Protocol

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

(20218)

Medical Benefit		**Effective Date**: 01/01/11	**Next Review Date**: 07/19
Preauthorization	No	**Review Dates**: 09/10, 07/11, 07/12, 07/13, 07/14, 07/15, 07/16, 07/17, 07/18	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With acute cardiac ischemia	Interventions of interest are: • Progenitor cell therapy	Comparators of interest are: • Standard therapy	Relevant outcomes include: • Disease-specific survival • Morbid events • Functional outcomes • Quality of life • Hospitalizations
Individuals: • With chronic cardiac ischemia	Interventions of interest are: • Progenitor cell therapy	Comparators of interest are: • Standard therapy	Relevant outcomes include: • Disease-specific survival • Morbid events • Functional outcomes • Quality of life • Hospitalizations
Individuals: • With refractory angina	Interventions of interest are: • Progenitor cell therapy	Comparators of interest are: • Standard therapy	Relevant outcomes include: • Disease-specific survival • Morbid events • Functional outcomes • Quality of life • Hospitalizations

DESCRIPTION

Progenitor cell therapy describes the use of multipotent cells of various cell lineages (autologous or allogeneic) for tissue repair and/or regeneration. Progenitor cell therapy is being investigated for the treatment of damaged myocardium resulting from acute or chronic cardiac ischemia and for refractory angina.

SUMMARY OF EVIDENCE

For individuals who have acute cardiac ischemia who receive progenitor cell therapy, the evidence includes two 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 has suggested that there may be benefits from improv-

ing left ventricular ejection fraction, reducing recurrent myocardial infarction, decreasing the need for further revascularization, and perhaps decreasing mortality, although a recent, large, individual patient data meta-analysis reported no improvement in these outcomes. No adequately powered trial has reported benefits in clinical outcomes (e.g., mortality, adverse cardiac outcomes, exercise capacity, 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 who have chronic cardiac ischemia who receive progenitor cell therapy, the evidence includes two phase 3 RCTs with more than 100 participants, systematic reviews of smaller, early-phase RCTs, and a non-randomized comparative trial. Relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. The studies included in the meta-analyses have reported only on 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. 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 about 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 who receive progenitor cell therapy, the evidence includes a systematic 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 insufficiently powered to evaluate clinical outcomes. Additional larger trials are needed to determine whether progenitor cell therapy improves health outcomes in patients with refractory angina. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Progenitor cell therapy, including but not limited to skeletal myoblasts or hematopoietic cells, is considered **investigational** as a treatment of damaged myocardium.

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

POLICY GUIDELINES

In some situations, the implantation may be an added component of a scheduled coronary artery bypass graft; in other situations, the implantation may be performed as a unique indication for a cardiac catheterization procedure.

BACKGROUND

ISCHEMIA

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.

Treatment

Current treatments for ischemic heart disease seek to revascularize occluded arteries, optimize pump function, and prevent future myocardial damage. However, current treatments do not reverse existing heart muscle damage.[1, 2] 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. Potential sources of embryonic and adult donor cells include skeletal myoblasts, bone marrow cells, circulating blood-derived progenitor cells, endometrial mesenchymal stem cells, adult testis pluripotent stem cells, mesothelial cells, adipose-derived stromal cells, embryonic cells, induced pluripotent stem cells, and bone marrow mesenchymal stem cells, all of which can differentiate into cardiomyocytes and vascular endothelial cells.

The mechanism of benefit after treatment with progenitor cells is not entirely understood. Differentiation of progenitor cells into mature myocytes and engraftment of progenitor cells into areas of the 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 the 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 has also suggested that injected stem cells secrete cytokines with antiapoptotic and proangiogenesis properties. Clinical benefit may result if these paracrine factors limit 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 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 (e.g., 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 also various 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 also is done using percutaneous, catheter-based techniques. Finally, progenitor cells may be delivered intravenously via a peripheral vein. With this approach, the cells must be able to target damaged myocardium and concentrate at the site of myocardial damage.

Adverse events of progenitor cell treatment include risks of the delivery procedure (e.g., thoracotomy, percutaneous catheter-based) and 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 also is a theoretical risk that tumors (e.g., teratomas) can arise from progenitor cells, but the actual risk in humans is currently unknown.

REGULATORY STATUS

The 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 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).[3] The RMAT designation may be given if: (1) the drug is a regenerative medicine therapy (i.e., 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), ixmyelocel-T (Vericel, formerly Aastrom Biosciences), MultiStem® (Athersys), and CardiAMPTM (BioCardia) are being commercially developed, but none has been approved by the FDA so far.

MyoCell® comprises 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®.

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

MultiStem® 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 from FDA to perform a trial of CardiAMP™.

RELATED PROTOCOLS

Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

Stem Cell Therapy for Peripheral Arterial Disease

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Lee MS, Makkar RR. Stem-cell transplantation in myocardial infarction: a status report. Ann Intern Med. May 4 2004;140(9):729-737. PMID 15126257
2. Mathur A, Martin JF. Stem cells and repair of the heart. Lancet. Jul 10-16 2004;364(9429):183-192. PMID 15246732

3. U.S. Food and Drug Administration. Regenerative Medicine Advanced Therapy Designation. 2018; https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm. Accessed March 12, 2018.
4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Progenitor cell therapy for treatment of myocardial damage due to ischemia. TEC Assessments. 2008;Volume 23:Tab 4.
5. Delewi R, Hirsch A, Tijssen JG, et al. Impact of intracoronary bone marrow cell therapy on left ventricular function in the setting of ST-segment elevation myocardial infarction: a collaborative meta-analysis. Eur Heart J. Apr 2014;35(15):989-998. PMID 24026778
6. de Jong R, Houtgraaf JH, Samiei S, et al. Intracoronary stem cell infusion after acute myocardial infarction: a meta-analysis and update on clinical trials. Circ Cardiovasc Interv. Apr 1 2014;7(2):156-167. PMID 24668227
7. 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
8. Gyöngyösi M, Wojakowski W, Lemarchand P, et al. Meta-analysis of cell-based CaRdiac stUdiEs (ACCRUE) in patients with acute myocardial infarction based on individual patient data. Circ Res. Apr 10 2015; 116(8): 1346-1360. PMID 25700037
9. Fisher SA, Doree C, Taggart DP, et al. Cell therapy for heart disease: Trial sequential analyses of two Cochrane reviews. Clin Pharmacol Ther. Jul 2016;100(1):88-101. PMID 26818743
10. Moazzami K, Roohi A, Moazzami B. Granulocyte colony stimulating factor therapy for acute myocardial infarction. Cochrane Database Syst Rev. May 31 2013;5(5):CD008844. PMID 23728682
11. Schächinger V, Erbs S, Elsasser A, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med. Sep 21 2006;355(12):1210-1221. PMID 16990384
12. Schächinger V, Erbs S, Elsasser A, et al. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. Eur Heart J. Dec 2006;27(23):2775-2783. PMID 17098754
13. Assmus B, Rolf A, Erbs S, et al. Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction. Circ Heart Fail. Jan 2010;3(1):89-96. PMID 19996415
14. 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. Jul 2011;32(14):1736-1747. PMID 21148540
15. Fisher SA, Doree C, Mathur A, et al. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. Cochrane Database Syst Rev. Dec 24 2016;12:Cd007888. PMID 28012165
16. Fisher SA, Brunskill SJ, Doree C, et al. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. Cochrane Database Syst Rev. Apr 29 2014;4(4):CD007888. PMID 24777540
17. Xu R, Ding S, Zhao Y, et al. Autologous transplantation of bone marrow/blood-derived cells for chronic ischemic heart disease: a systematic review and meta-analysis. Can J Cardiol. Nov 2014;30(11):1370-1377. PMID 24726092
18. Xiao C, Zhou S, Liu Y, et al. Efficacy and safety of bone marrow cell transplantation for chronic ischemic heart disease: a meta-analysis. Med Sci Monit. Oct 01 2014;20:1768-1777. PMID 25270584
19. Bartunek J, Terzic A, Davison BA, et al. Cardiopoietic cell therapy for advanced ischaemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 clinical trial. Eur Heart J. Mar 01 2017;38(9):648-660. PMID 28025189
20. Pokushalov E, Romanov A, Chernyavsky A, et al. Efficiency of intramyocardial injections of autologous bone marrow mononuclear cells in patients with ischemic heart failure: a randomized study. J Cardiovasc Transl Res. Apr 2010;3(2):160-168. PMID 20560030
21. Strauer BE, Yousef M, Schannwell CM. The acute and long-term effects of intracoronary Stem cell Transplantation in 191 patients with chronic heARt failure: the STAR-heart study. Eur J Heart Fail. Jul 2010;12(7):721-729. PMID 20576835

22. Losordo DW, Henry TD, Davidson C, et al. Intramyocardial, autologous CD34+ cell therapy for refractory angina. Circ Res. Aug 5 2011;109(4):428-436. PMID 21737787
23. van Ramshorst J, Bax JJ, Beeres SL, et al. Intramyocardial bone marrow cell injection for chronic myocardial ischemia: a randomized controlled trial. JAMA. May 20 2009;301(19):1997-2004. PMID 19454638
24. Losordo DW, Schatz RA, White CJ, et al. Intramyocardial transplantation of autologous CD34+ stem cells for intractable angina: a phase I/IIa double-blind, randomized controlled trial. Circulation. Jun 26 2007;115(25): 3165-3172. PMID 17562958
25. Tse HF, Thambar S, Kwong YL, et al. Prospective randomized trial of direct endomyocardial implantation of bone marrow cells for treatment of severe coronary artery diseases (PROTECT-CAD trial). Eur Heart J. Dec 2007;28(24):2998-3005. PMID 17984132
26. Jimenez-Quevedo P, Gonzalez-Ferrer JJ, Sabate M, et al. Selected CD133(+) progenitor cells to promote angiogenesis in patients with refractory angina: final results of the PROGENITOR randomized trial. Circ Res. Nov 7 2014;115(11):950-960. PMID 25231095
27. Wang S, Cui J, Peng W, et al. Intracoronary autologous CD34+ stem cell therapy for intractable angina. Cardiology. Oct 2010;117(2):140-147. PMID 20975266
28. Povsic TJ, Henry TD, Traverse JH, et al. The RENEW Trial: Efficacy and safety of intramyocardial autologous CD34(+) cell administration in patients with refractory angina. JACC Cardiovasc Interv. Aug 8 2016; 9(15): 1576-1585. PMID 27491607
29. Khan AR, Farid TA, Pathan A, et al. Impact of cell therapy on myocardial perfusion and cardiovascular outcomes in patients with angina refractory to medical therapy: a systematic review and meta-analysis. Circ Res. Mar 18 2016;118(6):984-993. PMID 26838794
30. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. Jan 29 2013;61(4):e78-140. PMID 23256914