ISSN 1948-0210 (online)

World Journal of *Stem Cells*

World J Stem Cells 2017 April 26; 9(4): 68-76

Published by Baishideng Publishing Group Inc

WJSC World Journal of Stem Cells

Contents

Monthly Volume 9 Number 4 April 26, 2017

MINIREVIEWS

Contents

World Journal of Stem Cells
Volume 9 Number 4 April 26, 2017

NAME OF JOURNAL
World Journal of Stem Cells

ISSN
ISSN 1948-0210 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORIAL OFFICE
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World Journal of Stem Cells
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
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E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
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7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
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Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
April 26, 2017

World Journal of Stem Cells

Submit a Manuscript: http://www.f6publishing.com

World J Stem Cells 2017 April 26; 9(4): 68-76

DOI: 10.4252/wjsc.v9.i4.68

ISSN 1948-0210 (online)

MINIREVIEWS

Fifteen years of bone marrow mononuclear cell therapy in acute myocardial infarction

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Author contributions: Both authors equally contributed to the conception of the paper, the literature review and analysis, drafting and to critically revising and editing the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article. No financial support.

Manuscript source: Invited manuscript

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Received: January 6, 2017
Peer-review started: January 10, 2017
First decision: February 17, 2017
Revised: March 16, 2017
Accepted: April 18, 2017
Article in press: April 19, 2017
Published online: April 26, 2017

Abstract

In spite of modern treatment, acute myocardial infarction (AMI) still carries significant morbidity and mortality worldwide. Even though standard of care therapy improves symptoms and also long-term prognosis of patients with AMI, it does not solve the critical issue, specifically the permanent damage of cardiomyocytes. As a result, a complex process occurs, namely cardiac remodeling, which leads to alterations in cardiac size, shape and function. This is what has driven the quest for unconventional therapeutic strategies aiming to regenerate the injured cardiac and vascular tissue. One of the latest breakthroughs in this regard is stem cell (SC) therapy. Based on favorable data obtained in experimental studies, therapeutic effectiveness of this innovative therapy has been investigated in clinical settings. Of various cell types used in the clinic, autologous bone marrow derived SCs were the first used to treat an AMI patient, 15 years ago. Since then, we have witnessed an increasing body of data as regards this cutting-edge therapy. Although feasibility and safety of SC transplant have been clearly proved, it's efficacy is still under dispute. Conducted studies and meta-analysis reported conflicting results, but there is hope for conclusive answer to be provided by the largest ongoing trial designed to demonstrate whether this treatment saves lives. In the meantime, strategies to enhance the SCs regenerative potential have been applied and/or suggested, position papers and recommendations have been published. But what have we learned so far and how can we properly use the knowledge gained? This review will analytically discuss each of the above topics, summarizing the current state of knowledge in the field.

Key words: Bone marrow stem cells; Acute myocardial infarction; Cell therapy; Cardiac regeneration; Remodeling

Core tip: Since the first successful bone marrow stem cells transplantation performed 15 years ago in a patient with acute myocardial infarction, we have witnessed a mounting body of data as regards this cutting-edge therapy. During the reporting period, conflicting results have been stated, scientific papers have been under investigation, strategies

to enhance the stem cells regenerative potential have been applied and/or suggested, position papers and recommendations have been published. This review will analytically discuss each of the above topics, summarizing the current state of knowledge in the field.

Micheu MM, Dorobantu M. Fifteen years of bone marrow mononuclear cell therapy in acute myocardial infarction. *World J Stem Cells* 2017; 9(4): 68-76 Available from: URL: http://www.wjgnet.com/1948-0210/full/v9/i4/68.htm DOI: http://dx.doi.org/10.4252/wjsc.v9.i4.68

INTRODUCTION

The optimal management of acute myocardial infarction (AMI) still remains elusive, although it represents an illness with one of the highest morbi-mortality and one of the highest healthcare costs worldwide. The quick and efficient restoring of myocardial blood flow is the most appropriate strategy for reducing the size of the infarcted area. Even though standard-of-care therapy diminishes the area at risk to become necrotic, cardiac remodeling may occur in up to 60% of patients having suffered an AMI[1-3]. The conventional available treatments (whether pharmacological, interventional or surgical)[4] do not address the crucial issue of cell loss, thus being unable to completely prevent or reverse this pathological process which eventually leads to changes in size, shape, structure and function of the entire heart. One of the latest breakthroughs in this regard is stem cell (SC) therapy. By providing a potential source of new cells, heart function may be enhanced. Ideally, this process allows the replacement of non-functional cardiomyocytes and scar tissue with new fully functional contracting cells, as well as new blood vessels. Furthermore, transplanted SCs may secrete a variety of growth factors and cytokines, thereby enhancing myocyte survival and facilitating the migration of remote and/or resident cardiac SCs to the site of injury.

One of the first SC types which have been tested in clinical settings is autologous bone marrow SC. Since the first successful bone marrow SCs transplantation performed 15 years ago in a 46-year-old patient with AMI, we have witnessed a mounting body of data related to this effervescent domain: Conflicting results have been reported, scientific papers have been under investigation, strategies to enhance the SCs regenerative potential have been applied and/or suggested, position papers and recommendations have been published. A time line chart of accomplishments performed during the last fifteen years is depicted in Figure 1. But what have we learned so far and how can we properly use the knowledge gained? This review will analytically discuss each of the above topics, summarizing the current state of knowledge in the field.

HALLMARK CLINICAL TRIALS

Bone marrow is a very heterogeneous compartment with multiple SC populations with putative cardiac regenerative potential (*e.g*., hematopoietic SCs, mesenchymal SCs, endothelial progenitor cells, *etc*.).

The regenerative potential of adult autologous SCs after AMI was assessed for the first time in 2001 by a German group[5]. They used unfractionated bone marrow mononuclear stem cells (BMMNCs), which contained both hematopoietic and nonhematopoietic cells, a protocol that was extensively used subsequently. After selective catheterization of the infarct-related artery, the BMMNCs suspension has been intracoronary injected. Ten weeks later, the infarct area had been notably reduced (from 24.6% to 15.7%); in addition, cardiac function had improved by 20%-30%. Accordingly, the authors concluded that intracoronary administration of human autologous adult BMMNCs is feasibly in clinical settings and that it can promote myocardial regeneration after transmural infarction.

The following years were characterized by a series of small Phase Ⅰ clinical trials whose primary achievement was demonstrating the feasibility and safety of this ground-breaking therapy[6-10].

Since most of these studies have been comprehensively discussed in previous reviews[11-14], we will briefly point out their main characteristics. What they have in common is the small number of patients enrolled (with or without a control group) and the assessment of left ventricular ejection fraction (LVEF) as a surrogate marker of cardiac function. Although not designed to evaluate the efficacy of the therapy, the early trials reported a beneficial effect on cardiac function as revealed by increased global or regional LVEF, reduced endsystolic LV volumes and enhanced perfusion within the infarcted area 4 to 6 mo after SC transplantation depending on study design.

The next logical step was the appearance of randomized clinical trials (RCT) designed to test whether this therapy works. A wide variety of RCT have been conducted in this regard, with number of patients ranging from 20[15,16] to 204[17], but not all studies successfully blinding the participants and/or caregivers[15,16]. Studies varied also in terms of baseline LVEF, as well as diagnostic tests and procedures used to evaluate cardiac volumes and function. The most utilized imagistic method was cardiac echocardiography followed by cardiac magnetic resonance (CMR) - the "gold" standard for noninvasively characterizing cardiac function and viability, while LV angiography and single-photon emission computed tomography (SPECT) being exploited less frequently. Noteworthy, the timing of cell delivery after AMI, the quantity and quality of transplanted cells, as well as cell handling varied greatly, so is no wonder why apparently similar studies had different results.

Some of the hallmark studies using unfractionated bone marrow mononuclear SCs were conducted more

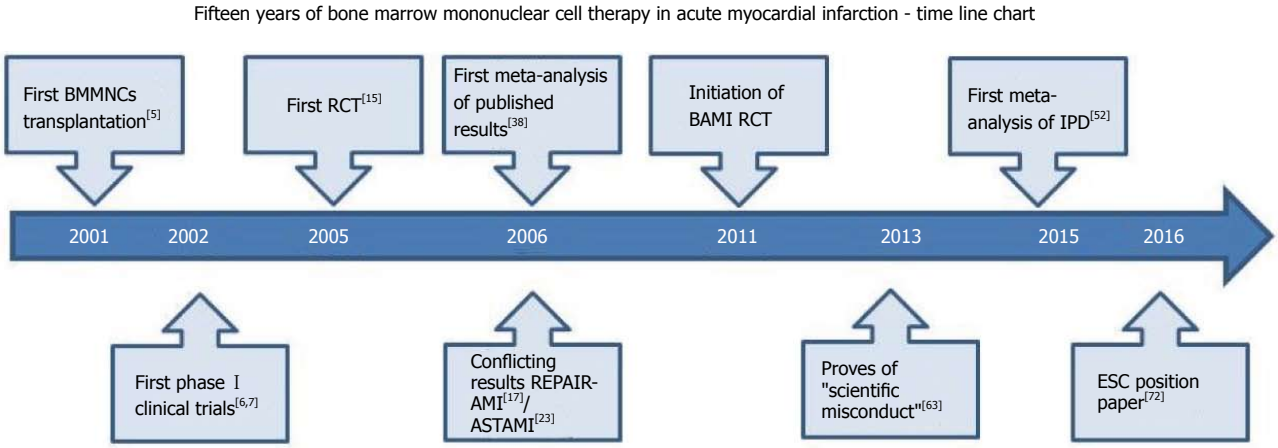

Figure 1 Fifteen years of bone marrow mononuclear cell therapy in acute myocardial infarction - time line chart. BMMNC: Bone marrow mononuclear stem cell; RCT: Randomized clinical trials; AMI: Acute myocardial infarction; IPD: Individual patient data.

than 10 years ago (Table 1). The BOOST study tested the usefulness of autologous BMMNCs intracoronary transfer 4.8 ± 1.3 d after AMI[10]. At baseline (n = 60), the two groups of patients were homogeneous in terms of LV volumes and function; 6 mo later, a mean global LVEF improvement of 6.7% in the cell therapy group and 0.7% in the control group (P value for between-group comparison = 0.0026) was documented, enhanced LV systolic function being predominantly witnessed in myocardial segments bordering the infarcted area.

Although significant augmentation of LV function after SCs transplant have been observed in the first months, this positive effect seems to be fading in time. Long-term benefit of SC therapy was assessed in BOOST surviving patients. Eighteen months after AMI (n = 59), there were no significant differences between groups as regards global LVEF (P = 0.27), although the speed to LVEF recovery was significantly higher in patients receiving SC transplant (P = 0.001)[18].

Moreover, 5 years after randomization (n = 56), statistical analysis of data revealed no difference between groups with reference to cardiac dimensions or function. Repetitive CMR examinations indicated an evident dilatation of LV volumes, whereas LV function decreased during 61 mo follow-up[19].

Reinfusion of enriched progenitor cells and infarct remodeling in acute myocardial infarction (REPAIR-AMI) - the largest study reported so far, also demonstrated the benefit of BMMNCs intracoronary infusion in patients with optimally treated AMI. From the 204 patients included, 103 were randomly assigned to placebo group and 101 to receive SC therapy. Both groups were well matched with respect to baseline characteristics, procedural characteristics of reperfusion therapy and associated pharmacological therapy during the study. Three to 7 d after successful stent implantation, cell suspension or placebo medium was injected in the infarct-related artery. Four months later, significant improvement in both global and regional LV function was documented in the cell treated group. Of note, the study led by Andreas Zeiher was the first trial to evaluate the interaction between the BMMNCs treatment effect and the timing of cell delivery. Subgroup analysis revealed superior recovery of contractile function when cell infusion was administered on day 5 or later after PCI, while earlier administration - within 4 d after reperfusion therapy - had only minimal effects as regards LVEF improvement. Furthermore, intracoronary administration of BMC abolished LV end-systolic volume enlargement after the infarction.

Even though REPAIR-AMI was not powered to detect significant differences in major adverse clinical events between the cell therapy and control group, a reduction in the combined outcome of death, recurrence of MI, or any revascularization procedure was noticed[17].

As opposed to BOOST trial - in which positive effects have faded in time, 2- and 5-year follow-up of REPAIR-AMI patients demonstrated a persistent reduction of the combined end point of death, recurrent MI and rehospitalization for heart failure in the BMMNCs group compared with placebo. In addition, 2 years after AMI, SC therapy was still associated with a significant improvement in regional left ventricular contractility of infarcted segments[20,21].

The significant and longstanding positive effects of SC therapy were further confirmed by a study conducted by Bodo-Eckehard Strauer's group: The BALANCE Study (Clinical benefit and long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with AMI) which randomized 124 patients to BMMNCs (62 patients) or control (62 patients) 7 ± 2 d after AMI[22]. The patients were followed-up at specific time intervals (*i.e.*, 3, 12, and 60 mo) by a variety of examinations (*e.g.*, coronary angiography, right heart catheterization, biplane left ventriculography, electrocardiogram at rest and exercise, echocardiography, late potential, heart rate variability and 24-h Holter electrocardiogram). The authors reported significant improvements as regards LV performance, quality of life and mortality in their 5-year data.

But there were also some studies (not few) that challenged these optimistic findings. In some cases, contradictory results of similar studies were revealed

Table 1 Hallmark clinical trials

Study name	Clinical trials (gov ID)	Principal investigator	No. of included patients
BOOST[10,18,19]	NCT00264316	Stefan Janssens	Treated (n = 30) Control (n = 30)
REPAIR-AMI[17,20,21]	NCT00279175	Andreas Zeiher	Treated (n = 101) Control (n = 103)
ASTAMI[23]	NCT00199823	Ketil Lunde	Treated (n = 50) Control (n = 50)
BALANCE[22]	-	Bodo-Eckehard Strauer	Treated (n = 62) Control (n = 62)
SWISS-AMI[24]	NCT00355186	Roberto Corti	Treated (n = 133) Control (n = 67)
TIME[25]	NCT00684021	Robert Simari	Treated (n = 79) Control (n = 41)
Late TIME[26]	NCT00684060	Robert Simari	Treated (n = 57) Control (n = 29)

simultaneously to the scientific community; this is the case of two well-known studies - REPAIR-AMI and ASTAMI respectively, which were published in the same issue of The *New England Journal of Medicine* in 2006[17,23]. As opposed to REPAIR-AMI, the trial conducted by the Norwegian group reported no changes in LVEF, LV volumes or infarct size assessed at 6 mo by SPECT, echocardiography and CMR in 97 patients treated with intracoronary BMMNCs *vs* placebo a median of 6 d post AMI.

The pile of negative findings expanded based on the results of 3 other studies - namely SWISS-AMI[24], TIME[25] and Late TIME[26] - thoroughly analyzed by Simari and colleagues in a paper on behalf of Cardiovascular Cell Therapy Research Network[27]. The Cardiovascular Cell Therapy Research Network (CCTRN) was intended to enable cell based therapies in the United States[28]; in this regard, CCTRN sponsored the TIME and LateTIME trials which aimed to evaluate the influence of BMMNCs delivery timing on LV function. The 3 studies mentioned above shared some similar characteristics, but differed in some other aspects. All were prospective, randomized, controlled trials designed to identify moderate to large placebo-adjusted LVEF improvements (from 3.5% to 5%) as assessed by CMR 4 or 6 mo after PCI. Cell dose and delivery were the same in each of the 3 studies - that was the intracoronary stop-flow technique described in the early 2000s[7], but cell handling varied: It was manual Ficoll processing in SWISS-AMI, while the investigators of the CCTRN studies went for automated Ficoll processing. The authors reported no benefit of intracoronary administration of BMMNCs related to LV function irrespective of the timing of delivery. But why apparently similar studies led to contradictory results? These conflicting outcomes have been debated - and to some extent explained - by a series of experts in the field[14,29,30].

A direct comparative analysis of methodology used in REPAIR-AMI[17] and ASTAMI[23] trials have revealed that seemingly minor changes in BMMNCs isolation and preservation protocols may have a major impact on functional activity of isolated cells, consequently affecting the clinical outcome. Seeger *et al*[29] collected bone marrow from healthy volunteers or patients with angiographically confirmed coronary artery disease. Equal aliquots from the same bone marrow aspirate were manipulated accordingly to either REPAIR-AMI (density gradient centrifugation using Ficoll, followed by overnight incubation in *ex-vivo* 10 medium + 20% autologous serum at room temperature), or ASTAMI (density gradient centrifugation using Lymphoprep, followed by overnight incubation in 0.9% NaCl + 20% heparin-plasma at 4 ℃) protocol. Obtained BMMNCs were subsequently tested for various parameters of phenotype and function, with quite divergent results. REPAIR-AMI isolation protocol generated a superior number of total BMMNCs, but also more haematopoietic and mesenchymal SCs as compared to ASTAMI. Furthermore, cells isolated and stored according to German study yielded better results in terms of proliferative capacity, ability to migrate to the chemoattractant SDF-1 and improvement in blood flow in a mouse model of hind-limb ischaemia.

Moreover, there is a substantial individual variability related to quantitative but also qualitative changes of adult bone marrow SCs with age, cardiovascular risk factors and associated comorbidities, decreasing the efficiency of cell therapy particularly in patients who need it the most[31-35]. Studies have shown that young age and a superior number of $CD34^+$ cells were independent predictors for treatment response to cell therapy, demonstrating the importance of patient's cell product[36,37].

Additionally, the natural history of AMI has an unpredictable course modulated by upregulation and downregulation of a wide array of cytokines, growth and inflammatory factors. In specific subgroups of patients this changeable biological milieu could blur and/or make it difficult to distinguish a cell-based specific efficacy signal.

Some other potentially incriminated factors associated to result variability could be related to different times

between AMI and SCs delivery or to variability methods for the assessment of ventricular function and perfusion (ventriculography, echo-cardiography, CMR, SPECT).

META-ANALYSIS

Because of low sample size and small effects, individual studies were underpowered to identify significant differences in major adverse clinical events between SC therapy and control group. Therefore, new approaches were needed. In hope of obtaining clear answers regarding the effectiveness of SC therapy, several meta-analysis were carried-out since 2006, but the controversies continued[13,36,38-52]. Extensive or less-extensive analysis were completed on different number of RCT (5-43) including different number of patients (482-2732 patients)[38,53,54]. Subgroup analysis were performed based on different parameters such as baseline LVEF, timing of SCs infusion from onset of AMI, the dose of BMMNCs infused and patients age. Although earlier meta-analysis reported that intracoronary BMMNCs infusion is associated with significant improvements of LV function and remodeling particularly in younger patients and patients with a more severely depressed LVEF at baseline[13,36,45], recent analysis revealed that intracoronary cell therapy provided only modest[53,54] or no benefit in terms of clinical events or changes in LV function[52].

But then, why such discrepancy even between meta-analysis reports? This was the theme of 2 very recent reviews published by well-known experts in the field[55,56]. As one would expect, the first variation factor to point the finger to is related to differences in the methodology used in conducting systematic reviews. All meta-analyses except the one reporting negative findings relied on published summary results from multiple trials, while the latter was based on individual patient data (IPD) collected directly from the researchers responsible for each study and further centrally re-analyzed. The 2 methodologies varied in data collection, data checking and data analysis. Although ACCRUE (Meta-Analysis of Cell-Based Cardiac Studies; NCT01098591) database comprised a pool of 1252 IPDs from 12 randomized studies in AMI settings, it included only about 60% of the available published trials, as a result raising concern for potential bias. Of course, there are some other disparity factors involved, such as insufficient power of included studies, patients' heterogeneity and statistical heterogeneity[55,56].

In view of presented data, one can only state that meta-analyses failed as well to clarify whether or not SC therapy improves heart function and/or mortality in AMI patients. What is more, meta-analyses are not surrogates for large phase Ⅲ RCTs. Consequently, the scientific community is eagerly waiting for the ongoing BAMI trial to provide a more conclusive answer as regards the efficacy of bone marrow cell therapy in AMI settings. BAMI (the Effect of Intracoronary Reinfusion of Bone Marrow-Derived Mononuclear Cells on All Cause Mortality in AMI; NCT01569178) is the largest and most aspiring trial to date, funded by the European Commission Seventh Framework Programme. It currently involves 19 partners planning to include 3000 patients from 10 European countries. The study aims to standardize methods of bone marrow cell collection, handling and delivery, as well as to test if the product and delivery method can lead to a 25% reduction in mortality.

PRESENT AND FUTURE STRATEGIES TO IMPROVE BONE MARROW SCS REGENERATIVE POTENTIAL

Since BMMNCs yielded only modest improvements regarding LV function recovery after AMI, selected bone marrow SCs populations have been tested in clinical settings. Trials involving $CD34^+/133^+$ progenitor cells[57-61] or mesenchymal stem cells (MSCs)[62-65] had encouraging results, but none of these tested cells haven't been clearly demonstrated to yield superior outcomes.

Of course, strategies to increase the number and potency of low-abundance progenitor cells in bone marrow cells (*e.g.*, MSCs, $CD34^+/CD133^+$ cells) are needed. While in animal models a variety of genetic and nongenetic approaches aiming to improve therapeutic efficacy of transplanted cells have been tested, there is still a long road till translation into clinical settings. Some of the genetic strategies include enhancement of survival, proliferation and differentation capacity, as well as boost of paracrine factors synthesis. Nongenetic procedures in essence comprise preconditioning with various factors (physical factors, drugs, cytokines and growth factors), 3D aggregate formation or hydrogel encapsulation and coculture with other types of SCs (*e.g.*, cardiac SCs)[66,67].

In addition, unlike in chronic ischemic disease, strategies to improve bone marrow SCs regenerative potential in acute settings are limited by the relatively short window of opportunity.

DRAWBACKS

Most important drawbacks and limitations of BMMNCs in AMI settings are related to reduced regenerative potential of transplanted cells; therefore, finding strategies to intensify their survival, proliferation and differentation potential is a perpetual quest. But aside from these methodological features discussed in previous chapter, we would like to bring your attention to another issue, namely scientific inaccuracy. Unfortunately, SC research has not been avoided by scandals related to "scientific misconduct" in the field. It is the case of studies conducted by the German scientist Bodo-Eckehard Strauer. His papers have been comprehensively analyzed by Francis *et al*[68] who identified and exposed a series of discrepancies and contradictions such as number of patients receiving cells, baseline EF comparability and cell preparation. Although none of Strauer's studies have been retracted, their results cannot be trusted any more. Nevertheless, we chose to include them in our review in order to provide the reader

with an accurate depiction of SC therapy development in AMI settings, since the German investigator conducted not only the pioneering research in this area, but also one of the largest and most promising trials in the field. Besides affecting the credibility of the researchers, these inconsistencies may negatively influence the patients' decision when considering enrollment in a SC-based clinical trial.

PERSPECTIVES AND RECOMMENDATIONS

Predicting who will benefit and who will not from SC therapy is not currently possible, although efforts are being made in this direction[37]. In the era of Precision Medicine Initiative[69,70], being able to discriminate responders from nonresponders could be the first step toward tailored cell therapy. Prediction models for responder identification based on individual's characteristics are mandatory, in order that every single patient gets optimal treatment according to his individual variations in genes, environment and lifestyle.

Investigators of future trials should carefully choose hard clinically meaningful end points not limited to one effect, but rather reflecting different categories of consequences, such as structural evaluations of the heart, cardiovascular physiological measurements, biomarkers (including transcriptomic-based biomarkers), functional capacity and quality of life[71].

The European Society of Cardiology Working Group Cellular Biology of the Heart has recently provided a series of recommendations on how to improve the therapeutic application of cell-based therapies for cardiac regeneration and repair[72]. Accordingly, upcoming studies should be designed to address precise hypotheses on delivery types and mechanisms of efficiency, rather than safety and efficacy endpoints only; comparison of different cell types, or a combination of cell types in RCTs should be completed; in-depth cell characterization - including cell function should be done in every clinical trial; also, strategies to boost both cellular and paracrine effects should be developed.

CONCLUSION

A substantial knowledge has been gained in the past 15 years since the first bone marrow SCs transplantation have been performed in a patient with AMI, but there are a lot of challenges to be faced until this therapy will gain a definitive place in clinical arena.

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P- Reviewer: Lee T, Li SC, Sanchez-Mendoza A, Shetty PH
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

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