



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Autologous Skeletal Myoblast Transplant/Autologous Cell Therapy for Damaged Myocardium

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Granulocyte Colony Stimulating Factor Therapy [Filgrastim (Neupogen®), Pegfilgrastim (Neulasta®)]

Heart Transplantation

Total Artificial Heart

Ventricular Assist Devices (VADs)

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Coverage Policy

CIGNA does not cover the transplantation of cells into the myocardium because it is considered experimental, investigational or unproven.

General Background

Heart Failure

Heart failure, also called congestive heart failure (CHF), is a disorder in which the heart loses its ability to pump blood efficiently. CHF is almost always a chronic, long-term condition, although it can sometimes develop suddenly. Heart failure may affect the right side, the left side, or both sides of the heart. As the heart's pumping action is lost, blood may back up into other areas of the body, such as the liver, gastrointestinal tract, extremities and lungs. Many organs don't receive enough oxygen and nutrients and consequently suffer damage and reduced ability to function properly. Failure of both sides of the heart can affect most areas of the body . Symptoms of heart failure may include weight gain, swollen feet and ankles, shortness of breath, fatigue and loss of appetite.

The standard of care for initial treatment of CHF is pharmacotherapy. This therapy generally includes a diuretic, an angiotensin-converting enzyme (ACE) inhibitor and a beta blocker. Despite progress in the development and use of pharmacological agents, heart failure remains a chronic disease that results in progressive deterioration

of the patient's condition. Ventricular assist devices (VAD) can be used either as a bridge to recovery or transplantation or as destination therapy. Heart transplantation remains the most effective long-term treatment for patients with refractory heart failure symptoms (Dec., 2004).

Myocardial Infarction

A myocardial infarction (MI), or heart attack, occurs when heart muscle cells are damaged or die because of inadequate oxygen supply to the area. This deficit may be caused by blockage or constriction of coronary arteries. In the U.S., an estimated one million people per year visit emergency rooms for heart attacks (National Institutes of Health [NIH], 2007). Symptoms of heart attack may include chest pain, pain in the shoulders or jaw, shortness of breath, dizziness or lightheadedness, nausea, vomiting, sweating and anxiety. Late effects of MI may include formation of fibrous tissue, left ventricular (LV) remodeling, aneurysm formation, and progression of congestive heart failure.

The goal of initial treatment of acute MI is to restore oxygenated blood flow to the heart muscle to minimize cell death. The standard of care may include nitroglycerin, antithrombotics, beta blockers, ACE inhibitors and oxygen. Coronary angioplasty (with or without stenting) or coronary artery bypass graft (CABG) may be indicated (NIH, 2007).

Cell Therapy

Cell therapy for cardiac conditions is based on two major assumptions. The first is that the development of heart failure is linked to irreversible loss of heart muscle below a certain threshold. The second is that function can therefore be improved by replacing heart muscle with new cells that will graft to and function as heart muscle (Menasche, 2004). It appears that the underlying mechanisms of cell therapy are unknown. Proposed cell sources include skeletal myoblasts and bone marrow-derived stem cells, mostly considered in conditions of acute MI and heart failure (Zenovich, et al., 2007).

Skeletal Myoblast Transplantation

Skeletal muscle, unlike heart muscle, can repair itself after injury. Skeletal muscle contains immature myoblasts that can fuse with surrounding myoblasts or with damaged muscle fibers to regenerate functional skeletal muscle. In experimental models, researchers have demonstrated that skeletal myoblasts can be transplanted into infarcted cardiac muscle and nonischemic, globally dilated myocardium, with the subsequent development of elongated, striated cells that retain characteristics of both skeletal muscle and cardiac cells.

The process begins with a biopsy of the patient's skeletal muscle, followed by a process that expands the number of harvested cells. This process and any additional treatment of the cells (such as the use of heat or growth factor) vary among the studies. The length of time between the cardiac event and the cell transplantation also varies among studies and may depend on the preparation technique. There are also multiple methods of transplanting the cells into the myocardium. Initial animal studies employed transpericardial injections of cells in an open procedure. Research is underway to reduce the invasiveness of this procedure, using a variety of percutaneous techniques.

U.S. Food and Drug Administration (FDA)

The U.S. Food and Drug Administration (FDA) regulates cells that are processed in commercial laboratories, as well as the surgical devices used to inject the cells into the myocardium. The FDA has not yet issued approvals for any technology associated with the transplantation of autologous cells for the treatment of damaged myocardium. MyoCell™ and MyoCath™ (BioHeart, Fort Lauderdale, FL) are currently undergoing Phase I and II studies for investigation for FDA approval. MyoCell, which consists of expanded autologous skeletal myoblast, is delivered by the MyoCath, a transendocardial injection catheter. The system is being evaluated for feasibility as well as safety and efficacy in the treatment of post-infarct deterioration of cardiac function in subjects with congestive heart failure.

Literature Review for Skeletal Myoblast Transplantation

Animal studies have demonstrated that myoblast engraftment correlates with an improvement in LV function. Researchers have also found a correlation between the number of cells injected and the degree of functional improvement. Additionally, there is some evidence that skeletal muscle releases hepatocyte growth factor, which exerts an antifibrotic effect, enhancing cardiac performance and myocardial perfusion (Menasche, 2004). Early studies involving skeletal myoblast transplantation were frequently associated with ventricular tachycardia.

This finding has led to a change in study protocols that includes prophylactic cardioverter-defibrillator implantation and/or amiodarone therapy to prevent ventricular tachycardia (Boyle, et al., 2006).

In 2001, Menasche and colleagues began the first Phase I trial of skeletal myoblast transplantation for damaged myocardium (Menasche, 2003). Ten patients, all with documented heart failure and histories of myocardial infarct with residual damage, and all eligible for CABG, underwent the procedure. The time between cell harvesting and transplant was two to three weeks. Patients underwent the CABG, and at the end of the surgical procedure, the harvested cells were injected into the infarcted tissue. There was one patient with an early death, unrelated to the cell transplantation. Four of the patients subsequently developed ventricular tachycardia during the first three postoperative weeks. Approximately 60% of the initially damaged areas showed new systolic thickening (Menasche, 2004). The authors concluded that the preliminary results indicated the safety and feasibility of the procedure, and the efficacy requires confirmation by randomized studies. In 2006, Hagege et al. reported long-term follow-up of the Menasche Phase I cohort study. The authors noted that there were five hospitalizations for heart failure in three patients at approximately 28.6 months, allowing implant in two patients with a resynchronization pacemaker. An automatic defibrillator was implanted in five patients for nonsustained (n=1) or sustained (n=4) ventricular tachycardia. They noted that, although the patients were treated with beta-blocker/amiodarone combination therapy, there were 14 appropriate shocks for three arrhythmic storms in three patients at six, seven and 18 months after defibrillator implantation.

Herreros et al. (2003) reported on a study of twelve patients with old MI and ischemic coronary artery disease who underwent treatment with CABG and intramyocardial injection of autologous skeletal myoblasts. Left ventricular ejection fraction (LVEF) improved at three months. Echocardiography indicated a marked improvement in regional contractility in the cardiac segments treated with skeletal myoblast. An increase in adverse events was not noted. No cardiac arrhythmias were detected. The authors concluded that in patients with old MI, treatment with skeletal myoblast in conjunction with CABG is safe and feasible.

Smits et al. (2003) conducted a pilot safety and feasibility study of five patients with symptomatic heart failure (HF) after an anterior wall infarction. Autologous skeletal myoblasts were obtained from the quadriceps muscle and cultured in vitro for cell expansion. After a culturing process, the cells were transendocardially injected into the infarcted area. Assessment was performed by Holter monitoring, LV angiography, nuclear radiography, dobutamine stress echocardiography and magnetic resonance imaging (MRI). Results indicated that all cell transplantation procedures were uneventful, and no serious adverse events occurred during follow-up. One patient received an implantable cardioverter-defibrillator. Due to asymptomatic runs of nonsustained ventricular tachycardia. It was noted at three months that LVEF increased from 36 to 41% and at six months to 45%. Regional wall analysis by MRI demonstrated significantly increased wall thickening at the target areas and less wall thickening in remote areas. The authors concluded that the study demonstrated the potential and feasibility of percutaneous skeletal myoblast delivery as a stand-alone procedure for myocardial repair in patients with heart failure post-MI and that additional data is needed to confirm safety. Steendijk et al. (2006) reported on follow-up at six and 12 months for these five patients. Systolic and diastolic LV function was studied using invasive pressure-volume loop analysis. The patients were reevaluated in the catheterization laboratory using coronary angiography and left ventriculography. The data indicated a significantly increased cardiac output at six and 12 months. These findings are suggestive of an improvement in systolic function. Diastolic indices were not significantly altered at either six or 12 months. The authors concluded that, although the study is limited by small size, the results are promising in demonstrating improved pump function with a tendency for improved systolic function and unchanged diastolic function. They also concluded that this procedure has the potential to be an effective therapy in patients with ischemic heart failure.

Dib et al. (2005) published a report of a four-year follow-up of a Phase I, nonrandomized multicenter pilot study of autologous skeletal myoblast transplantation that was performed concurrently with a CABG or left ventricular assist device (LVAD) transplantation. Twenty-four patients with a history of previous MI and LVEF of less than 40% were enrolled in the CABG arm. In a second arm, six patients underwent LVAD as a bridge to heart transplantation. Myoblasts were successfully transplanted in all patients without any acute injection-related complication or significant long-term, unexpected adverse events. The authors summarized the main findings as: epicardial transplant of autologous skeletal myoblasts is feasible and safe; myoblast transplantation with bypass surgery was accompanied by an increase in LVEF, an increase in tissue viability and a reduction in ventricular systemic and diastolic volumes. In three of the 24 CABG patients, nonsustained ventricular tachycardia occurred, and was treated with medications and implantation of an internal cardioverter-defibrillator (ICD). The authors concluded that additional clinical trials of autologous myoblast transplantation are warranted.

Siminiak and colleagues (2004) also conducted a Phase I clinical trial to evaluate the safety and feasibility of skeletal myoblast transplant performed during CABG to treat damaged myocardium. A second endpoint of the study was the efficacy of the treatment in improving LV function. Ten patients underwent the procedure, performed in a fashion similar to that of the Menasche study. One patient died of an MI unrelated to the procedure. Two patients developed ventricular tachycardia within hours of the procedure, leading to revision of the protocol to include prophylactic intravenous amiodarone for all remaining patients. Some improvement was found in ejection fraction (EF) (mean 42% vs. 35.2%) in the first four months and was maintained throughout the 12-month follow-up period. Functional improvement, if any, was not discussed.

Siminiak et al. (2005) published results of a Phase I trial referred to as the percutaneous transc coronary-venous transplantation of autologous skeletal myoblasts in the treatment of post-infarction myocardial contractility impairment, or POZNAN trial. The aim of the trial was to assess the feasibility and safety of autologous skeletal myoblast transplant performed via a percutaneous trans-coronary venous approach in patients with post-infarction LV dysfunction. The study involved ten patients with heart failure. Skeletal myoblasts were obtained from a biopsy specimen and grown in cell culture. The transplantations were performed uneventfully in nine patients using the TransAccess™ Catheter System (Medtronic Inc., MN) under fluoroscopic and intravascular ultrasound guidance. In one patient, the procedure was not performed due to the inability to position the guiding wire. During the six-month follow-up, the New York Heart Association class improved in all patients, and the EF increased 3–8% in six out of the nine cases. The authors concluded that the data suggest the feasibility and procedural safety of myoblast transplantation when performed via the transc coronary-venous approach.

Menasche et al. (2008) reported on results of a Phase II study of skeletal myoblast transplantation referred to as the myoblast autologous grafting in ischemic cardiomyopathy or MAGIC trial (Menasche, et al., 2004; Menasche, et al., 2008). The randomized, placebo-controlled, double-blind trial involved 97 patients in 30 clinical centers in several European countries and Canada. Patients received either cells grown from a skeletal muscle biopsy or a placebo solution injected in and around the scar. An implantable cardioverter-defibrillator was placed in all patients. The primary outcomes were the six-month changes in global and regional LV function as assessed by echocardiography. The safety end-points included a composite index of major cardiac adverse events and ventricular arrhythmias. Patients were randomized to receive myoblasts (400 [n=33] or 800 [n=34] million) or the placebo (n=30). The myoblast transfer did not improve regional or global LV function beyond that seen in the control group. The absolute change in ejection fraction (median [interquartile range]) between 6 months and baseline was 4.4% (0.2; 7.3), 3.4% (–0.3; 12.4), and 5.2% (–4.4; 11.0) in the placebo, low-dose, and high-dose groups, respectively (p=0.95). There were a higher number of arrhythmic events in the myoblast-treated patients, but six-month rates of major cardiac adverse events and of ventricular arrhythmias did not differ significantly between the groups.

Stem-Cell Transplantation

Stem cells are also being studied as possible sources for cellular transplantation to damaged myocardium. Stem cells can differentiate into any type of cell, depending on their microenvironment. As they mature, they can acquire all the characteristics of the target tissue, such as myocardium and cardiac vessels. This technology may be more appropriate for use early after infarction, since stem cells transplanted into an area of scar tissue may differentiate into scar tissue rather than into healthy myocardium.

Stem cells can be harvested from either peripheral blood or bone marrow. Bone marrow is the richest source of stem cells, with the potential to differentiate into cardiomyocytes and blood vessels, but the invasiveness of bone marrow harvesting may present a problem, particularly in the immediate post-MI period. Bone marrow-derived stem cells consist of several types of cells, including hematopoietic stem cells, endothelial progenitors, and mesenchymal stem cells. Peripheral blood contains stem cells in such small numbers that the cells must be mobilized prior to harvesting. This is accomplished by using granulocyte colony stimulating factor (G-CSF). G-CSF is also associated with mobilization of other immune cells, however, and may therefore lead to nonspecific inflammation. Different methods of stem delivery are being investigated. They include (Oettgen, 2006):

- Transvascular route: in this method, stem cells are infused directly into the coronary arteries. This method appears to be well-suited to treat patients with acutely infarcted and reperfused myocardium.
- Direct injection of stem cells into the ventricular wall: this method is used in patients who present with established cardiac dysfunction and when a transvascular approach may not be possible. There are three approaches to direct injection:

- Transendocardial approach: in this method, a needle catheter is advanced across the aortic valve and positioned against the endocardial surface. Cells are then injected directly into the left ventricle. Electrophysiological mapping may be used to differentiate sites of viable, ischemic or scarred myocardium.
- Transepicardial approach: in this method, the cells are injected during open heart surgery. This method allows direct visualization of the myocardium and identification of regions of scar and border zones of infarcted tissues.
- Delivery of cells through one of the cardiac veins directly into the myocardium. The attempt to position the catheter within a particular coronary vein may be considered more time-consuming and technically challenging.

Literature Review for Myocardium Stem-Cell Transplantation

In a study by Assmus et al. (2002), 20 patients with reperfused acute MI received intracoronary infusion of stem cells derived from either bone marrow or peripheral blood into the infarct artery within six days after MI. The study is referred to as the TOPCARE-AMI trial. Stem-cell transplantation was associated with a significant increase in LVEF, improved wall motion in the infarct zone and reduced end-systolic LV volumes at four-month follow-up. These results were compared to those of a nonrandomized matched reference group, which did not experience significant improvement in either measure. Additional measures of the experimental group (i.e., wall motion, coronary blood flow reserve in the infarct artery, and myocardial viability) also improved significantly compared to baseline. There was no difference in the measured parameters between those who received bone-marrow stem cells and those who received peripheral-blood stem cells.

Strauer et al. (2002) documented a controlled study that compared 10 patients who were treated with intracoronary transplantation of autologous bone-marrow cells in addition to standard therapy after MI with 10 patients who received standard therapy alone. At three-month follow-up, the infarct region had decreased significantly, and the infarction wall movement velocity had increased significantly in the experimental group compared both to its baseline and to the results of the control group.

A study by Chen et al. (2004) confirmed these results. The researchers conducted a randomized, controlled clinical trial of 69 patients who underwent primary percutaneous coronary intervention within 12 hours after onset of acute MI. The experimental group received intracoronary injection of autologous bone-marrow mesenchymal stem cells, while the control group received saline. Increased LVEF and decreased perfusion defects were found in the experimental group but not in the control group.

Perin et al. (2003) conducted a prospective, nonrandomized, open-label study for the purpose of evaluating the hypothesis that transendocardial injections of autologous bone marrow cells in patients with end-stage ischemic heart disease could safely promote neovascularization and improve perfusion and myocardial contractility. Twenty-one patients were included, with the first 14 patients placed in the treatment group and seven patients to the control group. The treatment group received transendocardial delivery of bone marrow cells. At two-month follow-up there was a significant reduction in total reversible defect and improvement in global LV function within the treatment group. At four months evaluation, there was improvement in EF from the baseline and a reduction in end-systolic volume in the treated patients. The authors concluded that: 1) the study demonstrates relative safety of intramyocardial injection of bone marrow-derived stem cells in patients with severe heart failure; 2) there is potential for improving myocardial blood flow with associated enhancement of regional and global LV function; and 3) that further investigation in a larger randomized trial is warranted.

Schachinger et al. (2004) published the results at one year from the TOPCARE-AMI trial. In addition to the first 20 patients whose results were included in the four-month follow-up report, an additional 39 patients were included in the study, and their results were also covered in the one-year follow-up report. One patient experienced distal embolization before the cell therapy. During the follow-up, one patient in each cell group developed MI, and one of these patients died of cardiogenic shock. No further cardiovascular events, including ventricular arrhythmias or syncope, occurred during the one year of follow-up. LVEF significantly increased, and end-systolic volumes significantly decreased without differences between the two cell groups. Magnetic resonance imaging at one year revealed an increased EF, reduced infarct size and absence of reactive hypertrophy, suggesting functional regeneration of the infarcted ventricles. The authors concluded that the results of the study indicate that intracoronary infusion of stem cells is safe and feasible in patients after MI successfully revascularized by stent implantation and, although the mechanisms of functional improvement are not clear, there is rationale for larger randomized, double-blind studies.

Kang et al. (2004) reported on a prospective, randomized study to examine the feasibility and efficacy of G-CSF therapy and subsequent intracoronary infusion of collected peripheral blood stem cells in patients with MI, referred to as the MAGIC trial. Twenty-seven patients were randomized into three groups: cell infusion, G-CSF alone and a control group. The G-CSF injection and intracoronary infusion of stem cells did not result in inflammation and ischemia during the periprocedural period. Exercise capacity increased, and myocardial perfusion improved significantly in patients who received cell infusion. There was an unexpectedly high rate of in-stent restenosis noted in the patients who received G-CSF, and the enrollment to the study was stopped. It was noted by the authors that aggravation of restenosis could be a serious problem and that the data warrants a more cautious approach to stem-cell therapy.

Woolert et al. (2004) conducted a trial to assess whether intracoronary transfer of autologous bone-marrow cells could improve global LVEF at six-month follow-up. The trial was referred to as the intracoronary autologous bone-marrow cell transfer after MI trial or the BOOST trial. Sixty patients were randomly assigned to either a control group that received optimum post-infarction medical treatment, or a group that received optimum medical treatment along with intracoronary transfer of autologous bone- marrow cells four to eight days after percutaneous coronary intervention. After six months, mean global LVEF had increased by 0.7 percentage points in the control group and 6.7 percentage points in the bone-marrow group. The transfer of bone marrow cells appeared to improve LV function primarily in the myocardial areas adjacent to the infarcted area. The cell transfer did not appear to increase the risk of adverse clinical events, in-stent restenosis, or proarrhythmic effects. The authors concluded that larger trials are needed to address the effect of bone-marrow cell transfer on clinical end points such as incidence of heart failure and survival. Additional follow-up of the BOOST trial was published in 2006. Myer et al. (2006) noted that the difference in LVEF improvement between the groups was significant after six months, but not after 18 months. Mean global LVEF in the bone marrow transfer group improved by 6.7 percentage points after six months and by 5.9 points after 18 months. However, it was also noted that global LVEF also increased somewhat in the control group, by 0.7 points at six months and 3.1 points by 18 months. This had the result of rendering the intergroup comparison at 18 months no longer statistically significant. The authors noted that no parameter could be identified that discriminated among patients who responded to bone marrow cells transfer with lasting improvements of LVEF. They concluded that in this study, a single dose of bone marrow cells did not provide long-term benefit on LV function after acute MI compared with the randomized control group; however, there may be an acceleration of LVEF after MI with bone marrow cell therapy.

Strauer et al. (2005) conducted a study with the objective of evaluating the usefulness of stem-cell therapy in patients with chronic MI. Eighteen patients with chronic MI were treated with intracoronary transplantation of autologous bone marrow mononuclear cells and were compared with a control group of 18 patients without cell therapy. After three months, it was noted that in the transplantation group, infarct size was reduced by 30%, and global LVEF and infarction wall movement velocity increased significantly. In the control group, no significant changes were observed in these areas. No complications were noted immediately or three months after cell transplantation. The authors note that from one study, it cannot be determined which cell-biologic and molecular mechanisms are responsible for heart muscle repair or which factor is the predominant feature. The authors concluded that these results represent a stable basis to proceed to the next research step: a large prospective randomized study.

Kueth et al. (2005) undertook a prospective, nonrandomized study to evaluate whether treatment with G-CSF to mobilize bone marrow cells is feasible and safe and promotes neovascularization and myocardial function in patients with an acute MI. Fourteen patients were included in the treatment group and nine patients in the control group. The patients in the treatment group received G-CSF subcutaneously forty-eight hours after recanalization and stent implantation. No severe side effects were noted. There was a significant improvement noted in regional wall motion and perfusion within the treatment group. A control angiography of the treatment group after 12 months indicated an in-stent restenosis in one patient. The authors concluded that in patients with acute MI, this treatment appears to be feasible and safe, and a randomized trial is required to define the role of this therapy.

Erbs et al. (2005) conducted a randomized double-blind, placebo-controlled study to evaluate the impact of intracoronary infusion of stem cells on coronary vasomotion and LV function in patients after recanalization of chronic coronary total occlusion. Twenty-six patients were randomly assigned to the treatment or control group. G-CSF was used to augment the number of stem cells. At three months, MRI revealed a reduction in infarct size

by 16% and an increase in LVEF by 14% in the treatment group. At the beginning of the study, patients in both groups were noted to have a similar number of hibernating myocardial segments. At three months, the number of myocardial segments with hibernation was significantly reduced by 31% in the treatment group, whereas no change was noted in the control group.

Lunde et al. (2005) is currently conducting a randomized, controlled, prospective open-label study to test whether intracoronary transplantation of autologous mononuclear bone marrow cells improves LVEF after anterior wall acute MI, referred to as the ASTAMI trial. Patients with acute anterior wall ST-elevation MI who had been treated with acute percutaneous coronary intervention were randomized to either an intracoronary transplantation of autologous bone marrow cell or to control group. LV function, exercise capacity, biochemical status, functional class, quality of life and complications were validated at baseline and will be validated during a 12-month follow-up. By August 2004, 49 patients were included in the study, with 24 patients randomized to the treatment group. Twenty patients had chest pain, and 16 patients had ischemic electrocardiogram (ECG) changes during the transplantation procedure. One patient had ventricular fibrillation 24 hours after transplantation. In the control group, one patient had ventricular tachycardia three days after MI. At 30 days after MI, there were no reinfarctions or stent thrombosis after the transplantation of stem cells, and complications appeared small in both groups.

Findings from the above ASTAMI trial were reported at the American Heart Association (AHA) Scientific Sessions 2005 (AHA, 2005). It was reported that the injection of BMC did not improve function or reduce damage. It is noted in the report at the AHA website that "they found no significant differences between the treatment and control groups. The ejection fraction, a measure of the heart's ability to pump, had improved virtually the same in both groups, as had the size of the heart's damaged area." It was noted that results in this area of study remain inconclusive, and further research is needed to explore methods for cell therapy. In 2006, Lunde et al. published results from the ASTAMI study. Patients treated with intracoronary injection of mononuclear BMC in the infarct-related coronary artery at median of six days after MI neither improved LVEF nor reduced LV end-diastolic volume or infarct size at six months, as compared with the control group. The two groups did not differ significantly in changes in LV end-diastolic volume or infarct size and similar rates of adverse events. They concluded that with the methods used, there were no effects found of intracoronary injection of autologous mononuclear BMC on global LV function and that further research is needed before intracoronary injections of BMC can be recommended for patients with acute MI.

Assmus et al. (2006) reported on a controlled crossover study of 75 patients with stable ischemic heart disease who had had an MI at least three months previously. The patients were randomly assigned to receive either no cell infusion (23 patients) or infusion of progenitor cells derived from bone marrow (BMC) (28 patients) or circulating blood (CPC) (24 patients) into the patient's coronary artery supplying the most dyskinetic LV area. The patients in the control group were then subsequently randomly assigned to receive CPC or BMC. The patients who received the BMC or CPC then crossed over to receive CPC or BMC, respectively, at three months' follow-up. The results indicated that the absolute change in LVEF was significantly greater among patients receiving BMC than among those receiving CPC or no infusion. This increase in global cardiac function appeared to be related to significantly enhance regional contractility in the area targeted by intracoronary infusion of BMC. The authors concluded that intracoronary infusion of progenitor cells is safe and feasible in patients with healed MI and that transplantation of BMC is associated with moderate but significant improvement in LVEF after three months. They also note that studies on a larger scale are warranted to examine its potential effects on morbidity and mortality among patients with post-infarction heart failure.

Schachinger et al. (2006) conducted a double-blind, placebo-controlled, multicenter trial, referred to as the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction, or REPAIR-AMI trial. The purpose was to determine whether intracoronary infusion of enriched BMC is associated with improved global LV function in patients with MI treated with state-of-the-art methods. Two-hundred and four patients with acute MI were randomly assigned to receive an intracoronary infusion of progenitor cells derived from bone marrow or placebo medium into the infarct artery three to seven days after successful reperfusion therapy. At four months, it was noted that the absolute improvement in the global LVEF was significantly greater in the BMC group than in the placebo group. Patients with baseline LVEF at or below the median value of 48.9% appeared to derive the most benefit. At one year, intracoronary infusion of BMC was associated with a reduction in the prespecified combined clinical end point of death, recurrence of MI, and any revascularization procedure. The authors concluded that intracoronary administration of BMC is associated with improved recovery of LV

contractile function in patients with acute MI. They noted that large-scale studies are warranted to examine the potential effects of progenitor-cell administration on morbidity and mortality.

Meluzin et al. (2006) conducted a randomized controlled study with the aim of: 1) verifying the safety and efficacy of autologous transplantation of mononuclear BMC in patients with acute MI and; 2) determining the impact of the dose of transplanted cells on myocardial function and perfusion. The study included 66 patients with a first acute MI who were randomized into three groups. Two groups were given mononuclear BMC in either higher or lower cell dose. Twenty-two patients without cell transplantation served as the control group. At three months, follow-up echocardiography and SPECT results indicated that there was a significant and dose-related improvement in the regional systolic function of the infarcted wall after cell transplantation. As compared to controls, a higher cell dose significantly improved global LV function. The authors did note that there were the following limitations with this study: patients included in the control group did not undergo the identical procedures as the low-dose and high-dose group; there is heterogeneity in times from infarct onset to reperfusion; and the number of patients is relatively small to draw definitive conclusions. The authors concluded that BMC transplantation appears to improve regional myocardial function of infarcted wall in a dose-dependent manner, and a larger, controlled, and optimally multicenter study is necessary to answer questions of cell-dose effect.

Mocini et al. (2006) conducted a study to evaluate the feasibility and safety of bone marrow mononuclear cell transplantation in patients with recent MI undergoing CABG. The study included 36 patients with an MI within the past six months undergoing CABG. Eighteen patients underwent CABG with BMC transplantation, while 18 patients served as control subjects and underwent conventional CABG. The cell transplantation was performed by direct injections in the border zone of the recently infarcted area. No major transplant-related adverse event was detected. It was noted at follow-up that transplanted patients had an improvement in LVEF and wall motion score index. The incidence of arrhythmias was similar in the two groups. The authors concluded that the direct injection of BMC in the myocardium during CABG is feasible and safe, and larger studies are needed to assess the efficacy of such an approach.

Ge et al. (2006) conducted a randomized, double-blind clinical trial to study whether emergent intracoronary autologous bone marrow cell transplantation is applicable for the treatment of acute MI. Twenty patients who were admitted within 24 hours of onset of acute MI were randomly allocated to receive intracoronary autologous BMC transplantation (n=10) or bone marrow supernatant (n=10), immediately after primary percutaneous coronary intervention. LVEF, LV diastolic internal diameter and myocardial perfusion defect scores were examined respectively by echocardiography and single-photon emission computed tomography at one week and six months after MI. The study noted the following results from one week to six months after MI: EF was enhanced in the BMC group and was unchanged in the control group; LV diastolic internal diameter remain unchanged in the BMC group but was significantly enlarged in the control group; and myocardial perfusion defect scores decreased from 21 to 13 in the BMC group but were unchanged in the control group. The authors concluded that emergent intracoronary transplantation of bone marrow mononuclear after MI appeared to improve cardiac function, prevented myocardial remodeling, and increased myocardial perfusion at six months' follow-up. In addition, it was noted that this data indicated that future stem-cell transfer studies in a larger patient population and in patients with more profound LV dysfunction are warranted.

Janssens et al. (2006) conducted a randomized, double-blind, placebo-controlled study to investigate the effect of autologous bone marrow-derived stem-cell transfer in the infarct-related artery on LV function and structure. The study involved 67 patients from whom bone marrow was harvested one day after successful percutaneous coronary intervention for ST-elevation acute MI. Patients were assigned to either optimum medical treatment and infusion of placebo (n=34) or bone marrow stem cells (n=33). The primary outcome was increase in LVEF and secondary were change in infarct size and regional LV function at four-month follow-up. All measurements were assessed by MRI. The findings included mean global LVEF four days after percutaneous coronary intervention was 46.9% in controls and 48.5% in stem-cell patients. This increased after four months to 49.1% in controls and 51.8% in stem-cell patients. Compared to the placebo infusion, the stem-cell transfer was associated with a significant reduction in myocardial infarct size and better recovery of regional systolic function. It was noted by the authors that myocardial perfusion and metabolism increased similarly in both groups. The authors note that these results do not indicate that cell transfer did not greatly increase LVEF, which refuted the primary hypothesis that in timely reperfused MI, stem-cell transfer would significantly augment functional recovery. The authors summarized that they noted no incremental effect of autologous bone marrow stem cell on global LV functional recovery in patients with timely reperfused MI. It was also noted by the authors that the

intervention in its present form does not offer sufficient benefit to be incorporated in reperfusion therapy for MI with moderate reduction in global LV function.

Li et al. (2007) conducted a controlled trial to investigate the effects and safety of autologous peripheral blood stem-cell transplantation by intracoronary infusion in patients with acute MI. Seventy patients were allocated to one of two groups: one was peripheral blood stem-cell group (n=35) and the other was a control group (n=35) that received optimum post-infarction medical treatment (i.e., standard drug and coronary artery intervention therapy). Changes in LV function were assessed at the six-month follow-up. Thirty-five cases finished follow-up in the treated group, while 23 finished in the control group. At six months in the treated group, there was a significant improvement in global LVEF, wall motion score index, and left end-systolic volume. In the control group, there was no significant improvement in EF, wall motion score index, or left end-systolic volume. There were a total of 25 cases with complications during the mobilization, separation and infusion of stem cells, with no death observed. The authors concluded that autologous peripheral blood stem-cell transplantation by intracoronary infusion is feasible and safe and appears that it can improve LV function at six-month follow-up.

Kang et al. (2007) reported on two-year follow-up results of the three groups in the above-noted MAGIC trial (Kang, et al., 2004). At two years, the cell infusion group showed improved left ventricular systolic function and remodeling compared to baseline, but the G-CSF alone group did not. The cell infusion group demonstrated better improvements of LVEF ($+6.2\% \pm 3.6\%$ vs. $-4.3\% \pm 10.1\%$, $p=0.004$) and end-systolic volume (-15.7 ± 13.0 vs. $+0.3 \pm 16.7$ ml, $p=0.075$) compared to the G-CSF alone group at six months' follow-up, and these trends were maintained until two years of follow-up ($p=0.094$ and 0.046 , respectively). The improvements in the cell infusion group are not significantly better than that of the control group due to the small sample size. The patients who had been given G-CSF administration demonstrated a tendency of modest increase of binary restenosis (50% vs. 30%, $p>0.05$) and a greater late loss of minimal luminal diameter ($p>0.05$) at six months' follow-up as compared to the control group. It appears that until two years' follow-up, intracoronary cell infusion with mobilized peripheral blood stem cells by G-CSF is better than G-CSF alone but not significantly better than the control group. The authors concluded that the efficacy and safety of intracoronary infusion of mobilized peripheral blood stem cells with G-CSF should be evaluated in a large, randomized controlled trial.

Solheim et al. (2008) reported on inflammatory responses after intracoronary injection of autologous bone marrow cells (mBMC) in the above-noted ASTAMI trial (Lunde, et al., 2005). Fasting blood samples were drawn the day before stem-cell transplantation and one day, three days, two to three weeks, and three months after the transplantation for determination of circulating levels of selected inflammatory markers and mRNA levels in whole blood samples. The results of the blood samples indicated that from baseline to day one, the levels of interleukin 6 and the expression of tumor necrosis factor α mRNA increased significantly in the BMC group compared to the control group ($p<0.05$ for both). The decrease in interleukin 6 levels from baseline to two to three weeks in the mBMC group was less pronounced than in the controls ($p<0.05$), as was also the decrease in C-reactive protein levels from baseline to day one and three in the mBMC group ($p<0.05$). On the other hand, from baseline to three months, the levels of tumor necrosis factor α and monocyte chemoattractant protein 1 increased less in the mBMC group ($p<0.05$ for both). The authors concluded that "Intracoronary injection of mBMC in patients with AMI [acute MI] induces a marked short-term inflammatory response, but a slightly reduced inflammation after 3 months which may have implications for the timing of stem-cell transplantation in AMI."

A technology assessment was performed by Blue Cross Blue Shield Association (BCBSA), Technology Evaluation Center (TEC) (2008) to determine whether treatment with autologous progenitor cells improves clinical outcomes for patients with damaged myocardium due to ischemia. Fifteen articles met the inclusion criteria for the review: nine articles discussed patients with acute ischemic heart disease treated with progenitor cell therapy and six articles discussed treatment of patients with chronic ischemic heart disease. The primary limitation of the studies is the small quantity of literature that reports on clinical outcomes, with a very small overall number of hard clinical outcomes such as recurrent MI and death across all trials. The report included the following findings regarding the studies:

- The evidence for a beneficial impact on physiologic outcomes, particularly LVEF, is fairly strong, but the magnitude of effect does not appear to be large. Consequently, it does not appear certain whether the improvement in LVEF translates to meaningful improvements in clinical outcomes.
- The evidence for a decrease in infarct size is less robust than that for LVEF, but shows a similar pattern of incremental improvement for patients receiving progenitor cell therapy. As with LVEF, the threshold

for improvement in infarct size that translates to a clinically meaningful benefit appears to be uncertain.

- Regarding chronic ischemic heart disease, there is only very scant evidence on clinical outcomes, and therefore no conclusions can be drawn.
- There are only a small amount of clinical outcome events reported across the included studies, too few for meaningful analysis. Other clinical outcomes, such as New York Heart Association (NYHA) class, are confined to very small numbers of patients and not reported with sufficient methodology rigor to permit any conclusions

The TEC report concluded that the evidence is insufficient to permit conclusions with adequate confidence on the effect of progenitor cell therapy on clinical outcomes for patients with ischemic heart disease.

Meta-analyses and systematic reviews: Martin-Rendon et al. (2008) reported on a Cochrane review that evaluated the effectiveness of adult bone marrow-derived stem cells (BMSC) to treat AMI. The review included 13 randomized, controlled studies with 811 participants. The review noted that there were insufficient events on clinical outcomes such as mortality to draw clear conclusions. All the studies presented follow-up data for three to six months, with three studies with longer-term follow-up for more than 12 months. The outcome that had the most results in the studies was LVEF, with secondary outcomes including assessment of mortality, morbidity, adverse events, and left ventricular end systolic and end diastolic volumes. There was marked heterogeneity between the trials. It was noted that there was a consistent pattern that indicated that BMSC treatment generally improves short-term LVEF, with similar trends for left ventricular end systolic and end diastolic volumes, infarct size or cardiac wall motion. A positive correlation was seen between cell dose infused and the effect on LVEF as measured by magnetic resonance imaging. The authors concluded that the systematic review indicates that there is little evidence to assess the clinical effects of this treatment. There is a need for larger trials using optimal dosing and more reliable, patient-centered outcomes.

Abdel-Latif et al. (2007) conducted a systematic review and meta-analysis of randomized controlled trials and cohort studies of bone marrow derived cells (BMCs) transplantation to treat ischemic heart disease. Eighteen studies (12 randomized controlled studies and six cohort studies) with 999 patients were included in the review. The main outcomes for the review were change from baseline in mean LV ejection fraction, infarct scar size, LV end-systolic volume and LV end-diastolic volume. The adult BMCs used in the studies included BM mononuclear cells, BM mesenchymal stem cells, and BM-derived circulating progenitor cells. When BMC transplantation was compared to controls, the results included: improved left ventricular ejection fraction (pooled difference, 3.66%; 95% confidence interval [CI], 1.93%–5.40%; $p < 0.001$); reduced infarct scar size (–5.49%; 95% CI, –9.10% to –1.88%; $p = 0.003$); and reduced left ventricular end-systolic volume (–4.80 ml; 95% CI, –8.20 to –1.41 ml; $p = 0.006$). The authors note that the available evidence suggests that BMC transplantation is associated with modest improvements in physiologic and anatomic parameters in patients with both acute MI and chronic ischemic heart disease. The results support the conduction of large randomized trials to evaluate the long-term impact of BMC therapy as compared with standard of care on patient-important outcomes.

Lipinski et al. (2007) performed a meta-analysis of clinical trials on intracoronary cell therapy after acute MI to determine the impact of intracoronary cell therapy on post-infarction LV function. Ten controlled studies with 698 patients were included in the review, with a median follow-up of six months (range of 3 to 18 months). The primary end point in the studies was change in LVEF, with secondary end points including changes in infarct size, cardiac dimensions, and dichotomous clinical outcomes. Review of the studies indicated that subjects that received intracoronary cell therapy had a significant improvement in LVEF (3.0% increase; 95% CI 1.9 to 4.1; $p < 0.001$), as well as a reduction in infarct size (–5.6%; 95% CI –8.7 to –2.5; $p < 0.001$) and end-systolic volume (–7.4 ml; 95% CI –12.2 to –2.7; $p = 0.002$), and a trend toward reduced end-diastolic volume (–4.6 ml; 95% CI –10.4 to 1.1; $p = 0.11$). It was also noted that intracoronary cell therapy was associated with a minimally significant reduction in recurrent acute MI ($p = 0.04$) and with trends toward reduced death, rehospitalization for heart failure and repeat revascularization. Meta-regression suggested the possibility of an existence of a dose-response association between injected cell volume and LVEF change ($p = 0.066$). The authors concluded that the data confirms the beneficial impact of this therapy, and further multicenter randomized trials are supported.

Ongoing studies: A multicenter prospective, randomized, single-blind clinical trial is currently underway to compare the early and late intracoronary or combined (percutaneous intramyocardial and intracoronary) administration of bone marrow-derived stem cells to patients after acute MI with reopened infarct-related artery (MYSTAR study) (Nyolczas, et al., 2007). Three hundred-sixty patients are randomly assigned into one of four groups:

- Group A: early treatment with intracoronary injection, (21–42 days after MI)
- Group B: early treatment with combined application
- Group C: late treatment with intracoronary delivery (three months after MI)
- Group D: late treatment with combined administration of bone marrow-derived stem cells

The primary outcomes in this study are changes in resting myocardial perfusion defect size and left ventricular ejection fraction three months after the BMC therapy. Secondary end points include: evaluation of the safety and feasibility of the applications modes; changes in left ventricular wall motion score index; myocardial voltage and segmental wall motion; left ventricular end-diastolic and end-systolic volumes; and the clinical symptoms utilizing the Canadian Cardiovascular Society angina score and New York Heart Association functional class at follow-up. Follow-up will be initially at post-procedure and in-hospital evaluation and then at following intervals (\pm two weeks): three months, six months, and twelve months.

The clinical trials did not demonstrate any significant complications related to the procedure. These Phase I and II studies are preliminary but appear to demonstrate the safety and feasibility of the procedure. Large, multicenter, prospective randomized trials are currently underway to investigate the efficacy of stem-cell transplantation into the myocardium.

Professional Societies/Organizations

The National Heart, Lung, and Blood Institute (NHLBI) held a Working Group on Translation of Cell-Based Therapies for Cardiovascular Disease in August 2004. In considering how best to translate cardiovascular cell therapy into the clinical arena, the Working Group determined that cell therapy can be implemented more quickly and effectively through an integrated approach and recommended that the NHLBI establish a research network to conduct clinical studies of novel cell-based therapies. As a result of this working group, the NHLBI published a request for applications to participate in the Cardiovascular Cell Therapy Research Network (CCTRN), a cooperative network of cardiovascular cell therapy research centers. The program will provide support to maintain the necessary infrastructure to develop, coordinate, and conduct multiple collaborative proof-of-concept clinical treatment protocols to improve cardiovascular disease outcomes. The goal of the network is to promote the evaluation of novel cell therapy treatment strategies for individuals with cardiovascular disease. The network will provide the necessary infrastructure to develop, coordinate, and conduct multiple collaborative clinical protocols to facilitate application of emerging scientific discoveries into clinical investigations. Results of network studies are expected to be widely disseminated and to improve the scientific basis of care for affected individuals. The applications for this program were due in March 2006, with the earliest anticipated start date of December 1, 2006 (NIH, 2005).

The European Society of Cardiology (ESC) published a consensus statement concerning the clinical investigation of the autologous adult stem cells for repair of the heart. The statement noted the following regarding this treatment (Bartunek, et al., 2006):

- The use of autologous stem/progenitor cell therapy is not at a stage to be used in routine clinical practice.
- It is timely to perform the following studies that should be designed on the basis of the published data:
 - Further large, double-blind, randomized controlled trials for the use of autologous bone marrow cells in the treatment of AMI. The patient population should be all those presenting within 12 hours of AMI and treated with immediate revascularization, be it primary angioplasty or fibrinolysis.
 - A double-blind, randomized controlled trial for the use of autologous bone marrow cells in the treatment of MI in those patients presenting late (>12 h) or who fail to respond to therapy (candidates for 'rescue' angioplasty). Although, these groups may represent a small proportion of all patients with AMI, their prognosis remains poor.
 - Double-blind, randomized controlled trials for the use of autologous bone marrow cells or skeletal myoblasts in the treatment of heart failure secondary to ischemic heart disease. At some stage, the role of autologous stem/progenitor cells in the treatment of cardiomyopathies (in particular, dilated cardiomyopathy) will need to be examined.
 - A series of well-designed small studies to address safety or mechanism to test specific hypotheses (e.g., studies with labeled cells or to investigate paracrine or autocrine mechanisms). Such hypotheses would have arisen from basic science experiments.
 - Studies to confirm the risk/benefit ratio of the use of cytokines alone (e.g., granulocyte colony stimulating factor) or in conjunction with stem/progenitor cell therapy.

- The studies should include the following:
 - The end points should focus on robust clinical outcomes, as well as MACE (major adverse cardiac events), subjective benefit, and economic gain.
 - Outcome measures for future trials should be standardized so that comparisons can be made.
 - Questions concerning optimal timing of delivery, number of cells delivered, and the route of delivery (e.g., at the time of bypass surgery or by percutaneous techniques) will need to be addressed.
 - Studies in this field will need to recruit approximately 1000 patients to provide enough statistical power to be meaningful. The studies should be multicenter and ideally pan-European.
- It is not until the results of these studies are available that the role of autologous cells as a treatment could be considered.

Summary

Despite promising results in animal models and initial human studies, skeletal myoblast and stem-cell transplantation into damaged myocardium remains an unproven technology. Large-scale, long-term, randomized controlled clinical trials are necessary to establish the efficacy of these procedures. A number of technical issues remain unresolved, including optimum cell type, ideal number of cells, factors that promote engraftment, surgical delivery method and patient selection criteria. The long-term viability of the transplanted cells has not been proven. Additionally, none of the studies has demonstrated an improvement in patient functional status or survival.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
33999 [†]	Unlisted procedure, cardiac surgery

[†]**Note:** Experimental/Investigational/Unproven and not covered when used to report the transplantation of cells into the myocardium.

ICD-9-CM Diagnosis Codes	Description
	All codes

*Current Procedural Terminology (CPT®) ©2008 American Medical Association: Chicago, IL.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	2/15/2008	0287	Autologous Skeletal Myoblast Transplant/Autologous Cell Therapy for Damaged Myocardium

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.