BlueCross BlueShield of Alabama

Name of Policy:
Stem-cell Therapy for Peripheral Arterial Disease

Policy #:183
Category: Surgery

Latest Review Date: June 2014
Policy Grade: A

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

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

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 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 and advanced age) are also risk factors for a lower number of circulating progenitor cells.

The rationale of hematopoietic stem-cell/bone marrow-cell therapy in PAD is to induce arteriogenesis by boosting the physiological repair processes. This requires large numbers of functionally active autologous precursor cells, and subsequently a large quantity of bone marrow (e.g., 240-500 mL) or other source of stem cells. The SmartPReP2® Bone marrow Aspirate Concentrate System (Harvest Technologies) has been developed as a single-step point-of-care, bedside centrifugation system for the concentration of stem cells from bone marrow. The system is composed of a portable centrifuge and an accessory pack that contains processing kits including a functionally closed dual-chamber sterile processing disposable. 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 stem-cell/bone marrow concentrate is administered either intra-arterially or through multiple injections (20 to 60) into the muscle, typically in the gastrocnemius. Other methods of concentrating stem cells include the in vitro expansion of bone marrow-derived stem cells or use of granulocyte 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 stem cells.

The primary outcome in stem-cell therapy trials regulated by the U.S. Food and Drug Administration (FDA) is amputation-free survival. Standard outcomes for critical limb ischemia include the Rutherford criteria for limb status, healing of ulcers, the ankle-brachial index (ABI), transcutaneous oxygen pressure (TcO2), and pain-free walking. The Rutherford criteria include ankle and toe pressure, 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 > 0.1 is considered to be clinically significant. TcO2 is measured with an oxy-monitor; the normal value is 70-90 mmHg. Pain free walking may be measured by time on a treadmill, or more frequently by distance in a 400 meter walk.

Policy:

Treatment of peripheral arterial disease, including critical limb ischemia, with injection or infusion of cells concentrated from bone marrow aspirate does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

At the time this policy was created (May 2011), the literature, as identified through a search of the MEDLINE database and supplemented by recent review articles, consisted primarily of case series. The most recent update was performed through April 7, 2014. Systematic reviews, controlled studies and the larger case series are described below.

A 2011 Cochrane review identified two small studies with a total of 57 patients that met the review's inclusion criteria for local intramuscular transplantation of autologous mononuclear cells (monocytes) for critical limb ischemia (CLI). Studies were excluded that used

mesenchymal stem cells (MSCs) or bone marrow aspirate. In one of the studies intramuscular injection of bone marrow-derived mononuclear cells 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 are needed to adequately evaluate the effect of treatment with greater certainty.

In 2012, Liu et al reported a meta-analysis of six randomized trials (333 patients) that evaluated mononuclear cell transplantation in patients with CLI. 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 VI. Following is a description of some of the randomized controlled trials (RCTs) that were included in the meta-analysis.

A 2013 meta-analysis by Teraa et al included 12 RCTs with a total of 510 patients with critical limb ischemia. 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 effect on major amputation rates was identified (RR, 0.78-0.92).

Concentrated Bone Marrow Aspirate (Monocytes and Mesenchymal Stem Cells)
Randomized Controlled Trials
Intramuscular Injection. Prochazka et al reported a randomized study of 96 patients with critical limb ischemia and foot ulcer in 2010. Patient inclusion criteria were critical limb ischemia as defined by ankle-brachial index (ABI) 0.4 or less, ankle systolic pressure 50 mm Hg or less, or toe systolic pressure 30 mm Hg or less, and failure of basic conservative and revascularization treatment (surgical or endovascular). The patients were randomized into treatment with bone marrow concentrate (n=42) or standard medical care (n=54). The primary end points were major limb amputation during 120 days and degree of pain and function at 90- and 120-day follow-up. At baseline, the control group had a higher proportion of patients with diabetes (98.2% vs 88.1%), hyperlipidemia (80.0% vs 54.8%), and ischemic heart disease (76.4% vs 57.1% - all respectively). In addition, the control group had a higher proportion of patients with stage DIII (deep ulcers with osteitis) University of Texas Wound Classification (72% vs 40%, respectively). For the 42 patients in the treatment group, there was a history of 50 revascularization procedures; 46 of 54 patients in the control group had a history of revascularization procedures. Forty-two of the 42 patients in the bone-marrow group finished 90 days of follow-up, and 37 of 54 patients in the control group finished 120 days of follow-up. The reason for different times of follow-up for the primary outcome measure is unclear. Five patients in the bone-marrow group and 8 in the control group died of causes unrelated to the therapy during follow-up. At follow-up, the frequency of major limb amputation was 21% in patients treated with bone marrow concentrate and 44% in controls. Secondary end points were performed only in the group treated with bone marrow concentrate. In the treatment group with salvaged limbs, toe pressure and toe brachial

index increased from 22.66 to 25.63 mm Hg and from 0.14 to 0.17, respectively. Interpretation of this study is limited by unequal baseline measures, lack of blinding, different periods of follow-up, different loss to follow-up and different measures at follow-up for the two groups.

In 2011, Benoit et al reported an FDA-regulated double-blind pilot RCT of 48 patients with CLI who were randomized in a 2:1 ratio to bone marrow concentrate using the SmartPReP system or iliac crest puncture with intramuscular injection of diluted peripheral blood. At six-month follow-up, the difference in the percentage of amputations between the cell therapy group and controls (29.4% vs. 35.7%) did not achieve statistical significance. In a subgroup analysis of patients with tissue loss at baseline (Rutherford 5), intramuscular injection of bone marrow concentrate resulted in a lower amputation rate than placebo (39.1% vs. 71.4%). Power analysis indicated that 210 patients would be needed to achieve 95% power in a planned pivotal trial.

Intra-arterial Injection

Results from the multicenter PROVASA trial (Intraarterial Progenitor Cell Transplantation of Bone Marrow Mononuclear Cells for Induction of Neovascularization in Patients with Peripheral Arterial Occlusive Disease) were reported in 2011. In this double-blind Phase II trial, 40 patients with CLI who were not candidates or had failed to respond to interventional or surgical procedures were randomized to intra-arterial administration of BM-MNC or placebo. The cell suspension included hematopoietic, mesenchymal, and other progenitor cells. After three months, both groups were treated with BM-MNC in an open-label phase. Twelve patients received additional treatment with BM-MNC between six and 18 months. The primary outcome measure, a significant increase in the ABI at three months, was not achieved (from 0.66 at baseline to 0.75 at three months). Limb salvage and amputation-free survival rates did differ between the groups. There was a significant improvement in ulcer healing (ulcer area, 1.89 cm2 vs 2.89 cm2) and reduced pain at rest (improvement of about three vs 0.05) following intra-arterial BM-MNC administration. This is the only RCT to report intra-arterial administration of BM-MNC.

Observational Studies

A 2008 TACT report by Matoba et al assessed the three-year safety and clinical outcomes of intramuscular implantation of BM-MNC in a series of 74 patients with critical limb ischemia due to atherosclerotic peripheral arterial disease (PAD) and 41 patients with thromboangiitis obliterans (TAO, Buerger disease). The ischemic limbs were not candidates for surgical or nonsurgical revascularization. Twenty-six patients (23%) had a previous bypass operation. Bone marrow cells were aspirated from the ileum and the mononuclear cells sorted and concentrated to a final volume of 40 mL. The cells were implanted by intramuscular injection into the foot. Patients were followed every week for four weeks and at six, 12, 24, and 36 months thereafter. The overall survival, amputation-free interval, adverse events, ABI, transcutaneous oxygen pressure (TcO2), pain scale, ulcer size, and pain-free walking distance were evaluated at each time point. Three-year overall survival rates were 80% in patients with atherosclerotic PAD and 100% for patients with TAO, and the median follow-up time of surviving patients was 25 months (range, 0.8-69 months). The three-year amputation-free rate was 60% in atherosclerotic PAD and 91% in patients with TAO. Of the 24 amputations in patients with PAD, 83% occurred within six months. The ABI and TcO2 value did not significantly change, but there was a significant

improvement in the leg pain scale (6 to 2), ulcer size (3.5 cm2 to 0), and pain-free walking distance (about 25 meters to 100 meters) at six months.

Amann et al reported a pilot study of autologous bone marrow cell transplantation in 51 consecutive patients with impending major amputation due to end-stage CLI in 2009. Forty-five patients (88%) had undergone a mean of two unsuccessful attempts of operative and/or percutaneous revascularization of the ischemic limb. Six patients (12%) were technically not amenable to revascularization. Major amputation (above the ankle) had been recommended to 46 of the 51 patients (90%) by the treating vascular surgeons. For the first 12 subjects, 450 to 500 mL bone marrow was aspirated under general anesthesia and processed by the Ficoll method. For the remaining subjects, 240 mL bone marrow was aspirated under sedation and processed using an automated bedside density gradient centrifugation method. Patients were seen monthly up to six months and at least in half-year intervals after. Minimum follow-up was six months, and the mean follow-up was 411 days (range, 175-1186 days). No patients were lost to follow-up. Improvement in perfusion and subsequent limb salvage was achieved in 30/51 patients (59%) at six months and 27/51 (53%) at last follow-up (mean of 411 days). Seventeen minor amputations (six forefoot and 11 toe) were performed in the 30 patients with 24-week limb salvage. Complete wound healing was achieved in 15 of 21 patients with ischemic wounds. Perfusion increased in patients with limb salvage and did not change in patients who eventually underwent major amputation. Patients with limb salvage improved from a mean Rutherford category of 4.9 at baseline to 3.3 at six months. Analgesic consumption was reduced by 62%. Total walking distance improved in non-amputees from a median of 0 to 40 meters at 24 weeks. No unexpected long-term adverse events occurred.

Adverse Events

In 2012, Jonsson et al reported a high incidence of serious adverse events in patients treated with peripheral blood mononuclear cells, causing the investigators to terminate the study. Out of nine patients, two had a myocardial infarction that was believed to be related to the bone marrow stimulation, and one of the two patients died. Another patient had a minor stroke one week after stem cell implantation.

Expanded Monocytes and Mesenchymal Stem Cells

Randomized Controlled Trials

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

Granulocyte Colony-stimulating Factor

Randomized Controlled Trials

In 2013, Poole et al reported results of a Phase II double-blind, placebo-controlled study 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 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 GM-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 GM-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 a 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).

Comparative Studies

Randomized Controlled Trials

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

In 2002, the Therapeutic Angiogenesis by Cell Transplantation (TACT) study investigators published results of a pilot study and a small double-masked trial with 22 patients who were treated with BM-MNCs by intramuscular injection into the gastrocnemius of one leg and peripheral blood-mononuclear cells in the other leg as a control (randomized order). Patients qualified for marrow implantation if they had bilateral chronic limb ischemia, including rest pain, nonhealing ischemic ulcers, or both, and were not candidates for nonsurgical or surgical revascularization. Seventeen patients (85%) had been previously treated with percutaneous angioplasty, bypass graft, or both. The patients had resting ABI less than 0.6 in both limbs. Patients with poorly controlled diabetes mellitus or with evidence of malignant disorder during the past five years were excluded from the study. About 500 mL of bone marrow cells were aspirated from the ileum, separated, and concentrated to a final volume of about 30 mL. About three hours after marrow aspiration the cells were implanted by intramuscular injection into the gastrocnemius. Follow-up with ABI, TcO2, and pain-free walking time was performed every week for four weeks and every four months thereafter. Two patients discontinued the study after randomization due to clinical worsening before four weeks. At four weeks after treatment, ABI, TcO2, and rest pain were significantly improved in legs injected with BM-MNCs, compared with those injected with peripheral blood-mononuclear cells. For example, ABI increased by 0.1 in the leg treated with bone marrow-mononuclear cell and by 0.02 with peripheral blood-mononuclear cells. TcO2 improved by 17.4 mm Hg with BM-MNCs and by 4.6 mm Hg with peripheral blood-mononuclear cells. Rest pain in legs treated with bone marrow-mononuclear cells was resolved in 16 of 20 patients, while pain in legs treated with peripheral blood-mononuclear cells remained in 17 of 20 patients. These improvements were sustained at 24 week

follow-up. Digital subtraction angiography showed a marked increase in the number of visible collateral vessels in 60% of legs treated with bone marrow cells. No adverse events were reported.

Summary
Based on initial evidence from case series and small randomized trials, injection of bone marrow concentrate may hold promise as a treatment for critical limb ischemia due to peripheral arterial disease. The current literature consists primarily of case series and Phase II studies using a variety of cell preparation methods. Well-designed and well-conducted randomized controlled trials with a larger number of subjects are needed to evaluate the health outcomes of these procedures. A number of trials are in progress, including several large randomized double-blind placebo controlled trials. Results from these trials are needed to adequately evaluate the impact on net health outcome of this procedure. Further information on the safety and durability of the treatment is also needed. Therefore, infusion or injection of stem cells for peripheral arterial disease is considered investigational.

Key Words:

Critical Limb Ischemia, Peripheral Arterial Disease, Peripheral Artery Disease, Bone marrow concentrate, Harvest, Hematopoietic stem cells, Limb Ischemia, Monocytes, Mononuclear cells, Smart Prep, SmartPReP2®, Stem cells, RESTORE-CLI, PROVASA, MarrowStim™, Ixmyelocel-T

Approved by Governing Bodies:

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

Ixmyelocel-T (Aastrom) 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 two-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 FDA's Center of Biologic Evaluation and Research.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Coding:

Effective for dates of service on or after July 1, 2011*:

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.

*****The CPT codes were 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:

Medical Policy Group, May 2011
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Available for comment May 25 – July 11, 2011
Medical Policy Group May 2012 **(3)**: Updated Key Points, Key Words, & References
Medical Policy Panel, May 2013
Medical Policy Group May 2013**(3)**: Updated Description, Key Points, Approved by Governing Bodies and References; no change in policy statement
Medical Policy Panel, May 2014
Medical Policy Group, May 2014 **(3)**: 2014 Updates to Description, Key Points & References; no change in policy statement

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