



CIGNA MEDICAL COVERAGE POLICY

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

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Hyperlink to Related Coverage Policies

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

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Coverage Policy

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

General Background

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).

Cell therapy is being researched as treatment for several cardiac conditions including heart failure, or congestive heart failure (CHF), and after acute myocardial infarction (MI). 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. 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. A myocardial infarction (MI) 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. 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, thrombolytics, beta blockers, ACE inhibitors and oxygen. Coronary angioplasty (with or without stenting) or coronary artery bypass graft (CABG) may be indicated.

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

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.

Several Phase 1 studies have been published that examined the safety and feasibility of autologous skeletal myoblast transplantation (Dib, et al., 2005; Siminiak, et al. 2005; Siminiak, et al., 2004; Herreros, et al., 2003; Smits, et al., 2003; Menasche, et al., 2001). These non-randomized studies included small groups of patients with short follow-up time periods and utilized various methods of skeletal myoblast implantation. In general, the studies demonstrated that the procedure is safe and feasible and that further study is warranted. The 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).

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

Systematic reviews/Technology Assessments: Brunskill et al. (2009) conducted a systematic review of randomized, controlled trials to assess whether route of delivery and baseline left ventricular ejection fraction (LVEF) of the participants affects the outcome of autologous bone-marrow stem-cell (BMSC) treatment in patients with AMI and ischemic heart disease (IHD). The review included 21 trials with 1091 participants. Improvement in LVEF in favor of the control was observed when BMSC were administered by intracoronary infusion ($p < 0.00001$) in IHD patients. The effect on LVEF was statistically significant and in favor of BMSC when cells were delivered by intra-myocardial injection ($p = 0.0006$). The significant improvement in LVEF observed in AMI patients was independent from the baseline LVEF of the participants. In patients suffering from chronic IHD, increase in LVEF was significant only in the group with lower LVEF at baseline ($p = 0.0007$). The authors concluded that the clinical evidence suggests that route of delivery and baseline LVEF influence the effect of BMSC therapy in treating AMI and chronic IHD.

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.

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.

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.

Studies: Several randomized studies have been published regarding the efficacy of autologous stem cells for patients with acute ischemic disease (Wohrle, et al., 2010; Solheim, et al., 2008; Schachinger, et al., 2006; Lunde, et al., 2006; Li, et al., 2007; Janssens, et al., 2006; Meluzin, et al., 2006; Assmus, et al., 2006; Ge, et al., 2006; Woolert, et al., 2004; Myer, et al., 2006; Kang, et al., 2004; Kang, et al., 2007). In most of the studies, the most common physiologic outcome reported was left-ventricular ejection fraction (LVEF). In general, most of

the studies that reported this outcome, there was a greater increase in the LVEF for the experimental group compared with the control group. However, the evidence is not consistent and is considered preliminary. A primary limitation with the published studies is the small number of studies that report on clinical outcomes, with a very small overall number of hard clinical outcomes such as recurrent MI and death across all trials. It is not clear if the improvement in LVEF translates to meaningful improvements in clinical outcomes.

The REPAIR-AMI trial (Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction), a double-blind, placebo-controlled, multicenter trial, included 204 patients and examined whether intracoronary infusion of enriched BMC is associated with improved global LV function in patients with MI treated with state-of-the-art methods (Schachinger, et al., 2006). 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. Assmus, et al. (2010) reported on two-year outcomes from the REPAIR-AMI trial. At two years, the cumulative end point of death, myocardial infarction, or necessity for revascularization was noted to be reduced in the BMC group compared with placebo group (hazard ratio, 0.58; 95% CI, 0.36–0.94; p=0.025). In addition, the combined end point death and recurrence of myocardial infarction and rehospitalization for heart failure, reflecting progression toward heart failure, was reduced in the BMC group (hazard ratio, 0.26; 95% CI, 0.085–0.77; p=0.015). The authors note that larger studies focusing on clinical event rates are warranted to confirm the effects of BMC administration on mortality and progression of heart failure in patients with AMIs.

The ASTAMI study, a randomized, controlled, prospective open-label study, included 49 patients and examined whether intracoronary transplantation of autologous mononuclear bone marrow cells improves LVEF after anterior wall acute MI (Lunde, et al., 2006). 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. In 2008, Solheim et al. reported on inflammatory responses after intracoronary injection of autologous bone marrow cells (mBMC) in the ASTAMI trial. It was noted 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.” In 2009, Beitnes et al., reported on three year results from the ASTAMI study. The rates of adverse clinical events in the group were found to be low and equal. There were no significant differences noted between the groups or change of global LV systolic function by echocardiography or MRI imaging during the follow-up. It was found on exercise testing that the bone-marrow group had larger improvement in exercise time from 2–3 weeks to three years, but no change in peak oxygen consumption was noted. The researchers noted that other than the difference in exercise time, no other effects of treatment could be identified three years after cell therapy.

Early non-randomized studies of smaller groups of patients examined intracoronary infusion of stem cells to determine to safety and feasibility of the procedure (Assmus, et al., 2002; Strauer, et al., 2002; Chen, et al., 2004; Perin, et al., 2003; Strauer, et al., 2005; Kuethe, et al., 2005; Mocini, et al., 2006). In general these studies demonstrated that cellular therapy can be safely delivered by intracoronary and intramyocardial routes and that randomized, controlled studies are indicated (Jolicœur, et al., 2007).

The clinical trials did not demonstrate any significant complications related to the procedure. These 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 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®) © 2010 American Medical Association: Chicago, IL.

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Policy History

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

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