Medical Policy Manual Medicine, Policy No. 141

Cell Therapy for Peripheral Arterial Disease

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Critical limb ischemia due to peripheral arterial disease (PAD) results in pain at rest, ulcers, and significant risk for limb loss. Injection of hematopoietic cells concentrated from bone marrow is being evaluated for the treatment of critical limb ischemia when surgical or endovascular revascularization has failed.

MEDICAL POLICY CRITERIA

Treatment of peripheral arterial disease with injection or infusion of cells concentrated from bone marrow aspirate is considered **investigational** for all indications, including but not limited to critical limb ischemia and Buerger disease (thromboangiitis obliterans).

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Autologous Blood-Derived Growth Factors as a Treatment for Wound Healing and Other Conditions, Medicine, Policy No. 77
2. Autologous Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia, Medicine, Policy No. 100

3. Orthopedic Applications of Stem-Cell Therapy, Including Bone Substitutes Used with Autologous Bone Marrow, Medicine, Policy No. 142

BACKGROUND

Peripheral arterial disease (PAD) is a common atherosclerotic syndrome that is associated with significant morbidity and mortality. A less-common cause of PAD is Buerger disease, also called thromboangiitis obliterans, which is a nonatherosclerotic segmental inflammatory disease that occurs in younger patients and is associated with tobacco use. Development of PAD is characterized by narrowing and occlusion of arterial vessels and eventual reduction in distal perfusion. Critical limb ischemia is the endstage of lower extremity PAD in which severe obstruction of blood flow results in ischemic pain at rest, ulcers, and a significant risk for limb loss. The standard therapy for severe, limb-threatening ischemia is revascularization aiming to improve blood flow to the affected extremity. If revascularization has failed or is not possible, amputation is often necessary.

Two endogenous compensating mechanisms may occur with occlusion of arterial vessels, capillary growth (angiogenesis) and development of collateral arterial vessels (arteriogenesis). Capillary growth is mediated by hypoxia-induced release of chemo- and cytokines, such as vascular endothelial growth factor (VEGF), and occurs by sprouting of small endothelial tubes from pre-existing capillary beds. The resulting capillaries are small and cannot sufficiently compensate for a large occluded artery. Arteriogenesis with collateral growth is, in contrast, initiated by increasing shear forces against vessel walls when blood flow is redirected from the occluded transport artery to the small collateral branches, leading to an increase in the diameter of pre-existing collateral arterioles.

The mechanism underlying arteriogenesis includes the migration of bone marrow-derived monocytes to the perivascular space. The bone marrow-derived monocytes adhere to and invade the collateral vessel wall. It is not known if the expansion of the collateral arteriole is due to the incorporation of cells into the wall of the vessel or to cytokines released by monocytic bone marrow cells that induce the proliferation of resident endothelial cells. It has been proposed that bone marrow-derived monocytic cells may be the putative circulating endothelial progenitor cells. Notably, the same risk factors for advanced ischemia (diabetes, smoking, hyperlipidemia, and advanced age) are also risk factors for a lower number of circulating progenitor cells.

The rationale of hematopoietic 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 precursor cells, and subsequently, a large quantity of bone marrow (e.g., 240-500 mL) or other source of 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 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. The SmartPReP2® system is designed to concentrate a buffy coat of 20 mL from whole bone marrow aspirate of 120 mL. The concentrate of bone marrow aspirate contains a mix of cell types, including lymphocytoid cells, erythroblasts, monocytoid cells, and granulocytes. Following isolation and concentration, the hematopoietic cell/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 cells include the in vitro

expansion of bone marrow-derived cells or use of granulocyte colony-stimulating factor to mobilize peripheral blood mononuclear cells. There is some discrepancy in the literature regarding the nomenclature of cell types. Studies addressed in this policy include the use of mononuclear cells/monocytes and/or mesenchymal cells.

Standard outcomes for critical limb ischemia include the Rutherford criteria for limb status, healing of ulcers, the ankle-brachial index (ABI), transcutaneous oxygen pressure (TcO_2), and pain-free walking. The Rutherford criteria include ankle and toe pressure, the level of claudication, ischemic rest pain, tissue loss, nonhealing ulcer, and gangrene. The ABI measures arterial segmental pressures on the ankle and brachium, and indexes ankle systolic pressure against brachial systolic pressure (normal range 0.95 – 1.2). An increase greater than 0.1 is considered clinically significant. TcO_2 is measured with an oxymonitor; the normal value is 70-90 mm Hg. Pain free walking may be measured by time on a treadmill, or more frequently by distance in a 400-meter walk.

REGULATORY STATUS

Two devices have been identified that provide point-of-care concentration of bone marrow aspirate:

- The SmartPReP2® Bone Marrow Aspirate Concentrate System is a microprocessor-controlled dedicated centrifuge with decanting capability and an accessory BMAC IDE PAD Pack for processing a patient's bone marrow aspirate. The system is in a Phase III trial; expected completion of the trial is in 2014.

- The MarrowStim P.A.D. kit™ (Biomet Biologics) is in a Phase III trial for the treatment of PAD with completion expected May 2014.

Ixmyelocel-T (Vericel Corporation, formerly Aastrom Biosciences)) 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 III trial regulated by the U.S. Food and Drug Administration's Center of Biologic Evaluation and Research.

Pluristem Therapeutics is developing allogeneic cell therapy derived from full-term placenta (PLX-PAD cells). This product has been tested in a Phase I trial in patients with critical limb ischemia.

EVIDENCE SUMMARY

Evaluating the safety and effectiveness of cell therapy for the treatment of peripheral arterial disease (PAD) requires randomized comparisons of this therapy with placebo injections and with conventional medical therapy with respect to the following:

- Pain and functioning
- Prevention or delay of limb amputation
- Durability of treatment effects

Therefore, the following literature review focused on randomized controlled trials, systematic reviews, and meta-analyses.

SYSTEMATIC REVIEWS

Moazzami (2022) published a systematic review to evaluate benefits and harms of local intramuscular transplantation of autologous adult bone marrow mononuclear cells (BMMNCs) as a treatment for critical limb ischemia.[1] Four RCTs (n=176 patients) were included in which participants were randomly assigned to intramuscular administration of autologous adult BMMNCs or control. Controls varied and included no intervention, conventional conservative therapy, or placebo (e.g., diluted autologous peripheral blood or saline). Compared to controls, BMMNC treatment did not affect mortality (risk ratio [RR] 1.00, 95% confidence interval [CI] 0.15 to 6.63; 3 studies, 123 participants; very low-certainty evidence). It was uncertain if amputations were lower (RR 0.52, 95% CI 0.27 to 0.99; 4 studies, 176 participants; very low-certainty evidence). A possible small effect on amputation was lost after sensitivity analysis was performed (RR 0.52, 95% CI 0.19 to 1.39; 2 studies, 89 participants). No studies reported angiographic analysis. Ankle-brachial index reports were too heterogeneous to analyze data across studies. Three studies reported no changes between BMMNC treatment and controls. Pooled data showed no differences in side effects reported during follow-up (RR 2.13, 95% CI 0.50 to 8.97; 4 studies, 176 participants; very low-certainty evidence). Studies were limited by risk of bias, imprecision, and inconsistency.

Pu (2022) included 12 RCTs (n=630) in a meta-analysis of patients with atherosclerosis obliterans (the most common type of PAD), who were treated with stem cell therapy.[2] Autologous cell implantation was compared with placebo or standard care in all studies. A single injection of cell products was administered in all but one 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=0.004; I^2, 12%), major amputation (RR, 0.69; 95% CI, 0.50 to 0.94; p=0.02; I^2, 12%), and Ankle-Brachial Index (mean difference, 0.08; 95% CI, 0.02 to 0.13; p=0.004; 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).

Gao (2019) reviewed 27 randomized controlled trials (RCT)s which included 1,186 patients and 1,280 extremities.[3] 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 Ankle-Brachial Index (ABI) total carbon dioxide, and pain-free walking distance while the significant reduction was showed in amputation rate and rest pain scores. However, the result presented no significant improvement in major limb salvage.

Xie (2018) reviewed published a meta-analysis evaluating the safety and efficacy of autologous stem cell therapy in critical limb ischemia.[4] Cell therapy increased the probability of angiogenesis (relative risk (RR) = 5.91), ulcer healing (RR=1.73), and a reduction in amputation rates (RR=0.59). Compared with the control group, significant improvement in the cell therapy group was also seen in ankle-brachial index, transcutaneous oxygen tension, and pain-free walking distance.

In 2017, Rigato conducted a systematic review of autologous cell therapy for peripheral arterial disease.[5] There were 19 randomized trials, 41 uncontrolled studies, and seven non-randomized trials included in the review with major amputation being the primary outcome.

Heterogeneity was high amongst the studies included and authors could not rule out publication bias. Despite these limitations, the primary analysis showed that cell therapy reduced the risk of amputation by 37%, improved amputation-free survival by 18%, and improved wound healing by 59%, without affecting mortality. The efficacy of cell therapy on all outcomes was no longer significant in placebo-controlled randomized controlled trials and disappeared in randomized controlled trials with a low risk of bias.

Peeters Weem (2015) conducted a meta-analysis of ten randomized placebo controlled trials investigating bone marrow (BM) derived cell therapy in patients with critical limb ischemia (CLI) (n=499).[6] The majority of these studies had fewer than 50 patients. No significant differences were observed in any of the primary outcome measures, including major amputation rates (relative risk [RR] 0.91; 95% CI 0.65 to 1.27), survival (RR 1.00; 95% CI 0.95 to 1.06), and amputation free survival (RR 1.03; 95% CI 0.86 to 1.23) between the treatment and placebo groups. Secondary outcomes were significantly better in the cell treated group than the controls, including: the ankle brachial index (mean difference 0.11; 95% CI 0.07 to 0.16), transcutaneous oxygen measurements (mean difference 11.88; 95% CI 2.73 to 21.02), and pain score (mean difference -0.72; 95% CI -1.37 to -0.07).

Liew (2015) published a meta-analysis of 16 RCTs of cell therapy versus no cell therapy in CLI (n=774).[7] Outcome measures included major amputation, complete ulcer healing, ankle-brachial index (ABI), and all-cause mortality. Compared with no cell therapy, cell therapy significantly reduced major amputation (odds ratio [OR]: 0.54; 95% CI: 0.34 to 0.87: p=0.01) and improved ulcer healing (OR: 2.90; 95% CI: 1.44 to 5.82; p<0.01) and ABI (OR: 5.91; 95% CI: 1.85 to 18.86; p<0.01) compared to no treatment. When the tissue of origin was assessed, mononuclear cells derived from peripheral blood (OR: 0.29; 95% CI: 0.12 to 0.72; p<0.01) and cells from bone marrow concentrate (OR: 0.44; 95% CI: 0.21 to 0.93; p=0.03) significantly lowered the risk of major amputation. However, when reanalysis was done using placebo-controlled RCTs only, all estimates were nonsignificant, indicating the value of larger RCTs to assess the potential efficacy of cell treatment for CLI.

Wang (2014) reported significant improvements for all endpoints based on a meta-analysis of 31 articles involving 1,214 patients treated with cell therapy.[8] The studies included both RCTs and nonrandomized single-arm studies. Comparative data for 1-year amputation free survival (AFS) was available from 3 trials with a total of 162 patients. Significantly fewer amputations were reported in the treatment groups (n=88) receiving cell therapy (OR 9.05, 95% CI 3.58 to 18.08, p<0.00001). Significantly improved AFS rate (OR 22.33, 95% CI 4.14 to 120.5, p=0.0003) was also reported in the three-year follow-up data which was available for 97 patients, 51 of whom received cell therapy. Adverse events were associated with the disease process rather than the cell therapy, including extremity pain. The authors noted that the outcomes of the meta-analysis should be interpreted with caution due to a number of limitations in the included studies. These limitations included insufficient data from RCTs, minimal long-term follow-up data, inclusion of data from low-quality, non-controlled trials, and differences between studies in the indexes applied. The authors concluded that further multi-center studies are needed to determine the therapeutic effects of cell therapy for CLI.

A 2013 meta-analysis by Teraa included 12 RCTs with a total of 510 patients with critical limb ischemia.[9] Eight of the trials had fewer than 50 patients. Meta-analysis of all of the trials showed significant improvements with bone marrow-derived cell therapy on both subjective and objective intermediate end points (pain score, pain-free walking distance, ankle-brachial index, transcutaneous oxygen measurements) and on amputation rates (relative risk [RR], 58).

Overall, there were 38 amputations in the experimentally-treated limbs compared with 62 amputations for control limbs. However, when only placebo-controlled trials were included, no significant effect on major amputation rates was identified (RR, 0.78 to 0.92). The authors concluded that the divergent results between placebo- and nonplacebo-controlled RCTs stress the need for well-designed, larger, placebo-controlled RCTs with long-term follow-up.

Liu (2012) conducted a meta-analysis of six randomized trials (333 patients) that evaluated mononuclear cell transplantation in patients with CLI.[10] Cell therapy was found to decrease the incidence of amputation in patients with CLI with an odds ratio (OR) of 0.37. The rate of amputation free survival was increased in patients with Rutherford class 5 CLI (OR = 3.28) but was not significantly different in patients with Rutherford class 4. A 2011 Cochrane review, updated in 2014, identified two small studies with a total of 57 patients that met the inclusion criteria for local intramuscular transplantation of autologous mononuclear cells (monocytes) for critical limb ischemia (CLI).[11, 12] Studies were excluded that used mesenchymal stem cells (MSCs) or bone marrow aspirate. In the first study, intramuscular injection of bone marrow-derived mononuclear cells was compared with standard conservative treatment. In the second study peripheral blood derived mononuclear cells were collected following injections of granulocyte colony-stimulating factor 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. No additional studies were found for the 2014 update of this systematic review.

A systematic review and meta-analysis by Fadini (2010) included 37 RCTs and controlled and non-controlled nonrandomized studies.[13] Bone marrow derived autologous cell therapy resulted in significant improvement in measures of ischemia, wound healing, and amputation rates. However, granulocyte colony stimulating factor mobilized peripheral blood cells was not associated with significant improvement in the same endpoints. Patients with Bruerger disease showed larger benefit than patients with atherosclerotic PAD. Results also suggested that the intramuscular route of administration was more effective than the intra-arterial route. The authors concluded that autologous bone marrow cell therapy was feasible and relatively safe for patients with PAD and large, placebo-controlled RCTs are needed to confirm these findings.

RANDOMIZED CONTROLLED TRIALS

Dubsky (2022) compared standard therapy with bone marrow derived mononuclear cell (BM-MNC) therapy in patients with chronic limb ischemia and diabetic foot.[14] 40 patients 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 to no treatment (difference, 21.8 mm Hg; p=0.034). There were more healed ulcers at 12 weeks in the BM-MNC group (31.3% vs. 0%; p=0.48). Amputation rate and amputation-free survival were 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.

Gupta (2017) evaluated the efficacy and safety of intramuscular adult human bone marrow-derived, cultured, pooled, allogeneic mesenchymal stromal cells in a phase II prospective, open-label dose-ranging study.[15] Ninety patients were nonrandomly allocated to three groups:

1 million cells/kg body weight (n=36), 2 million cells/kg body weight (n=36), and standard of care (n=18). Compared with the standard of care group, greater reduction in rest pain and healing of ulcers occurred in the 2 million cells/kg body weight group (0.3 units per month and 11.0% decrease in size per month, respectively) and in the 1 million cells/kg body weight group (0.23 per and 2.0% decrease in size per month, 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 ankle brachial pressure index values and larger ulcers indicating potential investigator bias to allocate more severe patients to the treatment groups.

A 2017 randomized, double-blind, placebo-controlled, phase 2 exploratory clinical trial designed to assess the safety and efficacy of autologous bone marrow-derived aldehyde dehydrogenase bright (ALDHbr) cells in patients with peripheral artery disease was conducted in 82 patients with claudication and infrainguinal peripheral artery disease.[16] The primary end points were change from baseline to six months in peak walking time (PWT), collateral count, peak hyperemic popliteal flow, and capillary perfusion measured by MRI. There were no significant differences in primary or secondary endpoints between trial and control groups in this study.

A 2017 randomized, double-blind, placebo-controlled trial with 38 patients evaluated the efficacy of cell therapy using BM-MNC product compared to a placebo of cell-free product[17]. The primary outcome of interest was amputation while secondary outcomes included pain, ulcers, $TcPO_2$, and ankle-brachial index value. After six months of follow-up, results using logistic regression suggested no difference between groups. When using a different analytic technique (jackknife analysis), there was a lower risk of amputation for the trial group versus the control (OR 0.55, 95% CI (0.52 to 0.58). There were no differences between groups in secondary outcomes.

The randomized, double-blind, placebo-controlled rejuvenating endothelial progenitor cells via transcutaneous intra-arterial supplementation (JUVENTAS) trial evaluated the clinical effects of repeated intra-arterial infusion of BM-MNCs in 160 patients with nonrevascularizable critical limb ischemia.[18] Patients received repeated intra-arterial infusion of BM-MNCs or placebo (autologous peripheral blood erythrocytes) into the common femoral artery. The primary outcome measure, the rate of major amputation after 6 months, was not significantly different between the 2 groups (19% for BM-MNCs vs 13% controls). Secondary outcomes of quality of life, rest pain, ABI, and T_{CO2} 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 placebo groups, who remained blinded to treatment.[19] The percentage of patients undergoing amputation was also similar in the two groups (BM-MNC group, 25.9%; control group, 25.3%).

In 2013, Poole reported results of a phase 2 double-blind, placebo-controlled study of G-CSF in 159 patients with intermittent claudication due to PAD.[20] Patients were treated with subcutaneous injections of G-CSF or placebo three times a week for four weeks. The primary outcome, peak treadmill walking time at three months, increased by 109 seconds (296 to 405 seconds) in the G-CSF group and by 56 seconds (308 to 376 seconds) in the placebo group (p=0.08). Changes in the physical functioning subscore of the SF-36 and distance score of the Walking Impairment Questionnaire (WIQ) were significantly better in patients treated with G-CSF. However, there were no significant differences between the groups in the ABI, WIQ distance and speed scores, claudication onset time, or mental or physical component scores of

the SF-36. Post hoc exploratory analysis found that patients with a greater than 100% increase in progenitor cells (CD34+/CD133+) had a significantly greater increase in peak walking time than patients who had less than 100% increase in progenitor cells (131 seconds vs 60 seconds). The authors noted several limitations to this RCT such as the inability, due to the study design, to determine whether dose changes or repeat administration would provide enhanced therapeutic benefit. In addition, patients in both groups were encouraged to walk to claudication several times a day in order to promote “homing” of progenitor cells in the treatment group; however, the investigators were concerned that this might also have improved the walking capacity in the placebo group. Finally, the study may not have been powered adequately to evaluate the primary end point or significant between-group differences in serious adverse events. Authors concluded that further study is warranted.

PRACTICE GUIDELINE SUMMARY

No clinical practice guidelines have been identified that address the use of cell transplantation as a treatment of peripheral arterial disease.

SUMMARY

There is not enough research to show that cell therapy improves health outcomes for people with peripheral artery disease. No clinical guidelines based on research recommend cell therapy for people with peripheral artery disease. Therefore, infusion or injection of cells for peripheral arterial disease is considered investigational.

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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	None	

Date of Origin: *September 2011*