BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.02.18 Progenitor Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia

Effective Policy Date: October 1, 2022

Original Policy Date: December 2011

Related Policies:

8.01.52 - Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)
8.01.55 - Stem Cell Therapy for Peripheral Arterial Disease

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

Description

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.

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.[2,] Treatment with progenitor cells (ie, 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 for regenerative medicine advanced therapy (RMAT).[3,]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.

OBJECTIVE

The objective of this evidence review is to determine whether the use of progenitor cell therapy improves the net health outcome in patients with damaged myocardium due to ischemia.

POLICY STATEMENT

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 (ie, 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

There are no specific codes for this procedure, either describing 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; in other situations, the implantation may be performed as a unique indication for a cardiac catheterization procedure.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Multiple progenitor cell therapies such as MyoCell (U.S. Stem Cell, formerly Bioheart), Ixmyelocel-T (Vericel, formerly Aastrom Biosciences), MultiStem (Athersys), and CardiAMP^{TM} (BioCardia) are being commercially developed, but none has been approved by the U.S. Food and Drug Administration (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. 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 that has received RMAT designation.

The 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 and is designated as an FDA Breakthrough Device.

RATIONALE

Summary of Evidence

For individuals who have acute cardiac ischemia who receive progenitor cell therapy, 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 has suggested there may be benefits from improving left ventricular ejection fraction (LVEF), reducing recurrent MI, 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, 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 that the technology results in an improvement in the net health outcome.

For individuals who have chronic cardiac ischemia who receive progenitor cell therapy, the evidence includes 2 phase 3 RCTs with more than 100 participants, 2 phase 2 RCTs with more than 100 participants, systematic reviews of smaller, early-phase RCTs, and a nonrandomized 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. Two phase 2 RCTs (CONCERT-HF and ixCELL-DCM) found significant benefit on heart failure-related death and other cardiac events with cell therapy compared to placebo. 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 that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology Foundation, American Heart Association, and the Society for Cardiovascular Angiography and Interventions

In 2015, the American College of Cardiology Foundation, American Heart Association, and the Society for Cardiovascular Angiography and Interventions issued a Focused Update on Primary Percutaneous Coronary Interventions for Patients With ST-Elevation Myocardial Infarction.[33,] This guideline was an update of the 2011 guideline for percutaneous coronary intervention[34,] and the 2013 guideline on managing ST-elevation myocardial infarction.[35,]In 2021, these same organizations published a guideline on coronary artery revascularization.[36,] Progenitor cell therapy was not mentioned in any of these guidelines.

The most recent guidance on treatment of heart failure with reduced ejection fraction from the American College of Cardiology foundation (2021) does not mention progenitor cell therapy.[37,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation. Feb 22 2022; 145(8): e153-e639. PMID 35078371
2. 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
3. U.S. Food and Drug Administration. Regenerative Medicine Advanced Therapy Designation. 2018; https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm. Accessed March 23, 2022.
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 meta-analysis. Med Sci Monit. Oct 01 2014; 20: 1768-77. PMID 25270584
19. Bolli R, Mitrani RD, Hare JM, et al. A Phase II study of autologous mesenchymal stromal cells and c-kit positive cardiac cells, alone or in combination, in patients with ischaemic heart failure: the CCTRN CONCERT-HF trial. Eur J Heart Fail. Apr 2021; 23(4): 661-674. PMID 33811444
20. 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
21. 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
22. Patel AN, Henry TD, Quyyumi AA, et al. Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial. Lancet. Jun 11 2016; 387(10036): 2412-21. PMID 27059887
23. 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

24. 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
25. 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
26. 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
27. 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
28. 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
29. 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
30. 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
31. 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
32. 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
33. 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
34. 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
35. 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
36. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. Jan 18 2022; 79(2): e21-e129. PMID 34895950
37. Maddox TM, Januzzi JL, Allen LA, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. Feb 16 2021; 77(6): 772-810. PMID 33446410

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
September 2013	Replace policy	Policy updated with literature search, references added and references reordered; policy statements unchanged.
September 2014	Replace policy	Policy updated with literature review. References 13-14, 22, 27, 32-34,and 39-40 added; policy statements unchanged.
September 2015	Replace policy	Policy updated with literature review; references 12, 29-30, and 33-34 added; references 35-36 deleted. Policy statements unchanged.
December 2017	Replace policy	Policy updated with literature review through June 22, 2017; references 10, 19, and 21-22 added; Rationale revised. Policy statements corrected from "not medically necessary€ to "investigational€ because products are not approved for marketing for cardiac use by the FDA.
September 2018	Replace policy	Policy updated with literature review through March 6, 2018; references 3, 16, 21, and 30 added. Policy statements unchanged.
September 2019	Replace policy	Policy updated with literature review through March 3, 2019; reference 31 added. Policy statements unchanged.
September 2020	Replace policy	Policy updated with literature review through March 9, 2020; references added. Policy statements unchanged.
September 2021	Replace policy	Policy updated with literature review through March 16, 2021; reference added. Policy statements unchanged.
September 2022	Replace policy	Policy updated with literature review through March 16, 2022; references added. Policy statements unchanged.