

Corporate Medical Policy

Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

File Name: progenitor_cell_therapy_for_the_treatment_of_damaged_myocardium_due_to_ischemia
Origination: 11/2004
Last CAP Review: 10/2018
Next CAP Review: 10/2019
Last Review: 10/2018

Description of Procedure or Service

Ischemia is the most common cause of cardiovascular disease and myocardial damage in the developed world. Despite impressive advances in treatment, ischemic heart disease is still associated with high morbidity and mortality. Current treatments for ischemic heart disease seek to revascularize occluded arteries, optimize pump function, and prevent future myocardial damage. However, current treatments are not able to reverse existing damage to heart muscle. Treatment with progenitor cells (i.e., stem cells) offers potential benefits beyond those of standard medical care, including the potential for repair and/or regeneration of damaged myocardium.

The potential sources of embryonic and adult donor cells include skeletal myoblasts, bone marrow cells, circulating blood-derived progenitor cells, endometrial mesenchymal stem cells (MSCs), adult testis pluripotent stem cells, mesothelial cells, adipose-derived stromal cells, embryonic cells, induced pluripotent stem cells, and bone marrow MSCs, all of which are able to differentiate into cardiomyocytes and vascular endothelial cells.

The mechanism of benefit following treatment with progenitor cells is not entirely understood. Differentiation of progenitor cells into mature monocytes and engraftment of progenitor cells into areas of damaged myocardium has been suggested in animal studies using tagged progenitor cells. However, there is controversy concerning whether injected progenitor cells engraft and differentiate into mature myocytes in humans to a degree that might result in clinical benefit.

It also has been proposed that progenitor cells may improve perfusion to areas of ischemic myocardium. Basic science research also suggests that injected stem cells secrete cytokines with antiapoptotic and proangiogenesis properties. Clinical benefit may result if these paracrine factors are successful at limiting cell death from ischemia or stimulate recovery. For example, myocardial protection can occur through modulation of inflammatory and fibrogenic processes. Alternatively, paracrine factors may affect the intrinsic repair mechanisms of the heart through neovascularization, cardiac metabolism, and contractility, increase in cardiomyocyte proliferation, or activation of resident stem and progenitor cells. The relative importance of these proposed paracrine actions depends on the age of the infarct (eg, cytoprotective effects in acute ischemia and cell proliferation in chronic ischemia). Investigation of the specific factors induced by administration of progenitor cells is ongoing.

There are a variety of potential delivery mechanisms for donor cells, encompassing a wide range of invasiveness. Donor cells can be delivered via thoracotomy and direct injection into areas of damaged myocardium. Injection of progenitor cells into the coronary circulation can also be done using percutaneous, catheter-based techniques. Finally, progenitor cells can be delivered intravenously via a

Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

peripheral vein. With this approach, the cells must be able to target damaged myocardium and concentrate at the site of myocardial damage.

Adverse effects of progenitor cell treatment include the risk of the delivery procedure (e.g., thoracotomy, percutaneous catheter-based) and the risks of the donor cells themselves. Donor progenitor cells can differentiate into fibroblasts rather than myocytes. This may create a substrate for malignant ventricular arrhythmias. There is also a theoretical risk that tumors, such as teratomas, can arise from progenitor cells, but the actual risk of this occurring in humans is not known at present.

Regulatory Status

U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Progenitor cells are included in these regulations. FDA marketing clearance is not required when autologous cells are processed on site with existing laboratory procedures and injected with existing catheter devices. Several cell products are expanded ex-vivo and require FDA approval. The 21st Century Cures Act (December 2016) established new expedited product development programs including one for regenerative medicine advanced therapy (RMAT). The RMAT designation may be given if: (1) the drug is a regenerative medicine therapy, for example, a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product; (2) the drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and (3) preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs.

Multiple progenitor cell therapies such as MyoCell® (U.S. Stem Cell, formerly Bioheart), ixmylocel-T (Vericel, formerly Aastrom Biosciences), MultiStem® (Athersys), and CardiAMP™ (BioCardia) are being commercially developed, but none have been approved by the FDA so far.

MyoCell® consists of patient autologous skeletal myoblasts that are expanded ex vivo and supplied as a cell suspension in a buffered salt solution for injection into the area of damaged myocardium. In 2017, U.S. Stem Cell reprioritized its efforts away from seeking RMAT designation for MyoCell®.

Ixmylocel-T is an expanded multicellular therapeutic product produced from a patient's bone marrow by selectively expanding bone marrow mononuclear cells for 2 weeks. The expanded cell product enriched for mesenchymal and macrophage lineages might enhance potency. Vericel has received RMAT designation for Ixmylocel-T.

MultiStem® (Athersys) is an allogeneic bone marrow-derived adherent adult stem cell product.

CardiAMP™ Cell Therapy system consists of a proprietary assay to identify patients with a high probability to respond to autologous cell therapy, a proprietary cell processing system to isolate process and concentrate the stem cells from a bone marrow harvest at the point of care, and a proprietary delivery system to percutaneously inject the autologous cells into the myocardium. BioCardia has received an investigational device exemption for FDA to perform a trial of CardiAMP.

Related Policies:

Orthopedic Applications of Stem Cell Therapy
Stem Cell Therapy for Peripheral Arterial Disease

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

Progenitor cell therapy (including but not limited to skeletal myoblasts or hematopoietic stem cells) for the treatment of damaged myocardium is considered investigational. BCBSNC does not provide coverage for investigational services.

Infusion of growth factors (i.e., granulocyte colony stimulating factor) is considered investigational as a technique to increase the numbers of circulating hematopoietic stem cells as treatment of damaged myocardium. BCBSNC does not provide coverage for investigational services.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Progenitor Cell Therapy for the Treatment of Damaged Myocardium is covered

Not Applicable

When Progenitor Cell Therapy for the Treatment of Damaged Myocardium is not covered

Progenitor cell therapy, including but not limited to skeletal myoblasts or hematopoietic stem cells, for the treatment of damaged myocardium is considered investigational.

Infusion of growth factors (i.e., granulocyte colony stimulating factor) is considered investigational as a technique to increase the numbers of circulating hematopoietic stem cells as treatment of damaged myocardium.

Policy Guidelines

Progenitor cell therapy has been tested in patients with acute ischemia, chronic ischemia, and refractory angina. For all these conditions, there is a similar pattern of outcomes, with modest improvements demonstrated on physiologic outcomes, but limited impact on clinical outcomes. For acute cardiac ischemia the evidence includes 2 phase 3 randomized controlled trials (RCTs), numerous small early-phase RCTs, and meta-analyses of these RCTs. Relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. Limited evidence on clinical outcomes suggests that there may be benefits in improving left ventricular ejection fraction, reducing recurrent MI, decreasing the need for further revascularization, and perhaps even decreasing mortality, although a recent, large meta-analysis reported no improvement in these outcomes. No adequately powered trial has reported benefits in clinical outcome, such as mortality, adverse cardiac outcomes, exercise capacity, or quality of life. Overall, this evidence has suggested that progenitor cell treatment may be a promising intervention, but robust data on clinical outcomes are lacking. High-quality RCTs, powered to detect differences in clinical outcomes, are needed to answer this question. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with chronic cardiac ischemia who receive progenitor cell therapy, the evidence includes 2 phase 3 RCT with more than 100 participants, systematic reviews of smaller early-phase RCTs, and a nonrandomized comparative trial. Relevant outcomes are disease-specific survival,

Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

morbid events, functional outcomes, quality of life, and hospitalizations. Studies included in the meta-analyses reported only a small number of clinical outcome events. These findings from early phase 2 trials need to be corroborated in larger phase 3 trials. A well-conducted, phase 3 RCT trial failed to demonstrate superiority of cell therapy for its primary composite outcome that included death, worsening heart failure events, and other multiple events. Results of the nonrandomized STAR-Heart trial showed a mortality benefit as well as favorable hemodynamic effect, but a lack of randomization limits interpretation due to the concern of selection bias and differences in known and unknown prognostic variables at baseline between both arms. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have refractory angina and receive progenitor cell therapy, evidence includes a systemic review of RCTs, phase 2 trials and a phase 3 pivotal trial. Relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. The only phase 3 trial identified was terminated early and not sufficiently powered to evaluate clinical outcomes. Additional larger trials are needed to determine whether progenitor cell therapy improved health outcomes in patients with refractory angina. The evidence is insufficient to determine the effects of the technology on health outcomes.

In 2013, ACCF and AHA issued joint guidelines for the management of STEMI (ST-segment elevation myocardial infarction). Progenitor cell therapy is not recommended.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: There is currently no specific CPT code for either the laboratory component of processing the harvested autologous cells, or for the implantation procedure. In some situations, the implantation may be an added component of a scheduled coronary artery bypass graft (CABG). In other situations, the implantation may be performed as a unique indication for a cardiac catheterization procedure. Services should be submitted in the form of an appropriate unlisted code. Medical records for the explanation of the service rendered may be necessary.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy titled Autologous Cell Therapy for the Treatment of Damaged Myocardium

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.02.18, 4/16/04.

Specialty Matched Consultant Advisory Panel - 11/05.

Penn MS, Frances GS, Ellis SG, Young JB, McCarthy PM, Topol EJ. Autologous Cell Transplantation for the Treatment of Damaged Myocardium. *Progress in Cardiovascular Diseases*, Vol. 45, No. 1, (July/August) 2002: pp 21-32.

Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

Pagani FD, DerSimonian H, Zawadska A, Wetzel K, Edge AS, Jacoby DB, et al. Autologous Skeletal Myoblasts Transplanted to Ischemia-Damaged Myocardium in Humans. *J Am Coll Cardiol*. 2003; 41: 879-88.

Weissberg PL, Qasim A. Stem cell therapy for myocardial repair. *Heart*. 2005; 91: 696-702.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.02.18, 2/15/07

BCBSA Technology Evaluation Center. (2008, September). Autologous progenitor cell therapy for the treatment of ischemic heart disease. Retrieved 8/20/09 from http://blueweb.bcbs.com/global_assets/special_content/tec_assessments/vol23/23_04.pdf

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.02.18, 7/10/08

Policy re-titled to Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

National Institute of Health (NIH). The Enhanced Angiogenic Cell Therapy - Acute Myocardial Infarction Trial (ENACT-AMI). Clinical Trial NCT00936819. Retrieved on January 18, 2012 from <http://clinicaltrials.gov/ct2/show/NCT00936819?term=ENACT-AMI&rank=1>

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.02.18, 6/9/11

Losordo DW, Henry TD, Davidson C et al. Intramyocardial, autologous CD34+ cell therapy for refractory angina. *Circ Res* 2011; 109(4):428-36. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3190575/?tool=pubmed>

Hirsch A, Nijveldt R, van der Vleuten PA et al. Intracoronary infusion of mononuclear cells from bone marrow or peripheral blood compared with standard therapy in patients after acute myocardial infarction treated by primary percutaneous coronary intervention: results of the randomized controlled HEBE trial. *Eur Heart J* 2011; 32(14):1736-47. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/21148540>

Clifford DM, Fisher SA, Brunskill SJ, Doree C, Mathur A, Clarke MJ, Watt SM, Martin-Rendon E. Long-term effects of autologous bone marrow stem cell treatment in acute myocardial infarction: factors that may influence outcomes. *PLoS One*. 2012;7(5):e37373. Epub 2012 May 24. Retrieved from <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0037373>

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.02.18, 6/14/12

Medical Director review 7/2012

Specialty Matched Consultant Advisory Panel review 10/2012

Traverse JH, Henry TD, Pepine CJ et al. Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: the TIME randomized trial. *JAMA* 2012; 308(22):2380-9. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3652242/>

Donndorf P, Kaminski A, Tiedemann G et al. Validating intramyocardial bone marrow stem cell therapy in combination with coronary artery bypass grafting, the PERFECT Phase III randomized multicenter trial: study protocol for a randomized controlled trial. *Trials* 2012; 13:99. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3419083/>

Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.02.18, 6/13/13

Specialty Matched Consultant Advisory Panel review 10/2013

O'Gara PT, Kushner FG, Ascheim DD et al. 2013 ACCF/AHA guideline for the management of STElevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; 61(4):e78-140.

Fisher SA, Brunskill SJ, Doree C et al. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. *Cochrane Database Syst Rev* 2014; 4:CD007888.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.02.18, 6/12/14

Specialty Matched Consultant Advisory Panel review 11/2014.

Senior Medical Director review 11/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.02.18, 6/11/15

Specialty Matched Consultant Advisory Panel review 10/2015

Medical Director review 10/2015

Specialty Matched Consultant Advisory Panel review 10/2016

Medical Director review 10/2016

Pompilio G, Nigro P, Bassetti B, et al. Bone marrow cell therapy for ischemic heart disease: the never ending story. *Circ Res.* Aug 28 2015;117(6):490-493. PMID 26316604

Afzal MR, Samanta A, Shah ZI, et al. Adult bone marrow cell therapy for ischemic heart disease: evidence and insights from randomized controlled trials. *Circ Res.* Aug 28 2015;117(6):558-575. PMID 26160853

Fisher SA, Zhang H, Doree C, et al. Stem cell treatment for acute myocardial infarction. *Cochrane Database Syst Rev.* Sep 30 2015(9):CD006536. PMID 26419913

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.02.18, 12/2016

Medical Director review 12/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.02.18, 8/2017

Medical Director review 8/2017

Specialty Matched Consultant Advisory Panel review 10/2017

Medical Director review 10/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.02.18, 5/2018

Medical Director review 5/2018

Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

Specialty Matched Consultant Advisory Panel review 10/2018

Medical Director review 10/2018

Policy Implementation/Update Information

For Policy titled Autologous Cell Therapy for the Treatment of Damaged Myocardium

- 11/11/04 New policy issued. Autologous cell therapy for the treatment of damaged myocardium is considered investigational. References added. Notification 11/11/04. Effective 01/20/05.
- 11/17/05 Specialty Matched Consultant Advisory Panel review 11/7/05.
- 11/19/07 Information regarding MyoCell and MyoCath deleted from the Description section. Revised information in Policy Guidelines section to support continued investigational status. References updated. Specialty Matched Consultant Advisory Panel review meeting 10/29/07. No change in policy statement. (adn)
- 12/7/09 Description section extensively revised. Policy Guidelines section updated to reflect findings from BCBSA TEC Assessment. References updated. Specialty Matched Consultant Advisory Panel review 10/30/09. Policy status changed to Active Archive, no longer scheduled for routine literature review. (adn)
- 6/22/10 Policy Number(s) removed. (amw)

Policy re-titled to Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

- 5/1/12 Policy status changed to active and will undergo routine literature review. Policy re-titled from “Autologous Cell Therapy for the Treatment of Damaged Myocardium” to “Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia.” Description section updated. Policy Guidelines updated. References updated. Medical Director review 4/2012.
- 8/21/12 Policy Guidelines updated. References updated. Medical Director review 7/2012. No changes to Policy Statements. (mco)
- 11/13/12 Specialty Matched Consultant Advisory Panel review 10/2012. No changes to Policy Statements. (mco)
- 7/30/13 Description section updated. References updated. No changes to Policy Statements. (mco)
- 11/12/13 Specialty Matched Consultant Advisory Panel review 10/2013. No changes to Policy Statements. (mco)
- 8/12/14 References updated. Policy Guidelines and Description section updated. No changes to Policy Statements. (mco)

Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

- 1/13/15 References updated. Specialty Matched Consultant Advisory Panel review 11/2014. Senior Medical Director review 11/2014. No change to Policy statements. (td)
- 7/28/15 Policy Guidelines updated. References updated. Policy Statement remains unchanged. (td)
- 12/30/15 References updated. Specialty Matched Consultant Advisory Panel review 10/29/2015. Medical Director review 10/2015. (td)
- 11/22/16 Specialty Matched Consultant Advisory Panel review 10/2016. Medical Director review 10/2016. (jd)
- 1/27/17 Regulatory Status section added to distinguish FDA regulations. Policy Guidelines and references updated. Medical Director review 12/2016. (jd)
- 9/15/17 Description section and Policy Guidelines updated. No change to policy intent. References updated. Medical Director review 8/2017. (jd)
- 11/10/17 Specialty Matched Consultant Advisory Panel review 10/2017. Medical Director review 10/2017. (jd)
- 6/8/18 Regulatory status updated with the 21st Century Cures Act and CardiAMP Cell Therapy system. Policy guidelines and references updated. Medical Director review 5/2018. (jd)
- 11/9/18 Specialty Advisory Consultant Advisory Panel review 10/2018. Medical Director review 10/2018. (jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.