



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, 2021

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

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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.¹ 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).² 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™ (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.

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.

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, 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. 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 Stem Cell Transplantation in 191 Patients With Chronic Heart Failure (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.³¹ This guideline was an update of the 2011 guideline for percutaneous coronary intervention³² and the 2013 guideline on managing ST-elevation myocardial infarction.³³ Progenitor cell therapy was not mentioned in this update or in the 2013 guidelines.

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.

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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.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.