Meta-Analysis of Cell Therapy Studies in Heart Failure and Acute Myocardial Infarction

Mariann Gyöngyösi, Paul M. Haller, Derek J. Blake, Enca Martin Rendon

Abstract: **Heart failure (HF) is one of the leading causes of death worldwide and has reached epidemic proportions in most industrialized nations. Despite major improvements in the treatment and management of the disease, the prognosis for patients with HF remains poor with approximately only half of patients surviving for 5 years or longer after diagnosis. The poor prognosis of HF patients is in part because of irreparable damage to cardiac tissue and concomitant maladaptive changes associated with the disease. Cell-based therapies may have the potential to transform the treatment and prognosis of HF through regeneration or repair of damaged cardiac tissue. Accordingly, numerous phase I and II randomized clinical trials have tested the clinical benefits of cell transplant, mostly autologous bone marrow–derived mononuclear cells, in patients with HF, ischemic heart disease, and acute myocardial infarction. Although many of these trials were relatively small, meta-analyses of cell-based therapies have attempted to apply rigorous statistical methodology to assess the potential clinical benefits of the intervention. As a prelude to larger phase III trials, meta-analyses, therefore, remain the obvious means of evaluating the available clinical evidence. Here, we review the different meta-analyses of randomized clinical trials that evaluate the safety and potential beneficial effect of cell therapies in HF and acute myocardial infarction spanning nearly 2 decades since the first pioneering trials were conducted. (*Circ Res*. 2018;123:301-308. DOI: 10.1161/CIRCRESAHA.117.311302.)**

Key Words: cell transplantation ■ heart failure ■ meta-analysis ■ myocardial infarction ■ randomized controlled trials

Cardiovascular disease, of which ischemic heart disease (IHD) is a major component, is the leading cause of mortality accounting for approximately one third of deaths worldwide.[1] Although the death rate associated with IHD has gradually declined over the past 50 years, the incidence and prevalence of heart failure (HF) is on the increase and has become almost a pandemic. Paradoxically, the Centers for Disease Control and Prevention have recently reported an increase in the age-adjusted rate for HF-related mortality.[2] The majority of treatment options in HF are palliative or aimed at slowing down disease progression (eg, the prevention of cardiomyocyte loss or treatment of symptoms). In parallel to the increased incidence of HF, the use of new therapies, such as coronary interventions and resynchronization therapy, and the implantation of ventricular assist devices have also risen. As a consequence, hospitalization attributable to HF has become more frequent, imposing a real economic burden on healthcare providers across the world. Therefore, there is an unmet clinical need to improve heart performance of patients who suffer IHD and HF and restore heart function.

Unlike many other tissues, heart muscle has a limited capacity to adequately repair itself after injury leading to progressive maladaptive remodelling and left ventricular dysfunction. Given the limited propensity for the heart to repair itself after injury, numerous strategies to repair or regenerate the damaged tissue have been proposed and tested in preclinical models and small- to medium-sized phase I and phase II clinical trials.[3,4] One of the most promising strategies to repair or regenerate the damaged myocardium involves the use of cell-based therapies. Although several different experimental cell types have been tested in preclinical (animal) models and small-scale clinical trials, the most commonly used cells are bone marrow–derived stem cells (BMSCs)/bone marrow–derived progenitor cells or bone marrow mononuclear cells (BMMNCs), derived from the patient's own bone marrow and are, therefore, an autologous cell transplant. Bone marrow is a heterogeneous tissue containing multiple cell populations of which ≈1% are stem/progenitor cell populations of hematopoietic origin, multipotent mesenchymal stromal cells (MSCs), and endothelial progenitors.

From the Department of Cardiology, Medical University of Vienna, Austria (M.G., P.M.H.); Ludwig Boltzmann Cluster for Cardiovascular Research, Vienna, Austria (P.M.H.); 3rd Department of Medicine, Cardiology and Intensive Care Medicine, Chest Pain Unit, Wilhelminenhospital, Vienna, Austria (P.M.H.); Division of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, United Kingdom (D.J.B.); and Nuffield Division of Clinical Laboratory Sciences, Radcliffe Department of Medicine, University of Oxford, United Kingdom (E.M.R.).

Correspondence to Derek J. Blake, DPhil, Division of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, School of Medicine, Cardiff University, Hadyn Ellis Bldg, Maindy Rd, Cathays Cardiff, CF24 4HQ, United Kingdom, E-mail blakedj@cardiff.ac.uk; or Enca Martin Rendon, PhD, Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, United Kingdom, E-mail encamartinrendon@gmail.com

Circulation Research **is available at http://circres.ahajournals.org** **DOI: 10.1161/CIRCRESAHA.117.311302**

Nonstandard Abbreviations and Acronyms

ACCRUE	Meta-Analysis of Cell-based CaRdiac studies
AMI	acute myocardial infarction
BMMNCs	bone marrow mononuclear cells
BMSCs	bone marrow stem cells
G-CSF	granulocyte-colony stimulating factor
HF	heart failure
IHD	ischemic heart disease
IPD	individual patient data
LV	left ventricle
LVEF	left ventricular ejection fraction
MSCs	mesenchymal stromal cells
RCTs	randomized controlled trials
TSA	trials sequential analysis

Unfractionated BMMNCs have been extensively used in clinical trials with the aim of repairing damaged heart tissue. Enriched populations of BMSCs or bone marrow–derived progenitor cells can be isolated from BMMNCs using antibodies against different cell surface antigens, such as CD34 and CD133, through adaption to culture or by mobilization into the peripheral blood stream after stimulation with cytokines, such as G-CSF (granulocyte-colony stimulating factor). In addition to BMSCs, other cell types such as skeletal myoblasts, adipose tissue–derived stem/progenitor cells, endothelial progenitors, and cardiac progenitor cells have been tested in animal models and small clinical trials.[3]

All randomized control trials (RCTs) included in the meta-analyses described herein include a control arm(s) for each of the constituent trials. The control arm or placebo for many RCTs is often heterogeneous (no cells, unconditioned media or vehicle, mock injection, etc). Arguably, the most appropriate control for these studies is to use irradiated bone marrow stem cells that are unable to replicate. Although not included in the meta-analyses described herein, Wollert et al[5] have recently published a RCT for myocardial infarction where γ-irradiated stems cells were included in one of the control arms of the trial. Importantly, this trial found that BMSC therapy had no significant effect on left ventricular ejection fraction (LVEF) improvement in patients treated with viable bone marrow stem cells compared with the control population that received irradiated cells.

The focus of this review is on the meta-analyses of RCTs for cell therapy in HF and acute myocardial infarction (AMI) using ostensibly autologous BMSC transplants.

Meta-Analysis in Preclinical Models

Preclinical studies performed in animal models present a unique opportunity to conduct homogenous trials, for example, cell treatment in a prespecified time, similar animal strain and species, without confounding clinical factors. Recently, meta-analyses of a large number of preclinical studies of cell-based therapy in animal models of IHD have been published.[6–9] Frequently, clinical outcomes (eg, mortality) are not relevant in these studies, mostly because of the limited number of animals included in the studies and short follow-up times. However, efficacy parameters could be comparable to human clinical trials, especially in large animals where left ventricular (LV) function and trial outcomes are measured using similar imaging modalities (eg, magnetic resonance imaging). A meta-analysis of cell treatment studies in a mouse model of myocardial ischemia, including only studies using cardiac magnetic resonance imaging as a functional analytic method of LV performance (21 randomized studies with a total of 583 mice), resulted in a significant improvement in LVEF of 8.59% compared with the placebo-treated animals.[7] Likewise, 2 meta-analyses of 52 and 82 large animal trials (pooling data from 888 and 1415 animals, respectively) with iatrogenic IHD reported a 7.5% and 8.3% LVEF benefit of cell-based therapy in contrast to control animals.[6,8] Furthermore, a meta-analysis of cardiac progenitor cell (c-kit$^+$, Sca-1$^+$, cardiosphere and cardiosphere-derived cells) therapy studies in AMI (including 80 studies with 1970 rodents and large animals) reported a mean 10.7% LVEF increase in the cell-treated group compared with the control group.[9] Interestingly, cardiac progenitor cell therapy led to a significantly higher effect in rodents than in large animals (increase of LVEF of 11.7% and 5.2% in small and large animals, respectively). The increase in LVEF after cell transplantation in large animals closely relates to the 5% to 7% improvement in LVEF observed in human clinical trials.

Although Zwetsloot et al[9] found that the large animal studies were superior in quality to their small animal counterparts and showed less evidence of publication and attrition biases, the differences in LVEF improvement between large and small animal preclinical models are not fully understood. Although these unresolved differences may have a methodological or biological origin, it is noteworthy that the smaller effects on LVEF improvement in large animal studies are more closely reminiscent of the trial data derived from human subjects and as such may indicate that large animals are the more appropriate preclinical model for stem cell therapy for cardiac repair. To standardize animal studies, to avoid or reduce heterogeneity and to draw more meaningful conclusions, the National Heart, Lung and Blood Institute–sponsored CAESAR consortium (Consortium for Preclinical Assessment of Cardioprotective Therapies) and the Working Group on Cellular Biology of the Heart of the European Society of Cardiology have suggested that preclinical studies should also be performed as multicenter randomized blinded studies, similar to human clinical trials.[10,11]

Meta-Analyses of Cell Therapies in HF

Several small- or medium-sized phase I and II cell-based therapy studies have been conducted in HF patients. Currently, ≈2300 patients with ischemic HF or chronic IHD have been treated with different types of cells, mostly with autologous BMMNCs in 45 randomized trials. Other cell types, such as bone marrow–derived MSCs, adipose tissue MSCs, bone marrow and peripheral blood progenitor cells, cardiac progenitor cells (cardiospheres), or myoblasts, were also used. Patients with the characteristics of HF with reduced ejection fraction can mostly be characterized by postinfarction ischemic cardiomyopathy with severe coronary artery disease. Therefore, intramyocardial delivery of cell, either by surgical or percutaneous intervention, seems to be the preferred route of delivery for the intervention. This is in contrast to patients with recent AMI enrolled in cell therapy trials who received cell treatment by intracoronary delivery.

Because the average number of participants in trials is rarely over 50, most of the cell-based therapy studies in HF patients are statistically underpowered. Because of the technical challenges of these trials, namely, percutaneous or surgical intramyocardial cell delivery, patient enrollment in randomized trials is usually slow, commonly leading to premature study termination, and inconclusive trial results. Hence, systematic reviews and meta-analyses of cell-based regenerative therapies including larger numbers of patients are necessary to evaluate the clinical evidence of cell therapy interventions in this cohort of patients. Table 1 lists the characteristics and results of currently published meta-analyses that included randomized trials involving patients with signs of HF and aimed to assess the effect of cell therapy on LVEF.[12–24] All trials included in these meta-analyses used autologous cells, and no restriction was made with respect to the type of cells used. The summary table shows nonuniform patient populations, including also some studies with recent AMI or refractory angina. The majority of trials delivered the cells intramyocardially via percutaneous intervention, because surgical intramyocardial therapeutic cell delivery requires coronary artery bypass surgery and injection of the cells into the nonrevascularizable (hibernating) areas of the diseased myocardium. Furthermore, intracoronary cell infusion into selected arteries may not be sufficient in cases of multivessel or small vessel disease or occluded coronary arteries. Most of the meta-analyses reported significant changes in left ventricular parameters (Table 2), namely, LVEF, left ventricular end-diastolic volume, and left ventricular end-systolic volume. However, the clinical outcomes of these meta-analyses are inconclusive (Table 1) because only 5 of the 13 meta-analyses reported a significant reduction in the risk of mortality in favor of the cell treatment in HF patients.[19,21–24]

Apart from 2 meta-analyses (Cheng et al[18] and Fisher et al[24]), all studies reported a significant increase in LVEF in cell-treated patients compared with the control groups. These discrepancies are potentially explained by differences in statistical power related to the sample size in each study. Cheng et al included only 5 RCTs in their meta-analysis and could, therefore, be underpowered to detect statistically significant changes in LVEF. Conversely, the meta-analysis of Fisher et al included 1114 patients from 38 trials and would, therefore, have greater statistical power to detect an effect. It seems that with the inclusion of larger number of patients

Table 1. Meta-Analysis of Human Randomized Clinical Trials Including Patients With Ischemic Heart Failure Using Autologous Cells

HF Trials	No. of Studies	Patients Treated/ Controls	Patient Population	Mortality	Application (No. of Trials)	Conclusion
Brunskill et al[12]	21	565/526	AMI, CIHD	NR	IM surgical (4), IM perc.(1), IC (17)*	Only IM delivery was effective
Jiang et al[13]	18	490/490	AMI, CIHD	NS	IM surgical (2), IC (16)	Cell therapy was effective only in patients with AMI
Donndorf et al[14]	6	94/85	CIHD	NS	IM surgical (6)	Safe and effective
Zhao et al[15]	10	250/207	CIHD	NR	IM surgical (5), IC (6)*	Cell therapy was effective only with CABG but not with PCI
Wen et al[16]	13	378/280	IHD, HF	NR	IM surgical (4), IM perc. (6), IC (4)*	Cell therapy is more effective in patients with IHF
Kandala et al[17]	10	283/236	ICMP	NS	IM surgical (7), IC (4)*	Cell more effective with IM delivery
Cheng et al[18]	5	135/75	Ischemic HF	NS	IM surgical (1), IM or perc. (4)	6 min walking distance† NYHA decrease†
Fisher et al[19]	23	659/478	CIHD, HF	sig.	IM surgical (3), IM perc. (9), IC (12)*	NYHA class and rehospitalization sig.
Xiao et al[20]	20	453/322	CIHD	NS	IM surgical (8), IM perc.(8), IC (5)*	Route of delivery, baseline EF and type of cells influence significance
Xu et al[21]	19	440/309	CIHD	sig.	IM surgical (7), IM perc.(7), IC (6)*	Safe and effective
Tian et al[22]	11	272/220	CIHD	sig.	IM surgical (5), IM perc. (6)	More effective if revascularization was possible
Fisher et al[23]	31	626/895	HF	sig.	IM surgical (7), IM perc.(12), IC (12)	Sig. for rehospitalization
Fisher et al[24]	38	1114/793	CIHD, HF, refractory AP	sig.	IM surgical (7), IM perc. (17), IC (13)	Low quality of evidence

AMI indicates acute myocardial infarction; AP, angina pectoris; CABG, coronary artery bypass graft; CIHD, chronic ischemic heart disease; EF, ejection fraction; HF, heart failure; IC, intracoronary; ICMP, ischemic cardiomyopathy; IM, intramyocardial; NR, not reported; NS, not significant; NYHA, New York Heart Association; and perc., percutaneous.

*Including trials with more than one delivery route.

†Statistical significance between groups in subgroup analyses.

Table 2. Results of the Left Ventricular Function Parameters in Meta-Analyses Including Patients With Ischemic Heart Failure

HF Trials	Patient Population	LVEF Difference, %	LVESV Difference, mL	LVEDV Difference, mL
Brunskill et al[12]	CIHD	3.71*	NR	NR
Jiang et al[13]	AMI and CIHD	2.93*	−10.67*	8.61*
Donndorf et al[14]	CIHD	5.4*	NS	9.55
Zhao et al[15]	CIHD	4.59*	−0.36*	−0.38*
Wen et al[16]	IHD and HF	3.83*	−16.29	−13.76
Kandala et al[17]	ICMP	4.48*	−20.64*	−16.71*
Cheng et al[18]	Ischemic HF	0.11 (NS)	NR	NR
Fisher et al[19]	CIHD and HF	2.62*	−14.64*	NS
Xiao et al[20]	CIHD	3.05*–3.35*	−11.75*	−7.8*
Xu et al[21]	CIHD	3.54*	−8.96*	−0.75
Tian et al[22]	CIHD	4.91*	−10.66*	−7.82
Fisher et al[23]	HF	4.02–4.66*	NR	NR
Fisher et al[24]	CIHD, HF, refractory AP	3.01 (NS)	NR	NR

AMI indicates acute myocardial infarction; AP, angina pectoris; CIHD, chronic ischemic heart disease; HF, heart failure; ICMP, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NR, not reported; and NS, not significant.

*$P<0.05$.

in the meta-analysis, the observed treatment effect on LVEF regresses to a point where the changes are no longer significant. Importantly, this finding is also observed in the largest meta-analyses for AMI.[25,26] Although LVEF is one of the most commonly used surrogate and prognostic markers in HF and an outcome measure in cell therapy RCTs, differences in the techniques used to measure LVEF are a source of heterogeneity when evaluating different studies.[27] Furthermore, the physiological and clinical significance of the small percentage changes in LVEF reported in most cell therapy RCTs has yet to be established.

Based on several pitfalls of the publication-based meta-analyses, namely, the high heterogeneity of the trials, different follow-up times, doubled publications, and mixed patient population, an individual patient data (IPD)–based meta-analysis of HF cell-based therapy trials would be desirable, such as the ACCRUE (Meta-Analysis of Cell-based CaRdiac stUdiEs) study in AMI patients.[25]

Meta-Analysis of Cell Therapy Trials in Acute Myocardial Infarction

As is the case with HF and IHD, several small- or medium-sized phase I and II cell-based therapy RCTs have been undertaken in patients with AMI. Currently, ≈2700 patients have been included in meta-analyses of 41 RCTs of autologous cell therapy transplantation in AMI using predominantly BMSCs. It should be noted that many more AMI patients have been treated with cell therapies; however, many RCTs and prospective uncontrolled studies do not meet the selection criteria for meta-analyses and were, therefore, excluded from further analysis. Patients who suffered AMI underwent revascularization, mostly percutaneous coronary intervention, and received cell treatment after revascularization. Participants recruited to these trials presented LV dysfunction even after percutaneous coronary intervention, and, therefore, the rationale was that LVEF and LV volumes could be improved by cell transplantation. Therefore, changes in LVEF and LV volumes were the primary outcome of these trials. Cells were delivered mostly by infusion into the infarct-related coronary artery (intracoronary cell delivery).

Table 3 summarizes meta-analyses of bone marrow–derived cell therapies for AMI published in the past 11 years. The first meta-analysis of cell therapy trials for AMI published in 2006 that included 482 patients enrolled in 5 RCTs found a nominally significant (P=0.04) increase in LVEF between baseline and follow-up in the treatment group compared with controls but, more importantly, showed no difference in LVEF between treatment groups at follow-up, on average 5 months later.[28] By contrast, the first large-scale meta-analysis of cell therapy for AMI collating data on 811 patients from 13 RCTs found a modest improvement in LVEF (2.99%), and a significantly reduced left ventricular end-systolic volume by 4.74 mL and myocardial lesion area by (3.51%) in patients treated with BMSCs compared with controls (Table 3). Subgroup analysis revealed that there was a statistically significant difference in LVEF in favor of BMSCs when cells were infused within 7 days after AMI and when the BMSC dose administered was higher than 10^8 cells. However, patients in the control group also showed a greater increase in LVEF if they were included into the trial within 7 days post-AMI.[25] In addition, the authors reported anecdotal trends in favor of benefit for most clinical outcomes examined, although none were statistically significant.

Meta-analysis of further trials incorporating increasing numbers of patients and longer follow-ups has produced largely similar results (Table 3), although their conclusions have been equivocal. Broadly speaking, these studies have reported modest but significant changes in LV function allied

Table 3. Meta-Analyses of Human Randomized Clinical Trials for Patients With Acute Myocardial Infarction

AMI Trials	Sample Size (No. of Studies)	Follow-Up, mo	Mortality	LVEDV Changes, mL	LVESV Changes, mL	% Change in EF (by MRI)
Hristov et al[28]	482 (5)	4–6	NR	NR	NR	NR
Lipinski et al[49]	698 (10)	6	NS	–4.6	–7.4*	NR
Martin-Rendon et al[50]	811 (13)	3–6	NS	–2.47	–4.74*	NR
Zhang et al[51]	525 (6)	5	NR	–0.15	NR	NR
Zhang et al[52]	660 (7)	6	NS	–0.15	–0.25*	NR
Bai et al[53]	814 (10)	6	NR	NR	NR	NR
Kuswardhani and Soejitno[54]	906 (10)	4–60	NS	–3.08*	–5.52*	NR
Takagi and Umemoto[55]	877 (15)	NR	NR	–0.18*	–0.35*	nr
Clifford et al[29]	1765 (33)	<12	sig.	–3.52*	–4.47*	1.78*
Zimmet et al[30]	1830 (29)	3–6	NS	–3.39*	–3.51*	NR
Delewi et al[56]	1641 (16)	3–6	NR	NR	NR	0.16*
Chen et al[57]	510 (5)	NR	NR	–2.29	–4.47	NR
Jeong et al[58]	1072 (17)	3–6	NR	–3.46	–4.98*	NR
de Jong et al[59]	1513 (22)	6	NS	–2.8	–4.05*	0.13 (NS)
Liu et al[60]	262 (8)	6–24	sig.	0.69	–0.99	NR
Fisher et al[26]	2732 (41)	6–60	NS	NR	NR	1.05 (NS)
Gyöngyösi et al[25] (IPD)	1275 (12)	12	NS	1.2	0.4	NR
Cong et al[61]	1318 (17)	12	NS	–1.69	–3.92*	NR
Wang et al[35] (MSC)	449 (8)	1–24	NR	NR	NR	NR
Xu et al[31]	2307 (34)	3–61	NS	NR	NR	NR

AMI, acute myocardial infarction; EF, ejection fraction; HF, heart failure; IPD, individual patient data; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MSC, mesenchymal stem cells; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; and sig., significant.

*$P<0.05$.

with no improvement in mortality in patients treated with cell therapies compared with the placebo arm of the trial. Larger meta-analyses such as those reported by Clifford et al[29] and Zimmet et al[30] found significant changes in LV function and LVEF (1.78%, Clifford et al) measured using magnetic resonance imaging, commonly regarded as the reference method for estimating LV volumes and ejection fraction. Although the improvements in LVEF may be statistically significant, it is unlikely that these small changes are clinically relevant.

In addition to the clinical heterogeneity of these trials, early meta-analyses also observed statistical heterogeneity. Many of the larger meta-analyses in AMI have attempted to explain some of the heterogeneity associated with cell therapy for AMI and have included subgroup analyses to examine the effects of different variables on LV function and clinical outcomes. For example, Delewi et al found that intracoronary delivery of BMSCs led to a moderate improvement of LVEF and a reduction in recurrent AMI and readmission to hospital for HF, unstable angina, or chest pain. Similarly, patients receiving intracoronary BMSCs within a 3- to 7-day window post-AMI were found to have improved LVEF and decreasing end-systolic and end-diastolic volumes compared with patients treated within 24 hours or beyond 7 days after AMI, suggesting that transplant timing may be a relevant source of heterogeneity in some meta-analyses.[31] A recent meta-analysis focusing on cell therapy trials in both AMI and IHD collated data from 48 RCTs that enrolled a total of 2602 patients (n=1954 for AMI and n=648 for IHD) found that LVEF improved by 2.92% and reduced infarct size by 2.25%.[32] The authors also concluded that BMSC therapy improved clinical outcomes, including all-cause mortality and recurrent myocardial infarction, albeit with differences between AMI and coronary IHD diagnoses. For example, subgroup analysis found that although cell therapy did not reduce risk of mortality in AMI patients, there was a significant reduction in deaths among patients with IHD.

Another major source of heterogeneity in RCTs and therefore subsequent meta-analyses is associated with biological properties or phenotypes of the cell populations used for transplantation. As mentioned above, heterogeneous cell populations have been used in clinical trials including unfractionated BMMNC, enriched CD34-positive or CD133-positive hematopoietic progenitor cells, peripheral blood-derived progenitor cells, or bone marrow–derived MSCs. Data derived from the REPAIR-AMI trial (Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction) suggested that basal migratory capacity or SDF-1 (stromal cell-derived factor-1)–induced migratory capacity of BMSCs may be associated with a range of clinical outcomes.[33] Assmus et al found that the more migratory cells were associated with

improved survival free of cardiac, cardiovascular, and unknown death and rehospitalization. Robust phenotypic differences in the ability of cardiosphere-derived cells from IHD patients to support vessel formation have recently been reported.[34] These data suggest that not all patients may be suitable for autologous cell transplants. Although current meta-analyses and their associated RCTs have yet to consider the phenotypes of the transplanted cells, this is clearly one of the major sources of trial heterogeneity and may explain why certain patients may benefit from cell therapy while others do not.

In addition to BMSCs, a meta-analysis of cell therapies from AMI using MSCs has recently been published. Wang et al[35] (Table 3) analyzed data from 8 studies containing a total of 449 participants treated with MSCs derived from bone marrow, adipose tissue, and umbilical cord (allogenic) reporting no increase in LEVF in the treatment groups compared with controls. Subgroup analysis found that transplantation time, route of delivery, and cell dose may affect LVEF in AMI patients treated with MSCs. Specifically, the injection of no more than 10 million MSCs, via percutaneous coronary intervention, improved left ventricular systolic function when administered within a week of AMI.

Individual Patient Data and Trial Sequential Analysis

Before undertaking large-scale clinical trials (phase III), meta-analyses remain one the most widely used methods to evaluate the benefit of a given intervention. However, findings derived from trial meta-analyses can be misleading if pitfalls in study designs, risk of reporting bias, and variation across studies are not carefully considered.[36,37] To address some of the limitations and inherent biases associated with meta-analysis of RCTs, meta-analyses of IPD and trial sequential analysis (TSA) have recently been applied to AMI trials.[25,26,38] In addition to summary statistics derived from meta-analyses of multiple trials, similar analyses can be performed using IPD.[39] As its name suggests, IPD meta-analyses use prospective data derived from individual patients of all included studies removing the reliance on summary statistics for subsequent analyses. Thus, IPD-based meta-analyses contain transparent controlled data with unique definitions allowing data to be reanalyzed en masse. Although IPD meta-analyses can help reduce bias associated with data analysis and reporting compared with trial meta-analyses, they cannot avoid bias or pitfalls associated with trial design. The first IPD-based meta-analysis of cell therapy trials for AMI, ACCRUE (meta-Analysis of Cell-based CaRdiac stUdiEs), collated data from 12 RCTs containing 1252 individuals (767 receiving cell therapy and 485 controls; Table 3).[25] In agreement with the largest trials-based meta-analyses described above, the ACCRUE study found that intracoronary cell therapy for AMI had no apparent benefit on left ventricular function (including measurements of LV function made by magnetic resonance imaging) and clinical outcomes in the treated group compared with the untreated controls.

TSA has been used to resolve some of the inherent problems associated with trial meta-analysis such as insufficient statistical power.[40,41] TSA leverages cumulative data to effectively reduce type I and type II errors and can be used to estimate information size, similar to power calculations used in individual trials. Fisher et al[38] conducted a TSA on 41 AMI trials that included 2739 participants (Table 3). All trials administered bone marrow–derived cells (mononuclear cell, bone marrow–derived MSCs, hematopoietic progenitors, and circulating progenitor cells). An a priori threshold of relative risk reduction in mortality of 35% was established as similar figure was empirically associated to percutaneous coronary intervention in AMI.[42] In summary, cell therapies as currently tested in clinical trials do not seem to have a beneficial effect on clinical outcomes when administered to AMI patients.

Based on TSA for AMI, the required information size to detect an effect of 35% relative risk reduction in mortality in favor of cell treatment was estimated to be 4055 participants. Similarly, the required information size to detect a 35% relative risk reduction of rehospitalization was 3392 participants. However, in practice, many more patients will be required to detect smaller effect sizes. This study demonstrates that the current AMI RCTs and meta-analyses lack sufficient statistical power to detect clinically relevant outcomes explaining the inconsistent findings reported in different RCTs and their earlier meta-analyses that used shorter follow-up times.

Concluding Remarks

Most meta-analyses reviewed herein seem to agree that the potential beneficial effect of cell therapies for HF and AMI is still inconclusive and statistically underpowered. In AMI, trial meta-analyses (including TSA) and IPD-based meta-analysis have drawn similar conclusions, suggesting that cell-based therapies for AMI had no apparent clinical benefit. In addition, several recently published large RCTs that have yet to be included in meta-analyses, enrolling patients with ischemic HF and AMI, published neutral results regarding changes in LVEF between the cell-treated and control groups.[5,43–45] Furthermore, the recently published global position paper on cardiovascular regenerative medicine stated that, even if cell-based therapy in HF patients proved to be safe, the results are neither positive nor consistent.[46]

In addition to the concerns regarding statistical power, the quality of the evidence in meta-analyses is confounded by 2 major sources of variation: (1) pitfalls in trial design and (2) inconsistencies reporting and interpreting trial results. Therefore, there is a need for trial standardization and deep data sharing to improve reproducibility. To this end, the ACCRUE consortium and guidelines published by the International Committee of Medical Journal Editors recommend data sharing on publication of trial results (eg, sharing of the deidentified IPDs in a confidential form within 6 months of the publication).[47,48] These efforts will hopefully resolve the majority of the controversies in data interpretation and, therefore, will direct future clinical trials.

Sources of Funding

This work was generously funded by grants from Heart Research UK (E.M. Rendon, RG/2642/14/16) and the Medical Research Council (D.J. Blake, MR/L010305/1).

Disclosures

None.

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Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Meta-Analysis of Cell Therapy Studies in Heart Failure and Acute Myocardial Infarction

Mariann Gyöngyösi, Paul M. Haller, Derek J. Blake and Enca Martin Rendon

Circ Res. 2018;123:301-308
doi: 10.1161/CIRCRESAHA.117.311302
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7330. Online ISSN: 1524-4571