



Louisiana

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

Policy # 00486

Original Effective Date: 12/16/2015

Current Effective Date: 12/20/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers progenitor cell therapy, including but not limited to skeletal myoblasts or hematopoietic cells as a treatment of damaged myocardium to be **investigational**.*

Based on review of available data, the Company considers infusion of growth factors (ie, granulocyte colony stimulating factor [GCSF]) as a technique to increase the numbers of circulating hematopoietic cells as treatment of damaged myocardium to be **investigational**.*

Background/Overview

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. 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 (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 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 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

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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 (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 also are 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 effects of progenitor cell treatment include risks of the delivery procedure (eg, 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 (eg, teratomas) can arise from progenitor cells, but the actual risk in humans is currently unknown.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The U.S. 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.

Multiple progenitor cell therapies such as MyoCell^{®†} (Bioheart, Sunrise, FL), ixmyelocel-T (Vericel, formerly Aastrom Biosciences), and MultiStem^{®‡} (Athersys) are being commercially developed, but none have been approved by 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.

Ixmyelocel-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.

MultiStem is an allogeneic bone marrow–derived adherent adult stem cell product.

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Centers for Medicare and Medicaid Services (CMS)

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

Rationale/Source

Progenitor cell therapy for the treatment of damaged and ischemic myocardium is a rapidly evolving field. There are several areas of uncertainty, including patient selection, cell type, and procedural details (eg, timing and mode of delivery). The overall body of evidence is characterized by numerous randomized controlled trials (RCTs) and a number of meta-analyses of these RCTs. A 2015 meta-analysis by Afzal et al (search through August 2014) identified 48 RCTs on bone marrow cell (BMC) therapy for acute or chronic ischemic heart disease. Selected RCTs were mostly small in size and highly variable regarding patient populations, types of progenitor cells used, and delivery methods. Some cell products have achieved orphan drug status from the U.S. FDA based on phase 2 trials. The present evidence review focuses on phase 3 trials with at least 100 patients per arm and systematic reviews of RCTs.

In the present evidence review, relevant clinical trials and meta-analyses are reviewed for 3 different indications: (1) acute cardiac ischemia (myocardial infarction); (2) chronic cardiac ischemia; and (3) refractory or intractable angina in patients who are not candidates for revascularization. This evidence review focuses on the impact of progenitor cell therapy on clinical outcomes but also includes data on physiologic outcomes, such as a change in left ventricular ejection fraction (LVEF).

TREATMENT WITH PROGENITOR CELLS FOR ACUTE CARDIAC ISCHEMIA

Systematic Reviews

Bone Marrow Cells

Four meta-analyses published from 2014 to 2015, including a Cochrane review and an individual patient data meta-analysis evaluating the use of progenitor cell therapy for the treatment of acute ischemia (myocardial infarction), are described below. Table 1 details the reviews and summarizes the analyses.

Two meta-analyses on BMC infusion for the treatment of acute myocardial infarction (AMI) were published in 2014 and included many of the same studies. Delewi et al published a meta-analysis of 16 trials (total N=1641 patients). The meta-analyses of de Jong et al included 22 RCTs (total N=1513 patients). Thirteen RCTs (1300 patients) appeared in both systematic reviews. Both analyses found statistically significant increases in LVEF with BMC infusion compared with placebo. Subgroup analyses by Delewi et al showed that the treatment benefit was greater among younger patients (age <55 years) and among patients with more severely depressed LVEF at baseline (<40%), while subgroup analysis by de Jong et al that included only trials with end points derived from magnetic resonance imaging (9 trials), showed that the therapy did not have an effect on cardiac function, volumes, or infarct size. With a median follow-up of 6 months, there was no difference between BMC infusion and placebo in all-cause mortality, cardiac mortality, restenosis rate, thrombosis, target vessel revascularization, stroke, recurrent AMI, or implantable cardioverter

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defibrillator implantations. Based on these findings, de Jong et al concluded that, although safe, intracoronary infusion of BMCs did not improve clinical outcomes.

A 2015 Cochrane review by Fisher et al on stem cell treatment for AMI included 41 trials (total N=2732 patients). Many were small trials and conducted outside the United States; others were reported only as conference proceedings. Studies varied by cell dose, cell type, and timing of administration. Overall, cell treatment was not associated with any changes in the risk of all-cause mortality, cardiovascular mortality, or a composite measure of mortality, reinfarction, and rehospitalization for heart failure at long-term follow-up. Reviewers concluded that there was insufficient evidence for a beneficial effect of cell therapy for patients experiencing an AMI and that adequately powered trials are needed.

Gyöngyösi et al (2015) conducted an individual patient data meta-analysis of 12 RCTs (total N=1252 patients), including the REPAIR-AMI trial (reviewed below), using a collaborative, multinational database, ACCRUE (meta-Analysis of Cell-based CaRdiac study; NCT01098591). Eight trials had low risk of bias, and 4 single-blind (assessor) trials had medium-to-low risk of bias. Adjusted (for cardiovascular risk factors) random-effects meta-analyses showed no effect of cell therapy on the primary end points of major adverse cardiac and cerebrovascular events (a composite of all-cause death, AMI recurrence, coronary target vessel revascularization, and stroke). The meta-analysis was limited by variations in the time from AMI to cell delivery (median, 6.5 days) and in imaging modalities used to assess cardiac function (magnetic resonance imaging, single-proton emission computed tomography, angiography, echocardiography).

Fisher et al (2016) reported on the results of a trial sequential analysis using cumulative data obtained from 2 previous Cochrane reviews with updated results to March 2015. The intent of the analysis was to obtain estimates of sample size required for a meta-analysis to detect a significant treatment effect while controlling for random errors due to repeat testing. Thirty-seven AMI trials that assessed bone marrow cells and reported on mortality as an outcome were included. Of the 37, 14 reported no deaths. Of 23 trials that observed incidences of mortality in either trial arm, there were 43 (4.0%) deaths in 1073 patients who received cell therapy compared with 38 (5.0%) deaths in 754 patients who did not. Results showed that there was insufficient evidence to detect a significant treatment effect of bone marrow-derived cells on mortality and rehospitalization in AMI (relative risk [RR], 0.92; 95% confidence interval [CI], 0.62 to 1.36). Results of the sequential analysis showed that at least 4055 participants would be required to detect a relative reduction in the risk of mortality of 35% in AMI patients. Most of the meta-analyses reported so far have not reached this sample size.

Granulocyte Colony Stimulating Factor

The body of evidence on the use of granulocyte colony stimulating factor (G-CSF) as a treatment for coronary heart disease is smaller than that for the use of stem cells. A few RCTs on the treatment of acute ischemia have reported physiologic outcomes. Additionally, meta-analyses of the available trials have been published. Moazzami et al (2013) published a Cochrane review of G-CSF for AMI. Literature was searched in November 2010, and 7 small, placebo-controlled randomized trials (total N=354 patients) were included. The overall risk of bias was considered low. All-cause mortality did not differ between groups (RR=0.6; 95%

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CI, 0.2 to 2.8; $p=0.55$; $I^2=0\%$). Similarly, change in LVEF, left ventricular end systolic volume, and left ventricular end-diastolic volume did not differ between groups. Evidence was insufficient to draw conclusions about the safety of the procedure. Similarly, reviewers concluded there was a lack of evidence for the benefit of G-CSF therapy in patients with AMI.

Table 1. Summary of Systematic Reviews and Meta-Analyses of the Use of Progenitor Cell Therapy for the Treatment of Acute Ischemia

Study (Year)	Dates	Trials	Patients	Study Design	Mean Time Between Acute Event and Cell Infusion	Median Trial Duration (Range), mo	Outcome		
							Δ LVEF, Mean Change or % Change	Risk All-Cause Mortality	Risk of CV Mortality
Delewi et al (2014)	1980-Feb 2013	16	1641	RCT	≤ 1 mo	6 (3-6)	2.55% (1.83% to 3.26%) $I^2=84\%$	NR	NR
De Jong et al (2014)	Jan 2002-Sep 2013	22	1513	RCT	≤ 1 mo	6 (3-60)	2.10% (0.68% to 3.52%) $I^2=80\%$	0.68 ^a (0.36 to 1.31)	0.73 ^a (0.32 to 1.65)
Fisher et al (2015)	Through Mar 2015	41	2732	RCT	≤ 14 d	<12	1.05 ^b (-0.56 to 2.67)	0.80 ^c (0.43 to 1.49)	0.72 ^c (0.28 to 1.82)
						≥ 12	1.27 ^b (-1.14 to 3.68)	0.93 ^c (0.58 to 1.50)	1.04 ^c (0.54 to 1.99)
Gyöngyösi et al (2015)		12	1252	RCT or cohort	≤ 14 d	6 (3-12)	0.96 (-0.2 to 2.1)	0.70 $p=0.499$	NR

CV: cardiovascular; LVEF: left ventricular ejection fraction; NR: not reported; RCT: randomized controlled trial.

^a Mantel-Haenszel odds ratio (95% confidence interval).

^b As measured by magnetic resonance imaging.

^c Relative risk (95% confidence interval).

Randomized Controlled Trials

Key studies, including RCTs with more than 100 patients per arm, are described next.

REPAIR-AMI Trial

REPAIR-AMI was a double-blinded trial that infused bone marrow-derived progenitor cells or a placebo control infusion of the patient's serum; it enrolled 204 patients from 17 centers in Germany and Switzerland who had acute ST-segment elevation myocardial infarction and met strict inclusion criteria. At 12-month follow-up, there were statistically significant decreases in the progenitor cell group compared with the control group for myocardial infarction (0 vs 6, $p<0.03$) and revascularization (22 vs 37, $p<0.03$), as well as for the composite outcome of death, myocardial infarction, and revascularization (24 vs 42, $p<0.009$), all respectively. Two-year clinical outcomes from the REPAIR-AMI trial, performed according to a study protocol amendment filed in 2006, were reported in 2010. Eleven deaths occurred during the 2-year follow-up, 8 in the placebo group and 3 in the progenitor cell group. There was a significant reduction in myocardial infarction (0% vs 7%), and a trend toward a reduction in rehospitalizations for heart failure (1% vs 5%) and revascularization (25% vs 37%) in the active treatment group. Analysis of combined events (all combined events included infarction) showed significant improvement with progenitor cell therapy after AMI. There was no increase in ventricular arrhythmia or syncope, stroke, or cancer. It was noted that investigators and patients were unblinded at 12-month follow-up. Also, the REPAIR-AMI trial was not

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powered to determine definitively whether administration of progenitor cells reduces mortality and morbidity after AMI; the relatively small sample size might have limited the detection of infrequent safety events. Thus, this analysis should be viewed as hypothesis-generating, providing the rationale to design a larger trial addressing clinical end points.

HEBE Trial

In 2011, Hirsch et al reported on multicenter RCT that compared bone marrow or peripheral blood mononuclear cell infusion with standard therapy in 200 patients with AMI treated with primary percutaneous coronary intervention. Mononuclear cells were delivered 3 to 8 days after AMI. Blinded assessment of the primary end point (the percentage of dysfunctional left ventricular segments that had improved segmental wall thickening at 4 months) found no significant difference between the treatment groups (38.5% for bone marrow vs 36.8% for peripheral blood) and controls (42.4%). There was no significant difference between the groups in LVEF; change in left ventricular volumes, mass, or infarct size; or rates of clinical events. At 4 months, a similar percentage of patients had New York Heart Association (NYHA) class II or higher heart failure (19% for bone marrow, 20% for peripheral blood, 18% for controls).

Section Summary: Treatment With Progenitor Cells for Acute Cardiac Ischemia

The evidence on progenitor cell therapy for patients with myocardial infarction includes 2 RCTs (200 patients), numerous small RCTs, and meta-analyses of these RCTs. Studies varied by types of cell used and methods and timing of delivery. Most studies reported outcomes for LVEF and/or myocardial perfusion at 3 to 6 months. These studies generally reported small-to-modest improvements in these intermediate outcomes. Limited evidence on clinical outcomes has suggested that there may be benefits in improving LVEF, reducing recurrent myocardial infarction, decreasing the need for further revascularization, and perhaps even decreasing mortality, although a recent, large, IPD meta-analysis reported no improvement in these outcomes. No single adequately powered trial has reported benefits in clinical outcomes, 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.

TREATMENT WITH PROGENITOR CELLS FOR CHRONIC CARDIAC ISCHEMIA

Systematic Reviews

In 2014, Fisher et al published a Cochrane review of autologous stem cell therapy for chronic ischemic heart disease and congestive heart failure. Literature was searched through March 2013, and 23 RCTs (total N=1255 patients) were included. The overall quality of the evidence was considered low because there were few events of interest (deaths, hospital readmissions). In long-term (≥ 12 months), but not short-term (< 12 months), follow-up, there were statistically significant reductions in all-cause mortality (RR=0.3; 95% CI, 0.1 to 0.5; $p < 0.001$; $I^2 = 0\%$) and rehospitalizations due to heart failure (RR=0.3; 95% CI, 0.1 to 0.9; $p = 0.039$; $I^2 = 0\%$) in patients who received stem cell infusion compared with controls (no stem cell infusion). Statistically significant improvements in LVEF and NYHA classification in stem cell groups were observed at both 6 months and 1 year or later. Evidence was considered of moderate quality for these outcomes, but statistical heterogeneity was moderate to substantial. Similar results were reported in 2014 meta-analyses

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conducted by Xu et al and by Xiao et al. Additional research in larger studies is required to confirm these results.

Fisher et al (2016) reported the results of a sequential trial analysis using cumulative data obtained from 2 previous Cochrane reviews with updated results to March 2015. The intent of the analysis was to obtain estimates of sample size required for a meta-analysis to detect a significant treatment effect while controlling for random errors due to repeat testing. A total of 22 trials that included all-cause mortality were included. Six trials reported no deaths, while the remaining 16 trials reported 25 (5.6%) deaths in 444 patients who received cells compared with 50 (15.9%) deaths in 315 patients who did not. Meta-analysis of the pooled data revealed a significant reduction in mortality associated with cell therapy in patients with heart failure (RR=0.42; 95% CI; 0.27 to 0.64; $p<0.001$).

Randomized Controlled Trials

Patel et al (2016) reported on the results of a well-conducted pivotal phase 2B double-blind randomized trial in which 126 patients with NYHA class III or IV symptomatic heart failure due to ischemic dilated cardiomyopathy (LVEF $\leq 35\%$), an automatic implantable cardioverter defibrillator, and who were ineligible for revascularization procedures were randomized to ixmyelocel-T (n=66) or placebo (n=60). The primary end point was a composite of all-cause death, cardiovascular admission to hospital, and blindly adjudicated unplanned clinic visits for heart failure. The proportion of patients with an observed primary end point was 49% (25/51) and 38% (22/58) in the placebo and ixmyelocel-T arm, respectively (RR=0.63; 95% CI; 0.42 to 0.97; $p=0.034$). According to study authors, the primary end point was driven by the reduction in overall all-cause deaths (7% vs 14%) and cardiovascular admissions to hospital (30 vs 42) in patients who received ixmyelocel-T compared with those who received placebo. The proportion of patients with serious adverse event was 75% (41/51) and 53% (31/58), respectively. Although the trial demonstrated a mortality benefit of ixmyelocel-T in patients with dilated cardiomyopathy with no reasonable treatment options likely to provide clinical benefit, there were a few design limitations. The trial was powered to assess the primary outcome using a per-protocol analysis rather than intention-to-treat analysis. Thus, the results did not capture three deaths and nine patients removed from all of the analysis populations due to inadequate cell product or adverse events. However, the results were consistent when the results were analyzed using a per-protocol analysis. Two patients in the placebo arm who each experienced and 7 hospital admissions could have driven the results of the primary outcome measure in favor of ixmyelocel-T. Ixmyelocel-T is currently not approved for any indication in the United States.

Bartunek et al (2017) reported the results of a well-conducted double-blind trial in which 271 patients with NYHA class II or greater symptomatic heart failure (LVEF $\leq 35\%$) were randomized to bone marrow-derived mesenchymal cardiopoietic cells (n=120) or sham (n=151). The primary end point was Finkelstein-Schoenfeld hierarchical composite (all-cause mortality, worsening heart failure, Minnesota Living with Heart Failure Questionnaire score, 6-minute walk distance, left ventricular end-systolic volume, and ejection fraction) at 39 weeks. The trial did not meet its primary outcome measure. The probability that the treatment group had a better outcome on the composite primary end point was 0.54 (a value >0.5 favors active treatment; 95% CI, 0.47 to 0.61; $p=0.27$). Exploratory subgroup analysis reported treatment benefit in

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patients with baseline left ventricular end-diastolic volume of 200 to 370 mL (60% of patients) (0.61; 95% CI, 0.52 to 0.70; $p=0.015$). The proportion of patients who died within 39 weeks of the procedure was 9.2% (11/120) and 7.9% (12/151) in the cell therapy arm and the sham arm, respectively ($p=0.70$). There was no statistical difference in serious adverse events between treatment arms. One (0.9%) cardiopoietic cell patient and 9 (5.4%) sham patients experienced aborted or sudden cardiac death.

Nonrandomized Controlled Trials

STAR-Heart Trial

The STAR-Heart trial evaluated stem cell therapy for chronic heart failure due to ischemic cardiomyopathy. This 2010 was a nonrandomized open-label study of 391 patients with chronic heart failure. In this trial, 191 patients received intracoronary BMC therapy, and 200 patients who did not accept the treatment agreed to undergo follow-up testing served as controls. Mean time between percutaneous coronary intervention for infarction and admission to the tertiary clinic was 8.5 years. For BMC therapy, mononuclear cells were isolated and identified (included CD34-positive cells, AC133-positive cells, CD45-/CD14-negative cells). Cells were infused directly into the infarct-related artery. At up to 5 years after intracoronary BMC therapy, there was a significant improvement in hemodynamics (LVEF, cardiac index), exercise capacity (NYHA classification), oxygen uptake, and left ventricular contractility compared with controls. There also was a significant decrease in long-term mortality in the BMC-treated patients (0.75% per year) compared with the control group (3.68% per year, $p<0.01$). However, the study was limited by the potential for selection bias due to patient self-selection into treatment groups. For example, there was a 7% difference in baseline ejection fraction rates between groups, suggesting that the groups were not comparable on important clinical characteristics at baseline. Additionally, lack of blinding raises the possibility of bias in patient-reported outcomes such as NYHA class.

Section Summary: Treatment With Progenitor Cells for Chronic Cardiac Ischemia

The evidence on progenitor cell therapy for chronic ischemia includes 2 RCTs, a nonrandomized comparative trial, and systematic reviews of smaller RCTs. The studies included in the meta-analyses only reported on a small number of clinical outcome events, too few for meaningful analysis. The nonrandomized STAR-Heart trial showed a mortality benefit as well as a favorable hemodynamic effect but the lack of randomization limits interpretation due to concerns about selection bias and differences in known and unknown prognostic variables at baseline between arms. While a single small RCT demonstrated a statistically significant 37% relative reduction in total clinical events (death, cardiovascular admission to hospital, or unplanned clinic visits for heart failure) with ixmyelocel-T in patients with dilated cardiomyopathy with no reasonable treatment options likely to provide clinical benefit, the other trial failed to meet the primary end point that included death, worsening heart failure, and other multiple events. These findings from early phase 2 trials need to be corroborated in a larger phase 3 trial. 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.

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PROGENITOR CELL THERAPY FOR REFRACTORY ANGINA

Stem cell therapy also is being investigated in patients with intractable angina who are not candidates for revascularization. The evidence includes 2 phase 2 trials from 2009 and 2011 that compared infusion of stem cells from peripheral blood or bone marrow to placebo, and the following 2016 report from a phase 3 trial.

RENEW Trial

In 2016, Povsic et al reported on the industry-sponsored Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells (RENEW) trial. This 3-arm multicenter trial compared outcomes from the intramyocardial administration of autologous CD34+ cells using exercise capacity at 3, 6, or 12 months. Patients underwent cell mobilization with G-CSF for 4 days followed by apheresis. The peripheral cell product was shipped to a central processing facility (Progenitor Cell Therapy) for selection of CD34+ cells. The study was terminated after enrollment of 112 of a planned 444 patients before data analysis due to strategic considerations. The progenitor cell group had greater exercise capacity than the standard therapy group but was no better than the double-blinded placebo group, consistent with a placebo effect. Additionally, with only 122 participants, the study was not adequately powered to detect a between-group difference.

Section Summary: Progenitor Cell Therapy for Refractory Angina

Evidence on stem cell therapy for refractory angina includes phase 2 trials, and a phase 3 pivotal trial 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. No ongoing phase 3 trials on stem cell therapy for refractory angina were identified (see Table 2).

SUMMARY OF EVIDENCE

For individuals who have acute cardiac ischemia who receive progenitor cell therapy, the evidence includes 2 RCTs with 200 patients, numerous small 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 improving left ventricular ejection fraction, reducing recurrent myocardial infarction, decreasing the need for further revascularization, and perhaps even 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 the effects of the technology on health outcomes.

For individuals who have chronic cardiac ischemia who receive progenitor cell therapy, the evidence includes a nonrandomized comparative trial, 2 RCTs, and systematic reviews of smaller RCTs. Relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and

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hospitalizations. The studies included in the meta-analyses have reported on only a small number of clinical outcome events, too few for meaningful analysis. 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. While a single small RCT has demonstrated a statistically significant 37% relative reduction in total clinical events (death, cardiovascular admission to hospital, or unplanned clinic visits for heart failure) with ixmyelocel-T, the other trial failed to meet its primary composite end point that included death, worsening heart failure events, and other multiple events. These findings from early phase 2 trials need to be corroborated in a larger phase 3 trial. 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 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.

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12/16/2015 Medical Policy Implementation Committee approval. New policy.

12/01/2016 Medical Policy Committee review

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01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

12/07/2017 Medical Policy Committee review

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Next Scheduled Review Date: 12/2018

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Code Type	Code
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HCPCS	No codes
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- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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