

## EDITORIAL



## Cardiac Cell Therapy — Mixed Results from Mixed Cells

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Despite substantial advances in treatment, ischemic cardiac injury and the ventricular dysfunction it can provoke remain major causes of morbidity and mortality throughout the world. The endogenous regenerative capacity of the heart appears inadequate to repair injured myocardium, leading to the cumulative loss of cardiomyocytes over the lifetime of a patient. This may contribute to the prevalence of heart failure as a diagnosis at hospital admission — particularly among the elderly.

For these reasons, experiments in animals suggesting that the transfer of cells derived from bone marrow (BMC) could dramatically improve cardiac function after infarction through regeneration of the myocardium<sup>1</sup> or neovascularization<sup>2</sup> generated tremendous excitement. In addition, they stimulated clinical studies suggesting that this approach is feasible, safe, and potentially effective in humans.<sup>3,4</sup> In this issue of the *Journal*, Schächinger et al.,<sup>5</sup> Assmus et al.,<sup>6</sup> and Lunde et al.<sup>7</sup> — following authors of other recent reports<sup>8,9</sup> — provide a realistic perspective on this approach while leaving room for cautious optimism and underscoring the need for further study (Table 1).

In the largest study of cardiac cell therapy to date, Schächinger et al. report the results of the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial, a multicenter trial of the intracoronary infusion of BMC after successful percutaneous coronary intervention for acute myocardial infarction. At 4 months, the absolute improvement in left ventricular ejection fraction (LVEF), measured by angiography, was greater among patients treated with BMC than among those given placebo (5.5% vs. 3.0%,  $P=0.01$ ). Subgroup analysis suggested that the benefit was

greatest in patients with the worst LVEF at baseline. This double-blind and fully controlled trial provides the best evidence yet for beneficial effects of BMC after acute myocardial infarction. Enthusiasm is tempered somewhat by the modest size of the effect and by a recent report from the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) trial that the relative improvement in LVEF after infusion of BMC at 6 months, as compared with no infusion, was no longer significant at 18 months, suggesting that the main effect was an acceleration of recovery.<sup>9</sup>

It may be challenging to achieve significant improvements in LVEF in small cohorts of patients who have relatively preserved ventricular function and who are already receiving state-of-the-art therapy. Even some early trials of reperfusion in patients with acute myocardial infarction demonstrated either no improvement in LVEF<sup>10</sup> or a modest improvement.<sup>11</sup> Ultimately, the validation of cardiac cell therapy will require demonstration of benefit with regard to clinical outcomes — as was the case with reperfusion. Studies performed to date have not been designed or powered to evaluate clinical outcomes. Nevertheless, it is encouraging that the REPAIR-AMI investigators found the rate of adverse clinical events to be significantly lower at 1 year among patients receiving BMC than among those receiving placebo. Given the relatively small number of events, this result will require replication in larger cohorts. However, it reinforces the message that BMC infusion is not only feasible but also safe, and it raises the possibility that clinical benefits may exceed the modest improvement seen in ventricular function. Data on ventricular function at 1 year are not available.

**Table 1. Randomized, Controlled Trials of BMC for Cardiac Disease.\***

Trial or Investigator Group	Setting	Design	No. of Cells Administered in Treatment Group	Results
BOOST <sup>4,9</sup>	PCI after acute myocardial infarction	Randomized trial 30 patients received BMC; 30 received no infusion LVEF assessed by MRI	Approximately $2.5 \times 10^9$ unfractionated BMC	At 6 mo: LVEF 6% greater in BMC group than in control group At 18 mo: no significant difference in LVEF between the 2 groups
Janssens et al. <sup>8</sup>	PCI after acute myocardial infarction	Randomized, double-blind trial 33 patients received BMC; 34 received placebo infusion LVEF was assessed by MRI	Approximately $3 \times 10^8$ Ficoll-separated BMC	At 4 mo: no significant difference in overall LVEF; decreased infarct size and better regional function in BMC group
TOPCARE-CHD <sup>5</sup>	Chronic left ventricular dysfunction	Randomized, crossover trial In the second phase, 24 patients received CPC, 28 received BMC, 23 received no infusion LVEF assessed by left ventricular angiography	Approximately $2 \times 10^8$ Ficoll-separated BMC or approximately $2 \times 10^7$ Ficoll-separated, cultured CPC	At 3 mo: greater increase in LVEF (2.9 percentage points) in BMC group than in CPC group or control group
ASTAMI <sup>7</sup>	PCI after acute myocardial infarction	Randomized trial 47 patients received BMC; 50 received no infusion LVEF assessed by SPECT, echocardiography, and MRI	Approximately $7 \times 10^7$ Ficoll-separated BMC	At 6 mo: no significant difference in LVEF between the 2 groups
REPAIR-AMI <sup>5</sup>	PCI after acute myocardial infarction	Randomized, double-blind trial 101 patients received BMC; 98 received placebo infusion LVEF assessed by left ventricular angiography	Approximately $2.4 \times 10^8$ Ficoll-separated BMC	At 4 mo: greater absolute increase in LVEF in BMC group than in placebo group (5.5% vs. 3.0%) At 1 yr: reduction in combined adverse clinical events in BMC group as compared with placebo group

\* BOOST denotes Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration, PCI percutaneous coronary intervention, MRI magnetic resonance imaging, TOPCARE-CHD Transplantation of Progenitor Cells and Recovery of LV Function in Patients with Chronic Ischemic Heart Disease, CPC progenitor cells derived from circulating blood, ASTAMI Autologous Stem-Cell Transplantation in Acute Myocardial Infarction, SPECT single-photon-emission computed tomography, and REPAIR-AMI Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction.

In contrast, in the smaller Autologous Stem-Cell Transplantation in Acute Myocardial Infarction (ASTAMI) trial involving three noninvasive imaging methods, Lunde et al. did not find a significant improvement in LVEF at 6 months in the mononuclear BMC group, as compared with the control group. The study was powered to have an 80% chance of detecting a change of 5 percentage points in LVEF; thus, a smaller effect could have been missed. However, the change closest to achieving significance — the change in LVEF as measured by magnetic resonance imaging ( $P=0.054$ ) — actually favors the control group, arguing against this explanation. Technical differences in the characteristics or handling of the infused BMC might explain the different outcomes. Janssens et al. also did not detect an improvement in global ventricular function at 4 months in the BMC group as compared with the control group, although infarct size was re-

duced and regional wall motion was improved in the BMC group.<sup>8</sup> The identification of features of BMC preparations and of patients that are predictive of a favorable response should help to resolve these discrepancies and to focus future trials.

The Transplantation of Progenitor Cells and Recovery of LV Function in Patients with Chronic Ischemic Heart Disease (TOPCARE-CHD) trial by Assmus et al. evaluated the effects of BMC or progenitor cells derived from circulating blood (CPC) in patients with chronic ventricular dysfunction. In this randomized, crossover trial, the absolute change in LVEF was significantly greater among patients receiving BMC than among those receiving CPC. The groups received the other type of cell in the next phase of the trial, but the result was independent of the order in which the cells were given, suggesting that the BMC effect is somewhat specific. Which quanti-

tative or qualitative differences in the cell populations account for their different effects is currently unknown. Although the benefit observed after BMC infusion was modest (an increase in LVEF by 2.9 percentage points), it is remarkable that any benefit was seen in these patients, who were studied on average more than 6 years after infarction and who were already receiving optimal medical care. The TOPCARE-CHD trial suggests that BMC can have effects beyond simple acceleration of healing after infarction. Whether repeated infusions would yield additive benefits and whether these benefits would persist will be important questions for future trials.

Although the prospect of regeneration of cardiac tissue provided an initial stimulus for cell-based therapies,<sup>1</sup> subsequent work in animals has questioned the ability of BMC to effectively generate cardiomyocytes,<sup>12,13</sup> and clinical studies have suggested that only 1.3 to 2.6% of infused BMC are retained in the heart.<sup>14</sup> Functional benefits may also be mediated through paracrine secretion of growth factors or cytokines, which could indirectly promote survival of cardiomyocytes, mobilization of endogenous progenitor cells, or neovascularization.

Do these distinctions matter? As pointed out by others,<sup>15</sup> patients benefited from many established therapies — including aspirin — before we understood the underlying mechanisms. There is no doubt that the ultimate success or failure of cell therapy will rest on its ability to show clinical efficacy rather than on the imputed mechanism. However, the heterogeneous cell populations used make BMC infusion fundamentally different from most medical treatments. This complexity may help explain why apparently similar protocols can yield disparate results.<sup>5,7</sup> Identifying which — if any — of the cellular constituents is necessary for beneficial effects, and whether these effects are mediated directly by the transplanted cells or indirectly through involvement of other cells, would enable targeted delivery of essential components and is likely to be a critical step in the full realization of the potential of this therapeutic approach. Even aspirin might not be as effective if it were still being delivered as willow bark.

As articulated in the consensus statement of the task force of the European Society of Cardiology, the clinical need, feasibility, and safety of the treatment,<sup>15</sup> as well as the need to resolve

discrepant results, mandate additional clinical trials. However, as illustrated by recent randomized trials,<sup>4-9</sup> we should proceed in a manner that maximizes both the information gained and the safety of patients. Patients should be treated with cells only as part of randomized, controlled trials and only after they understand that neither the efficacy nor the long-term risks of this approach are established. Future trials should be powered to examine clinical end points and patients should be followed over the long term and for both beneficial and adverse effects. Simultaneously, we must continue to support basic and translational research that can help guide clinical investigation.

The enrollment of patients with a poor prognosis (i.e., large infarcts, poor left ventricular function) makes sense. They have the greatest need for therapeutic approaches and thus have the most favorable risk–benefit ratio. Demonstration of incremental benefit, as compared with conventional therapy, is easier in these populations, and subgroup analyses suggest that they are the most likely to benefit.<sup>5</sup> The enrollment of patients with heart failure who use left ventricular assist devices as a bridge to transplantation would also provide a unique opportunity to examine cellular and molecular mechanisms through analyses of cardiac tissue acquired both before cell infusion (at implantation) and after (at transplantation).

Recent randomized studies of cell therapy for heart disease<sup>4-9</sup> represent a milestone in this rapidly developing field while serving as a cogent reminder that many important clinical and fundamental questions have yet to be addressed. We should guard against both premature declarations of victory and premature abandonment of a promising therapeutic strategy. The ultimate success of this strategy is likely to depend on continued and effective coordination of rigorous basic and clinical investigations.

No potential conflict of interest relevant to this article was reported.

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