Medical Coverage Policy | Progenitor Cell Therapy for the Treatment of Damaged Myocardium due to Ischemia

EFFECTIVE DATE: 02|01|2017
POLICY LAST UPDATED: 05|19|2021

OVERVIEW
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.

MEDICAL CRITERIA
Not applicable

PRIOR AUTHORIZATION
Not applicable

POLICY STATEMENT
Medicare Advantage Plans
Progenitor cell therapy, including but not limited to skeletal myoblasts or hematopoietic cells, is considered not covered as a treatment of damaged myocardium as the evidence is insufficient to determine the effects of the technology on health outcomes.

Infusion of growth factors (ie, granulocyte colony stimulating factor) is considered not covered as a technique to increase the numbers of circulating hematopoietic cells as treatment of damaged myocardium as the evidence is insufficient to determine the effects of the technology on health outcomes.

Commercial
Progenitor cell therapy, including but not limited to skeletal myoblasts or hematopoietic cells, is considered not medically necessary as a treatment of damaged myocardium as the evidence is insufficient to determine the effects of the technology on health outcomes.

Infusion of growth factors (ie, granulocyte colony stimulating factor) is considered not medically necessary as a technique to increase the numbers of circulating hematopoietic cells as treatment of damaged myocardium as the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE
Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessity/not covered benefits/coverage.

BACKGROUND
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.

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. The relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life (QOL), and hospitalizations. Limited evidence on clinical outcomes has suggested there may be benefits from improving 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 (eg, mortality, adverse cardiac outcomes, exercise capacity, QOL). 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 2, phase 3 RCTs with more than 100 participants, systematic reviews of smaller, early-phase RCTs, and a nonrandomized comparative trial. The relevant outcomes are disease-specific survival, morbid events, functional outcomes, QOL, 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. The relevant outcomes are disease-specific survival, morbid events, functional outcomes, QOL, 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.

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. The 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 1 for regenerative medicine advanced therapy (RMAT). The RMAT designation may be given if: (1) the drug is a regenerative medicine therapy (ie, 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 CardiAMP™ (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-derivedadherent 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 the FDA to perform a trial of CardiAMP™.

CODING

Medicare Advantage Plans and Commercial Products

There are no specific codes for this procedure, either describing the laboratory component of processing the harvested autologous cells or for the implantation procedure. Claims should be filed with an unlisted CPT code.

RELATED POLICIES

Not applicable

PUBLISHED

Provider Update, July 2021
Provider Update, August 2020
Provider Update, January 2020
Provider Update, April 2018
Provider Update, April 2017

REFERENCES:

1. Lee MS, Makkar RR. Stem-cell transplantation in myocardial infarction: a status report. Ann Intern Med. May 04 2004; 140(9): 729-37. PMID 15126257
2. U.S. Food and Drug Administration. Regenerative Medicine Advanced Therapy Designation. 2018; https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm. Accessed March 17, 2021.
3. 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.
4. 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): 989-98. PMID 24026778
5. 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 2014; 7(2): 156-67. PMID 24668227
6. 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
7. Gyongyosi 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): 1346-60. PMID 25700037
8. 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
9. Lalu MM, Mazzarello S, Zlepnig J, et al. Safety and Efficacy of Adult Stem Cell Therapy for Acute Myocardial Infarction and Ischemic Heart Failure (SafeCell Heart): A Systematic Review and Meta-Analysis. Stem Cells Transl Med. Dec 2018; 7(12): 857-866. PMID 30255989
10. Moazzami K, Roohi A, Moazzami B. Granulocyte colony stimulating factor therapy for acute myocardial infarction. Cochrane Database Syst Rev. May 31 2013; (5): CD008844. PMID 23728682
11. Schachinger 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): 2775-83. PMID 17098754

12. Schachinger 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): 1210-21. PMID 16990384
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): 1736-47. 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): 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): 1370-7. 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 metaanalysis. Med Sci Monit. Oct 01 2014; 20: 1768-77. 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. Bartunek J, Terzic A, Davison BA, et al. Cardiopoietic stem cell therapy in ischaemic heart failure: long-term clinical outcomes. ESC Heart Fail. Oct 23 2020. PMID 33094909
21. 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): 160-8. PMID 20560030
22. 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): 721-9. PMID 20576835
23. 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): 984-93. PMID 26838794
24. 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
25. 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): 3165-72. PMID 17562958
26. 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
27. 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 07 2014; 115(11): 950-60. PMID 25231095
28. Wang S, Cui J, Peng W, et al. Intracoronary autologous CD34+ stem cell therapy for intractable angina. Cardiology. 2010; 117(2): 140-7. PMID 20975266
29. Losordo DW, Henry TD, Davidson C, et al. Intramyocardial, autologous CD34+ cell therapy for refractory angina. Circ Res. Aug 05 2011; 109(4): 428-36. PMID 21737787
30. 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 08 2016; 9(15): 1576-85. PMID 27491607
31. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial Infarction: An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA

guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv. May 2016; 87(6):
1001-19. PMID 26489034
32. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. Dec 06 2011; 124(23): e574-651. PMID 22064601
33. 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-e140. PMID 23256914