510(k) process:

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	Biomet Biologics, Inc.	5/26/2010	BK1000027
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	ThermoGenesis Corp.	07/10/2008	K081345
SmartPReP2 Bone Marrow Aspirate Concentrate System, SmartPReP Platelet	Harvest Technologies	12/06/2010	K103340

Concentration System			

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical 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)*

Treatment of peripheral arterial disease (PAD) and other occlusive conditions, 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** due to the lack of clinical evidence demonstrating an impact on improved net health outcomes**.**

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 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 by separate physicians

These CPT codes are constructed to allow reporting of the complete procedure and harvesting by a single physician (code 0263T) or separate reporting when the cell harvesting, and therapy injections are performed by separate physicians (0264T and 0265T).

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POLICY HISTORY		
Date	**Reason**	**Action**
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:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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