APPENDIX to Stem-Cell Therapy for Peripheral Arterial Disease Policy

Prior Authorization Requirements

This service (or procedure) is considered **investigational** in all instances. If you would like to submit additional information please forward to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

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 peripheral arterial disease (PAD) is to induce arteriogenesis by boosting the physiological repair processes.

Standard outcomes for critical limb ischemia (CLI) 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 to 1.2). An increase greater than 0.1 is considered to be clinically significant. Transcutaneous oxygen pressure is measured with an oxymonitor; the normal value is 70 to 90 mm Hg. Pain-free walking may be measured by time on a treadmill, or more frequently, by distance in a 400-meter walk.

Most of the published literature consists primarily of small case series. Several controlled studies and larger case series are described below.

In 2011, Mozzami et al. conducted a Cochrane search of randomized controlled trials (RCTs) to determine the effectiveness and safety of autologous adult bone marrow derived mononuclear cells (BMMNCs) as a treatment for CLI. Two small studies, out of a potential 37 studies, with a combined total of 57 patients, met the inclusion criteria. The authors concluded that the data from the published trials suggest there is insufficient evidence to support this treatment for CLI. Results were based on only two trials that had a very small number of participants. Therefore evidence from larger RCTs is needed.

In 2010, Prochazka and colleagues reported a randomized study of 96 patients with CLI and foot ulcer. Patient inclusion criteria were CLI as defined by ABI equal to or less than 0.4, ankle systolic pressure equal to or less than 50 mm Hg or toe systolic pressure equal to or less than 30 mm Hg, 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 endpoints 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% versus 88.1%), hyperlipidemia (80.0% versus 54.8%) and ischemic heart disease (76.4% versus 57.1%), 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% versus 40%), respectively. For the 42 patients in the treatment group, there was a history of 50 revascularization procedures; 46 of 54 patients in the control group had a history of revascularization procedures. All 42 patients in the bone marrow group finished 90 days of follow-up, and 37 of 54 patients in the control group finished 120 days of follow-up. The reason for 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 endpoints 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 mm Hg 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 2 groups.

Results from the multi-center 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. Walter et al. conducted this double-blind Phase II trial, in which 40 patients with CLI who were not candidates for or had failed to respond to interventional or surgical procedures, were randomized to intra-arterial administration of BMMNCs or placebo. The cell suspension included hematopoietic, mesenchymal, and other progenitor cells. After 3 months, both groups were treated with BMMNCs in an open-label phase. Twelve patients received additional treatment with BMMNCs between 6 and 18 months. The primary outcome measure, a significant increase in the ABI at 3 months, was not achieved (from 0.66 at baseline to 0.75 at 3 months). Limb salvage and amputation-free survival rates did differ between the groups. There was a significant improvement in ulcer healing (ulcer area 1.89 cm^2 versus 2.89 cm^2) and reduced pain at rest (improvement of about 3 versus 0.05) following intra-arterial BMMNC administration. This is the only RCT to report intra-arterial administration of BMMNCs.

In 2002, Tateishi-Yuyama et al. published results of the Therapeutic Angiogenesis by Cell Transplantation (TACT) study. The pilot study and small double-masked trial included 22 patients who were treated with BMMNCs 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 CLI, including rest pain, non-healing 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 5 years were excluded from the study. Follow-up with ABI, TcO_2 and pain-free walking time was performed every week for 4 weeks and every 4 months thereafter. Two patients discontinued the study after randomization due to clinical worsening before 4 weeks. At 4 weeks after treatment; ABI, TcO_2, and rest pain were significantly improved in legs injected with BMMNCs, compared with those injected with peripheral blood mononuclear cells. For example, ABI increased by 0.1 in the leg treated with BMMNCs and by 0.02 with peripheral blood mononuclear cells. Measurement of TcO_2 improved by 17.4 mm Hg with BMMNCs and by 4.6 mm Hg with peripheral blood mononuclear cells. Rest pain in legs treated with BMMNCs was resolved in 16 of 20 patients, while rest pain in legs treated with peripheral blood mononuclear cells remained in 17 of 20 patients. These improvements were sustained at the 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.

The 2008 TACT report by Matoba et al. assessed the 3-year safety and clinical outcomes of intramuscular implantation of BMMNCs in a series of 74 patients with CLI due to atherosclerotic PAD and 41 patients with thromboangiitis obliterans (TAO; Buerger's disease). The ischemic limbs were not candidates for surgical or nonsurgical revascularization. Twenty-six patients (23%) had a previous bypass operation. Patients were followed every week for 4 weeks and at 6, 12, 24, and 36 months thereafter. The overall survival, amputation-free interval, adverse events, ABI, TcO_2, pain scale, ulcer size, and pain-free walking distance were evaluated at each time point. Overall patient survival and amputation-free interval were defined as the primary endpoints of this study. 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 months to 69 months). The 3-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 6 months. Multivariate analysis indicated that the severity of ischemic pain at baseline and prior repeated bypass surgery were the major determinants that negatively affected the amputation-free interval of the therapy. The ABI and TcO_2 value did not significantly change, but there was a significant improvement in the leg pain scale, ulcer size, and pain-free walking distance at 6 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 2 unsuccessful attempts of operative and/or percutaneous revascularization of the ischemic limb. Six patients (12%) were technically not amenable to revascularization. Critical limb ischemia was confirmed if there was angiographic proof of arterial occlusion and one of the following criteria was fulfilled: ABI less than 0.6 or TcO_2 less than 30 mm Hg. Major amputation (above the ankle) had been recommended to 46 of the 51 patients (90%) by the treating vascular surgeons. Patients were seen monthly up to 6 months and at least in half-year intervals after. Minimum follow-up was 6 months, and the mean follow-up was 411 days (range: 175 days to 1,186 days). No patients were lost to follow-up. Improvement in perfusion and subsequent limb salvage was achieved in 30 patients (59%) at 6 months and 27 (53%) at last follow-up (mean of 411 days). Seventeen minor amputations (6 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, measured at 6 months with ABI and TcO_2, 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 6 months. Analgesic consumption was reduced by 62%. Total walking distance improved in non-amputees from a median of 0 meters to 40 meters at 24 weeks. No unexpected long-term adverse events occurred.

The TransAtlantic Inter-Society Consensus II (TASC II) 2007 Guidelines for the management of peripheral arterial disease state:

> Preliminary trials of intramuscular injection of autologous bone marrow mononuclear cells to stimulate vascular growth have been promising (Tateishi-Yuyama et al., 2002). Most trials are in Phase I or II and the appropriate use of gene therapy in vascular practice remains to be proven (p.142).

In summary, based on initial evidence from case series and small randomized trials, injection of bone marrow concentrate may hold promise as a treatment for CLI due to PAD. However, well-designed and well-conducted RCTs are needed to evaluate the health outcomes of this procedure. 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 (bone marrow concentrate) for PAD is considered investigational.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	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
HCPC	None	
ICD9 Procedure	99.79	Other therapeutic apheresis
ICD9 Diagnosis	All Diagnoses	

Type	Number	Description
Place of Service	All Places of Service	

Tables

N/A

Definitions

Thromboangiitis obliterans (Buerger's disease) - A chronic, recurring, inflammatory vascular occlusive disease affecting the arteries and veins of the hands and feet.

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

N/A

Key / Related Searchable Words

- Autologous bone marrow transplant
- BMMNC
- CLI
- Critical limb ischemia
- PAD
- Peripheral arterial disease
- Peripheral artery disease
- Stem-cell therapy

References

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- Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 8.01.55 (May 2012).
- Matoba S, Tatsumi T, Murohara T et al. Long-term clinical outcome after intramuscular implantation of bone marrow mononuclear cells (Therapeutic Angiogenesis by Cell Transplantation [TACT] trial) in patients with chronic limb ischemia. Am Heart J. 2008; 156(5):1010-8.

- Moazzami K, Majdzadeh R, Nedjat S. Local intramuscular transplantation of autologous mononuclear cells for critical lower limb ischaemia. Cochrane Database Syst Rev. 2011; (12):CD008347.
- Prochazka V, Gumulec J, Jaluvka F et al. Cell therapy, a new standard in management of chronic critical limb ischemia and foot ulcer. Cell Transplant. 2010; 19(11):1413-24.
- Tateishi-Yuyama E, Matsubara H, Murohara T et al. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: A pilot study and a randomised controlled trial. Lancet. 2002; 360(9331):427-35.
- TransAtlantic Inter-Society Consensus II (TASC II). TASC II 2007 Guidelines for the Management of Peripheral Arterial Disease. 2007. Retrieved October 16, 2012 from http://www.tasc-2-pad.org/upload/SSRubriqueProduit/Fichier2/597.pdf.
- Walter DH, Krankenberg H, Balzer JO et al. Intraarterial administration of bone marrow mononuclear cells in patients with critical limb ischemia: A randomized-start, placebo-controlled pilot trial (PROVASA). Circulation Cardiovascular Interventions. 2011; 4(1):26-37.

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
1/11/2013	BCBSA Medical Policy adoption	Medical Policy Committee

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

Click here to view the policy statement for this policy

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