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

Effective: December 1, 2023

Next Review: October 2024
Last Review: October 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Progenitor cell therapy describes the use of multipotent cells of various cell lineages (autologous or allogeneic) for tissue repair and/or regeneration. Progenitor cell therapy is being investigated for the treatment of damaged myocardium resulting from acute or chronic cardiac ischemia.

MEDICAL POLICY CRITERIA

I. Progenitor cell therapy, including but not limited to skeletal myoblasts or hematopoietic stem cells, is considered **investigational** as a treatment of damaged myocardium.

II. Infusion of growth factors (i.e., granulocyte colony stimulating factor [GCSF]) is considered **investigational** as a technique to increase the numbers of circulating hematopoietic stem cells as treatment of damaged myocardium.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Stem-cell Therapy for Peripheral Arterial Disease, Medicine, Policy No. 141
2. Orthopedic Applications of Stem Cell Therapy, Including Bone Substitutes Used with Autologous Bone Marrow, Medicine, Policy No. 142

BACKGROUND

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. Current treatments for ischemic heart disease seek to revascularize occluded arteries, optimize pump function, and prevent future myocardial damage. However, current treatments are not able to reverse existing damage to heart muscle.[1, 2] Treatment with progenitor cells (i.e., stem cells) offers potential benefits beyond those of standard medical care, including the potential for repair and/or regeneration of damaged myocardium.

Various types of autologous cell transplantation have been researched as a technique to either stimulate regeneration of the myocardium or modify ventricular remodeling after infarct. The ideal donor cell is uncertain, and there are scientific as well as ethical concerns involved in choosing the ideal source of donor cells.[1] The range of potential sources of donor cells includes embryonic stem cells, adult stem cell, fetal myocytes, and adult blood progenitor cells. The 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 are able to differentiate into cardiomyocytes and vascular endothelial cells.

The mechanism of benefit following treatment with progenitor cells is not entirely understood.[2, 3] 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.[3, 4] However, there is controversy concerning whether injected progenitor cells actually engraft and differentiate into mature myocytes in humans to a degree that might result in clinical benefit.[2]

Other mechanisms of benefit have been hypothesized. Progenitor cells may improve perfusion to areas of ischemic myocardium.[5] Basic science research also suggests that injected stem cells secrete cytokines with antiapoptotic and pro-angiogenesis properties.[5, 6] Clinical benefit may result if these paracrine factors are successful at limiting cell death from ischemia or stimulating recovery. For example, myocardial protection can occur through modulation of inflammatory and fibrogenic process. Alternatively, paracrine factors might 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 will depend on the age of the infarct, e.g., cytoprotective effects with acute ischemia versus cell proliferation with chronic ischemia. Investigation of the specific factors that are induced by administration of progenitor cells is ongoing.[3, 5, 7]

There is a variety of 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.[4, 8] Injection of progenitor cells into the coronary circulation

can also be done using percutaneous, catheter-based techniques. Finally, progenitor cells can 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 treatment with progenitor cells include the risk of the delivery procedure (e.g., thoracotomy, percutaneous catheter-based, etc.) and the risks of the donor cells themselves. Donor progenitor cells can differentiate into fibroblasts rather than myocytes.[1] This may create a substrate for malignant ventricular arrhythmias. There is also a theoretical risk that tumors, such as teratomas, can arise from progenitor cells, but the actual risk of this occurring in humans is not known at present.[1]

REGULATORY STATUS

U.S. Food and Drug Administration (FDA) approval is not required in situations in which autologous cells are processed on site with existing laboratory procedures and injected with existing catheter devices. However, there are several products that require FDA approval.

- MyoCell®[9] consists of 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. MyoCell SDF-1 (BioHeart Inc.) is similar to MyoCell®, but before injection, myoblast cells are genetically modified to release excess stromal-derived factor (SDF)-1. Increased SDF-1 levels at the site of myocardial damage may accelerate recruitment of native stem cells to increase tissue repair and neovascularization. For products, the myoblast isolation and expansion occurs at a single reference laboratory (BioHeart) and are, therefore, subject to FDA approval. Currently neither product is FDA-cleared. In addition, implantation may require the use of a unique catheter delivery system (MyoCath™)[10] that is FDA-cleared.

- An allogeneic human mesenchymal stem cell (hMSC) product (Prochymal®) is being developed by Osiris Therapeutics, Inc. for treatment of acute myocardial infarction.[11] Prochymal (also referred to as Provacel) is a highly purified preparation of ex vivo cultured adult hMSCs isolated from the bone marrow of healthy young adult donors. Prochymal has been granted “fast track” status by the FDA for Crohn's disease and graft-versus-host disease (GvHD), and has orphan drug status for GvHD from the FDA and the European Medicines Agency. Prochymal is being studied in Phase II trials for the treatment of acute myocardial infarction, pulmonary disease, and type 1 diabetes.

- MultiStem® (Athersys) is an allogeneic bone marrow-derived adherent adult stem-cell product. MultiStem has received orphan drug status from the FDA for GVHD and has received authorization from the FDA for a Phase II trial for treatment of acute myocardial infarction with an adventitial delivery system.

- Ixmyelocel-T is a patient-autologous, multicellular treatment containing selectively expanded mesenchymal cells, monocytes and alternatively activated macrophages from bone marrow (Varicel Corporation).[12] Ixmyelocel-T received orphan drug status from the FDA in 2007 for the treatment of cardiomyopathy.[13]

- CardiAMP™ Cell Therapy system consists of a proprietary assay to identify patients with a high probability to respond to autologous cell therapy, a proprietary cell processing system to isolate process and concentrate the stem cells from a bone marrow harvest at the point of care, and a proprietary delivery system to percutaneously inject the autologous cells

into the myocardium. BioCardia has received an investigational device exemption from FDA to perform a trial of CardiAMP™.

EVIDENCE SUMMARY

Autologous progenitor cell transplantation for the treatment of damaged myocardium is a rapidly evolving field, with a number of areas of substantial uncertainty.[1-3, 14]

- The mechanism of benefit is not well understood.
- Patient selection criteria are still evolving, and the current studies have been performed in highly selected populations.
- There is a lack of standardization in treatment protocols, with uncertainty in cell type and in the optimal methods for harvesting of donor cells, the timing of the transplantation, and the optimal delivery mode (directly into myocardium, intracoronary artery or sinus, or intravenously).
- Strategies to enhance cell engraftment and prolong cell survival are lacking.

The most clinically relevant outcome of any treatment of acute or chronic ischemic myocardial damage is improvement of symptoms, exercise tolerance, and quality of life, and reduction of future myocardial damage and mortality. Evaluating the safety and efficacy of progenitor cell therapy requires randomized comparisons with conventional medical treatments. These comparisons are necessary to determine whether any benefits of progenitor cell therapy outweigh any risks and whether the therapy offers advantages over conventional medical treatment.

ACUTE ISCHEMIA

Systematic Reviews

Fisher (2016) published a trial sequential analyses of two Cochrane reviews to address limitations associated with meta-analyses. The trial sequential analyses were conducted on two clinical outcomes using cell therapy, all-cause mortality and hospitalization for heart failure as well as left ventricular ejection fraction. The results of this analysis suggested that there is evidence of reduced risk of mortality and hospitalization in heart failure, but insufficient to determine if there was a treatment effect in acute ischemia. The cell therapy did not improve left ventricular ejection fraction by more than a mean difference of 4% in patients.

A 2012 Cochrane review included 33 RCTs (39 comparisons with 1,765 participants) on bone marrow-derived stem-cell (BMC) therapy for acute MI (AMI).[15] Twenty-five trials compared stem/progenitor cell therapy with no intervention, and 14 trials compared the active intervention with placebo. There was a high degree of statistical and clinical heterogeneity in the included trials, including variability in the cell dose, delivery and composition. Overall, stem-cell therapy was found to improve left-ventricular ejection fraction (LVEF) in both the short-term (<12 months, weighted mean difference of 2.9 percentage points, 95% confidence interval [CI], 2.0 to 3.7, I^2=73%) and long-term (12 to 61 months, weighted mean difference of 3.8 percentage points, 95% CI 2.6 to 4.9, I^2=72%). Stem-cell treatment reduced left-ventricular end systolic and end-diastolic volumes at certain times and reduced infarct size in long-term follow-up. There were positive correlations between mononuclear cell dose infused and the effect on LVEF and between the timing of stem-cell treatment and the effect on LVEF. Although the quality of evidence on LVEF was rated as high, the clinical significance of the change in LVEF is unclear. The quality of evidence on health outcomes was rated as moderate.

Stem/progenitor cell treatment was not associated with statistically significant changes in the incidence of mortality or morbidity (re-infarction, arrhythmias, hospital re-admission, restenosis, and target vessel revascularization), although the studies may have been underpowered to detect differences in clinical outcomes. Due to variability in outcomes measured, it was not possible to combine data on health-related quality of life or performance status.

Fisher (2015) published an updated Cochrane review assessing the safety and efficacy of stem-cell therapy for AMI.[16] Literature was searched through March 2015, and 41 RCTs with a total of 2,732 participants (1,564 cell therapy and 1,168 controls) were included.[16-24] There was a low degree of statistical heterogeneity and low risk of bias in the included trials, but substantial clinical heterogeneity within and between trials. At long-term follow-up (≥12 months) moderate quality evidence indicated that stem cell treatment was not associated with any changes in risk in all-cause mortality (6.3% vs 6.9%, relative risk [RR], 0.93, 95% CI 0.58 to 1.50), cardiovascular mortality (8.3% vs 7.2%, RR 1.04, 95% CI 0.54 to 1.99) or reinfarction/re-hospitalization (9.2% vs 14.0%, RR, 0.63, 95% CI 0.36 to 1.10). Similar results were reported for short-term follow-up. Stem cell therapy had no effect on morbidity or quality of life/performance, and the differences in mean LVEF between treatment groups, while reaching statistical significance in the majority of trials, was too low to be clinically relevant. While there remains insufficient evidence for a significant beneficial effect of stem cell therapy for AMI patients, the included RTCs may have been underpowered to detect differences in clinical outcomes.

Delewi (2014) published a systematic review of bone marrow cell therapy in patients with ST-elevation myocardial infarction (STEMI) that included 16 RCTs (n=1,641).[25] A meta-analysis of placebo-controlled RCTs that reported LVEF found statistically significant increases in LVEF with bone marrow stem-cell infusion compared with placebo (≤ six months, mean difference of 2.6 percentage points, 95% CI 1.8 to 3.3, p<0.001, I^2=84%). Statistically significant reductions in LV end diastolic volumes were reported. Based on these findings, the authors concluded that intracoronary bone marrow cell infusion "is associated with improvement of LV function and remodeling in patients after STEMI." Limitations of the meta-analysis included substantial statistical heterogeneity (I^2≥55%).

De Jong (2014) conducted a meta-analysis of major adverse cardiac and cerebrovascular events based on literature through August 2013.[26] The analysis included 22 RCTs (n=1,513), 13 of which (n=1,300) were also included in the Delewi (2014) meta-analysis. Analysis of placebo-controlled RCTs that reported LVEF found statistically significant increases in LVEF with bone marrow stem-cell infusion compared with placebo (≤18 months, mean difference of 2.1 percentage points, 95% CI 0.7 to 3.5, p<0.004, I^2=80%). With median follow-up of six months, there was no difference between bone marrow cell infusion and placebo in all-cause mortality, cardiac mortality, restenosis rate, thrombosis, target vessel revascularization, stroke, recurrent AMI, or implantable cardioverter defibrillator implantations. Infusion with bone marrow progenitor cells, but not bone marrow mononuclear cells, led to a statistically significant reduction in the rate of rehospitalization for heart failure (odds ratio vs placebo, 0.14, 95% CI 0.04 to 0.52, p=0.003). Based on these findings, the authors concluded that, although safe, intracoronary infusion of bone marrow stem cells does not improve clinical outcome and clinical efficacy "needs to be defined in clinical trials." Limitations of the meta-analysis included substantial statistical between-study heterogeneity (I^2≥55%).

Lipinski (2007) published a quantitative meta-analysis of studies that estimated the magnitude of benefit of progenitor cell treatment on LV function and infarct size.[27] This analysis included

10 controlled trials with a total of 698 patients. Results for the primary endpoint, change in LVEF, showed a statistically significant greater improvement of 3.0% (95% CI 1.9 to 4.1%, p<0.00001) for the progenitor cell group. There was also a statistically significant greater improvement in infarct size for the progenitor cell group with an incremental improvement of -5.6% over the control group (95% CI -8.7 to -2.5, p<0.001).

A 2008 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment systematically reviewed RCTs of progenitor cell therapy versus standard medical care for treatment of either acute or chronic myocardial ischemia.[28] The TEC Assessment focused on the impact of progenitor cell therapy on clinical outcomes, but also included data on physiologic outcomes such as change in LVEF. For acute ischemia, the TEC Assessment reviewed a total of 10 publications from six unique studies enrolling a total of 556 patients.[29-38] These trials had similar inclusion criteria, enrolling patients with acute ST-segment elevation MI treated successfully with percutaneous coronary intervention (PCI) and stenting, with evidence of residual myocardial dysfunction in the region of the acute infarct. Progenitor cell therapy was delivered via an additional PCI procedure within one week of the acute event.

The REPAIR-AMI trial was the largest trial in this review, and had the largest number of clinical outcomes reported.[31, 32] This was a double-blind trial that employed a sham placebo control infusion of the patients' own serum. This trial enrolled 204 patients with acute ST-segment elevation MI meeting strict inclusion criteria from 17 centers in Germany and Switzerland. At 12 months of follow-up, there were statistically significant decreases in the progenitor cell group for myocardial infarction (MI, 0 vs 6, p<0.03) and revascularization (22 vs 37, p<0.03) as well as for the composite outcome of death, MI, and revascularization (24 vs 42, p<0.009). The other trials had a very few number of clinical events, precluding meaningful analysis of clinical outcomes. The primary evidence from these other trials consists of physiologic outcomes measures such as change in LVEF and change in infarct size.

The primary endpoint in all six trials was change in LVEF. In each trial, there was a greater increase in the LVEF for the progenitor cell group compared with the control group. In four of the six studies, this difference reached statistical significance, while in two studies there was a nonsignificant increase in favor of the treatment group. The magnitude of the incremental improvement in LVEF was not large in most cases, with five of the six studies reporting an incremental change of 1.0% to 6.0%, and the final study reporting a larger incremental change of 18%.

At least four meta-analyses of BMC treatment for AMI were also found, each examining between six and 13 randomized, controlled trials, have been published since the 2008 TEC Assessment.[39-42] All four meta-analyses concluded that there was a modest improvement in LVEF for patients treated with progenitor cells. The mean estimated improvement in ejection fraction over control ranged from 2.9 to 6.1%. The studies also concluded that myocardial perfusion and/or infarct size was improved in the progenitor cell treatment group, although different outcome parameters were used. All four of the meta-analyses concluded that there were no demonstrable differences in clinical outcomes for patients treated with progenitor cells.

Gyöngyösi (2015) conducted an individual patient data meta-analysis of 12 RCTs (n=1,252) on autologous intracoronary cell therapy after AMI, including the REPAIR-AMI trial discussed above, using a collaborative, multinational database, ACCRUE (meta-Analysis of Cell-based CaRdiac study, NCT01098591).[43] All patients had STEMI treated with PCI. Mean (standard

deviation [SD]) baseline LVEF was approximately 46% (12%). Most studies used bone marrow mononuclear cells and administered cell therapies within two weeks after AMI. Median follow-up duration was six months. Eight trials had low risk of bias, and four single-blind (assessor) trials had medium-low risk of bias. Adjusted (for cardiovascular risk factors) random effects meta-analyses showed no effect of cell therapy on the primary end point, MACCE (major adverse cardiac and cerebrovascular events, a composite of all-cause death, AMI recurrence, coronary target vessel revascularization, and stroke) (186 events, 14.0% cell therapy vs 16.3% control, hazard ratio [HR], 0.86, 95% CI 0.63 to 1.18, I^2=0%); death (21 events, 1.4% cell therapy vs 2.1% control); or a composite of clinical hard end points (death, AMI recurrence, and stroke, 45 events; 2.9% cell therapy vs 4.7% control). Compared with controls, changes in LVEF (mean difference, 0.96%, 95% CI −0.2 to 2.1), end-diastolic volume (mean difference, 1.2 mL, 95% CI -3.4 to 5.8), or end-systolic volume (mean difference, 3.6 mL, 95% CI -3.4 to 4.1) were not observed. The study was limited by variation in the time from AMI to cell delivery (median, 6.5 days) and in imaging modality for assessing cardiac function (magnetic resonance imaging [MRI], single-proton emission computed tomography [SPECT], angiography, echocardiography).

Section Summary

Reported study outcomes have ranged from modest improvement to no improvement with cell therapy compared with placebo in patients with acute ischemia. The current evidence to date should be viewed as preliminary rather than definitive. Most studies reported secondary outcomes such as LVEF and revascularization; minimal data was included for the primary outcomes of recurrent MI or mortality rates. All of the trials had one or more methodologic limitations. The most common limitations were lack of double-blinding and failure to account for all randomized patients in the analysis. The REPAIR-AMI trial was the highest methodologic quality, and was double-blinded. However, this trial excluded 17 of 204 randomized patients from the analysis, and thus was not considered to meet the criteria for a high-quality trial. While the evidence for a beneficial impact on physiologic outcomes, particularly LVEF, is fairly strong, the magnitude of effect does not appear to be large. As a result, it is not certain whether the improvement in LVEF translates to meaningful improvements in clinical outcomes, but further adequately powered trials are still needed to prove the efficacy of this intervention.

CHRONIC ISCHEMIC HEART DISEASE (IHD)

Systematic Reviews and Technology Assessments

Fisher (2016)[44] published an update to a 2014 Cochrane review with meta-analysis of autologous stem-cell therapy for chronic ischemic heart disease and congestive heart failure.[45] The review included 38 RCTs (n=1,907). The overall quality of the evidence was considered low because selected studies were small (only three included >100 participants) and the number of events was low, leading to a risk of small-study bias and spuriously inflated effect sizes. Results of the 2016 Cochrane review are shown in Table 1. While reviewers were unable to detect evidence of publication bias using funnel plots, they noted that, of 28 identified ongoing trials, 11 trials with 787 participants were recorded as having been completed or were due to have been completed in advance of the search date, but had no publications. Therefore, publication bias cannot be ruled out. Similar results were reported in 2014 meta-analyses conducted by Xu (2014)[46] and by Xiao (2014)[47].

Table 1. Cochrane Review Results of Stem Cell Therapy for Chronic Ischemic Heart Disease[44]

Variables	Short-Term[a] Mortality	Long-Term[b] Mortality	Long-Term[b] Rehospitalization	Long-Term[b] MACE	Short-Term[a] NYHA Classification	Short-Term[a] LVEF (%)[c]
N	1,637	1,010	495	201	658	352
PE (95% CI), p value	0.48 (0.26 to 0.87), 0.02	0.68 (0.25 to 0.58), <0.001	0.62 (0.36 to 1.04), 0.07	0.68 (0.41 to 1.12), 0.13	-0.42 (-0.84 to -0.00), 0.05	3.01 (-0.05 to 6.07), 0.054
I^2 (p)	0% (0.76)	0% (0.97)	0% (0.70)	0% (0.80)	97% (<0.001)	59% (0.01)

CI: confidence interval

Fisher (2016) also reported on the results of a sequential trial analysis using cumulative data obtained from two previous Cochrane reviews with updated results to March 2015.[48] The intent of their analysis was to obtain estimates of sample sizes required for a meta-analysis to detect a significant treatment effect while controlling for random errors due to repeat testing. Twenty-two trials that included all-cause mortality were selected. Six trials reported no deaths, while the remaining 16 trials reported 25 (5.6%) deaths in 444 patients who received progenitor 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).

The 2008 TEC Assessment, described above, included a total of six trials randomizing 231 patients for treatment of chronic ischemic heart disease. Three of these trials randomized a total of 125 patients to progenitor cell therapy versus standard medical care.[49-51] The other three trials randomized a total of 106 patients undergoing coronary artery bypass grafting (CABG) to CABG plus progenitor cell treatment versus CABG alone.[52-54] Four trials employed bone-marrow-derived progenitor cells as the donor cell source, one trial used circulating progenitor cells (CPC), and the final trial included both a CPC treatment group and a bone-marrow-derived treatment group.[49] The primary physiologic measurement reported in these trials was change in LVEF. In all six trials there was a greater improvement in LVEF for the treatment group compared with the control group, and in four of six trials, this difference reached statistical significance. For the three trials of progenitor cell treatment versus standard medical care, the range of incremental improvement in LVEF was 2.7% to 6.0%. For the trials of progenitor cell treatment plus CABG versus CABG alone, the range of improvement in LVEF was 2.5% to 10.1%. Only one trial reported comparative analysis of data on the change in size of ischemic myocardium. This trial reported that there was no difference in size of ischemic myocardium between treatment groups.[53]

There are limited data from this group of studies on clinical outcomes, with only two studies reporting any clinical outcomes.[49, 54] Both trials reported on change in New York Heart Association (NYHA) class between groups. Assmus also reported an improvement in mean NYHA class of 0.25 (0 to 4 scale) for the bone-marrow treatment group and an improvement of 0.23 for the CPC group, compared with a worsening of 0.18 for the standard medical therapy group (p<0.01).[49] Adverse cardiac events were reported to be extremely small in number with no differences between groups. Patel reported a greater improvement in mean NYHA class for patients in the CABG plus progenitor cell group compared to CABG alone (2.7 vs 0.7, p value not reported), but no statistical testing for this outcome was reported.[54]

Recent systematic reviews of smaller size have been published that include several new RCTs.[55-57] Xu (2014)[46] published a meta-analysis of 19 RCTs (n=886) using similar study

inclusion criteria to the Cochrane review with additional RCTs. Statistically significant improvement of LVEF was detected, as was a significant decrease in all-cause death (RR= 0.49, 95% CI 0.29 to 0.84, p=0.01). Xiao (2014) [47] included 20 RCTs that assessed stem cell therapy safety and efficacy in two subgroups of CIHD patients: those with revascularization and without revascularization. Bone marrow cell (BMC) transplantation significantly improved LVEF in patients both with and without revascularization, and patients without revascularization also had other measures of cardiac function significantly improve after BMC transplantation. In both studies the increases in cardiac function, although statistically significant, are too low to be considered clinically relevant. Both studies concluded that additional research in larger studies are required to confirm the efficacy of efficacy of BMC transplantation in CIHD patients.

Randomized Controlled Trials

Bolli (2021) conducted a phase 2, double-blind, placebo-controlled RCT (CONCERT-HF) on behalf of the Cardiovascular Cell Therapy Research Network with funding from the National Heart, Lung, and Blood Institute.[58] This multicenter trial included 125 patients with ischemic heart failure and ejection fraction ≤40% and on guideline-directed therapy. Most patients were NYHA class II. At baseline, the mean age was about 62 years, mean LVEF was 28.6%, about 90% of patients were White, about 8% of patients were Black, and about 16% of patients were Hispanic. Patients were randomized to one of four treatment groups: autologous bone marrow-derived mesenchymal stromal cells, c-kit positive cardiac cells, a combination of both cell types, or placebo, all given by transendocardial injection. After 12 months, heart failure-related major adverse cardiac events (MACE) occurred in 24.1%, 6.5%, 9.1%, and 28.1% of patients who received mesenchymal stem cells, cardiac cells, combination cell therapy, and placebo, respectively (p=0.049). Other clinical event outcomes, including heart failure hospitalization, heart failure exacerbation, death, stroke, MI, and coronary artery revascularization, did not differ between groups. Quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire was improved at 12 months with combination cell therapy versus placebo (p=0.02); other secondary outcomes did not differ between groups at 12 months. The clinical applicability of this trial is limited by a small sample size and limited power to detect differences in clinical outcomes.

Bartunek (2017) reported on the results of a well-conducted double-blind trial in which 271 patients with NYHA class II or greater symptomatic heart failure (LVEF ≤35%) were randomized to bone marrow−derived mesenchymal cardiopoietic cells (n=120) or sham (n=151).[59] The primary outcome was Finkelstein–Schoenfeld hierarchical composite (all-cause mortality, worsening heart failure, Minnesota Living with Heart Failure Questionnaire score, six-minute walk distance, left ventricular end-systolic volume, and ejection fraction) at 39 weeks. Sixteen patients who died and three who withdrew consent after randomization were not included in analysis. In addition, 19 patients whose cell product did not meet release criteria were excluded from analysis in the cardiopoietic cell group. The probability that the treatment group had a better outcome on the composite primary outcome 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 patients, with baseline left ventricular end-diastolic volumes of 200 to 370 mL (60% of patients) (0.61, 95% CI 0.52 to 0.70, p=0.015). There was no statistical difference in serious adverse events between treatment arms. One (0.9%) cardiopoietic cell patient and nine (5.4%) sham patients experienced aborted or sudden cardiac death.

Pokushalov (2010) reported on the results of an RCT of intramyocardial injections of autologous bone marrow mononuclear cells (n=55) compared with optimal medical management (n=54) in patients who had chronic, ischemic heart failure.[60] The trial appears to have been conducted in Russia; dates of study conduct were not reported. Power calculations were not reported, and it is not clear if the trial was registered. Comparative treatment effects were not calculated for many outcomes. The RCT reported statistically significantly improvements in mortality rates at 12 months for cell therapy (11%) vs medical therapy (39%) favoring medical therapy (p<0.001)

Nonrandomized Studies

The STAR-Heart trial evaluated stem cell therapy for chronic heart failure due to ischemic cardiomyopathy. This nonrandomized open-label study, reported by Strauer (2010), evaluated 391 patients with chronic heart failure.[61] 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 five 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 trial was limited by the potential for selection bias (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

For chronic ischemic heart disease, too few primary clinical outcome events (e.g., mortality rates) have been reported across studies to permit meaningful analysis. Other clinical outcomes such as NYHA class are confined to very small numbers of patients and lack sufficient methodologic rigor to permit conclusions. One well-conducted, phase 3 trial failed to demonstrate superiority for cell therapy for the primary outcome that included death, worsening heart failure, and other multiple events. 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. 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.

REFRACTORY ANGINA

Stem-cell therapy is also being investigated in patients with intractable angina who are not candidates for evascularization.

Systematic Reviews

A meta-analysis by Khan (2016) included six RCTs studying cell-based therapy in patients with refractory angina.[62] The pooled outcomes of these trials were indices of angina (anginal episodes, Canadian Cardiovascular Society angina class, exercise tolerance, and antianginal medications, myocardial perfusion, and clinical endpoints. The authors created a composite end point, major adverse cardiac events, by combining myocardial infarction, cardiac-related hospitalization, and mortality. The analysis indicated that cell therapy led to improvements in many outcomes, compared with placebo, including anginal episodes (mean difference [MD] -7.81, 95% CI -15.22 to -0.41) Canadian Cardiovascular Society class (MD, -0.58, 95% CI -1.00 to -0.16), use of antianginal medications (standardized MD, -0.59, 95% CI -1.03 to -0.14), myocardial perfusion (standardized MD, -0.49, 95% CI -0.76 to -0.21), exercise tolerance (standardized MD, 0.331, 95% CI 0.08 to 0.55), risk of major adverse cardiac events (odds ratio, 0.49, 95% CI 0.25 to 0.98), and arrhythmias (odds ratio, 0.25, 95% CI 0.06 to 0.98). The authors suggest that these results require confirmation in larger, phase III RCTs.

The 2014 Cochrane review, described above, reported six studies that included patients with intractable or refractory angina.[45] Five studies measured angina frequency. Combined data showed a significant difference (p=0.0002) in the short-term (<12 months follow-up) in favor of the stem cell groups compared to standard treatment without stem cells. The impact of stem cell therapy on mortality in patients with intractable/refractory angina is unclear because participants included in the meta-analysis also had varying severity of IHD and heart failure. The authors ranked the level of evidence for this indication to be low quality and recommended further study in larger clinical trials to confirm present findings.

Li (2013) published a meta-analysis that included five RCTs (n=381) for stem cell therapy in patients with refractory angina.[63] Compared with controls, patients who received stem cells had a significant improvement in exercise tolerance (p=0.005), reduction in angina frequency (p=0.02), and lower risk of MI (p=0.04). No difference was found for risk of death (p=0.13). The authors concluded that the currently available findings require confirmation in larger studies with long-term follow-up.

Randomized Controlled Trials

Povsic (2016) reported on the industry-sponsored Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells (RENEW) trial.[64] This three-arm multicenter trial compared outcomes from the intramyocardial administration of autologous CD34-positive cells using exercise capacity at 3, 6, or 12 months. Patients underwent cell mobilization with G-CSF for four days followed by apheresis. The peripheral cell product was shipped to a central processing facility (Progenitor Cell Therapy) for selection of CD34-positivecells. The trial 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 trial was not adequately powered to detect a between-group difference.

Section Summary

Evidence on stem cell therapy for refractory angina includes early-phase trials, as well as a phase 3 pivotal rial 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.

TREATMENT WITH GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF)

Systematic Review

Moazzami (2013) published a Cochrane reiew of G-CSF for AMI.[65] Literature was searched in November 2010, and seven small, placebo-controlled RCTs (n=354) were included. Overall risk of bias was considered low. All-cause mortality did not differ between groups (RR 0.6, 95% CI 0.2 to 2.8, p=0.55, I^2=0%). Similarly, change in LVEF, LV end systolic volume, and LV end diastolic volume did not differ between groups. Evidence was insufficient to draw conclusions about the safety of the procedure. The study indicated a lack of evidence for benefit of G-CSF therapy in patients with AMI.

Randomized Controlled Trials

The following RCTs were published after the 2013 Cochrane summarized above:

Brenner (2016) evaluated G-CSF and Sitagliptin compared with placebo in 174 patients with AMI who had successful revascularization.[66] Both diabetic and nondiabetic patients were included. The primary endpoint of the trial was the hierarchically combined global left and right ventricular ejection fraction changes from baseline to six months follow-up, determined by MRI. There were no significant differences between groups for this endpoint, and they had a similar risk of major cardiac adverse events.

Achilli (2010, 2014) published six-month[67] and three-year[68] results of their multicenter, placebo-controlled RCT, STEM-AMI. Sixty consecutive patients with first anterior STEMI, who underwent primary PCI within 12 hours after symptom onset and had LVEF of 45% or less were enrolled. Patients were randomized 1:1 to G-CSF 5 mg/kg body weight or placebo. Standard STEMI care was provided to all patients. Among cardiac MRI outcomes (LVEF, LV end systolic volume, LV end diastolic volume) at six months and three years, only LV end diastolic volume at three years was statistically significantly improved in the G-CSF group compared with placebo. At three years, there was no statistical difference in clinical outcomes, including death, reinfarction, target vessel restenosis or revascularization, heart failure, and stroke. The study was likely underpowered to detect statistically significant differences in most of these parameters.

Hibbert (2014) randomized 86 patients with LVEF less than 45% after anterior-wall MI to receive either G-CSF or placebo.[69] Eighty patients completed six-month follow-up. While both groups had improved LV function, the improvement was lower in the G-CSF group than in the placebo group. Similar rates in both groups were reported for target vessel revascularization. Both groups had one or more major adverse cardiac events in eight (19%) patients. The authors cautioned that careful monitoring for safety is warranted in future studies of G-CSF in this population.

Section Summary

The small number of trials that use G-CSF as a treatment for acute ischemia generally did not report an improvement in physiologic or clinical outcomes. The 2013 Cochrane review of seven placebo-controlled trials reported a lack of evidence for benefit. This evidence is not supportive of the use of G-CSF in the treatment of acute ischemia.

PRACTICE GUIDELINE SUMMARY

There are no clinical practice guidelines that address the use of progenitor cell therapy for the treatment of damaged myocardium due to ischemia.

SUMMARY

There is not enough research to determine whether progenitor cell therapy can improve health outcomes for patients with ischemic heart disease. No clinical guidelines based on research recommend progenitor cell therapy for patients with ischemic heart disease. Therefore, progenitor cell therapy is considered investigational for the treatment of ischemic heart disease.

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CODES

NOTE: There are no specific codes for this procedure, either describing the laboratory component of processing the harvested autologous cells or for the implantation procedure. In

some situations, the implantation may be an added component of a scheduled coronary artery bypass graft (CABG); in other situations, the implantation may be performed as a unique indication for a cardiac catheterization procedure.

Codes	Number	Description
CPT	33999	Unlisted procedure, cardiac surgery
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
	38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPCS	None	

Date of Origin: *August 2004*