The article by Losordo et al1 in this issue of Circulation Research is an important addition to the relatively small body of literature in clinical cardiac stem cell therapy. Although the number of patients in the trial by Losordo et al is fairly small, only a handful of similarly sized trials have been published.2-4 In the recent past, the merit of performing clinical trials of cardiac cell therapy was debated in the literature.5,6 However, the study of regenerative cardiac medicine continues to move forward, despite the fact that opponents have highlighted the many challenges in the field, focusing mainly on the lack of mechanistic data. Nevertheless, other questions, such as the best cell type, cell dose, and delivery modality, are beginning to be answered. The performance of larger-scale studies is now being proposed. Interestingly, a large phase III trial of autologous bone marrow mononuclear cells (ABMMNCs) is ready to be initiated in Europe (Oral presentation by Anthony Mathur, PhD; June 2011, Eighth International Symposium on Stem Cell Therapy and Cardiovascular Innovations, Madrid, Spain).

Most clinical trials in cardiac cell therapy have been performed with ABMMNCs. Although the use of this mixed cell population may be considered a relatively broad or less sophisticated approach, ABMMNCs continue to be used because of the previous success with this approach. However, investigators are also seeking new, possibly more potent cell types in bone marrow subpopulations, such as aldehyde dehydrogenase bright (ALDH17) cells (characterized by a common enzyme), mesenchymal cells (a single bone marrow cell population), or as in the trial by Losordo et al, CD34 cells (endothelial progenitor cells characterized by a specific cell surface marker). Furthermore, ongoing clinical investigations are using other innovative approaches to obtain cells, such as different tissue sources, including cardiac tissue (SCIPIO [Cardiac Stem Cell Infusion in Patients With Ischemic Cardiomyopathy] and CADUCEUS [Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular Dysfunction] trials) and adipose tissue (PRECISE trial [A Randomized Clinical Trial of Adipose-Derived Stem Cells in Treatment of Nonrevascularizable Ischemic Myocardium]).8

On the basis of promising preclinical data and results from a phase I clinical trial,8 Losordo et al have addressed the utility of treating a unique patient population (those with refractory angina) with CD34+ cells. Specifically, in a randomized clinical trial conducted at 26 centers in the United States, Losordo et al treated 167 patients with refractory angina with either autologous, adult CD34+ stem cells injected directly into the heart by NOGA catheter or placebo. The direct transendocardial injection of CD34+ cells may be a more efficient method of obtaining greater cell numbers and functional results than less challenging delivery methods, such as intracoronary administration,10 especially in “chronic” patients who have not had a recent myocardial infarction. Patients were randomized into 3 treatment groups in a 1:1:1 scheme to receive low-dose CD34+ cells (1×10⁵ cells/kg body weight), high-dose CD34+ cells (5×10⁵ cells/kg body weight), or placebo. The investigators found that angina frequency and exercise tolerance improved significantly at 6 and 12 months after treatment in patients who received low-dose CD34+ cells compared with control subjects. Patients who received the higher dose of CD34+ cells also tended to do better than control patients, but the differences were not statistically significant. The benefits seen in low-dose cell–treated patients occurred in association with a significant improvement in total severity score stress images on single-photon emission computed tomography (−117±221 versus 0.1±161, P=0.002). Three deaths occurred, all in the control group. Myocardial infarction occurred in 7 patients in the control group, 3 in the low-dose CD34+ group, and 3 in the high-dose group. The low-dose cell–treated group showed a trend toward fewer major adverse cardiovascular events, including urgent revascularization, worsening congestive heart failure, and acute coronary syndromes.

These data suggest that low-dose CD34+ autologous cells injected directly into the heart of a patient with coronary heart disease reduce angina frequency and improve exercise tolerance in patients already undergoing maximal medical therapy who are not candidates for further coronary revascularization. This benefit correlated with improvement in the total stress myocardial perfusion defect, which suggests that it is mediated by an increase in coronary blood flow. Losordo et al attribute the benefits to a paracrine effect.

CD34+ adult, human stem cells have been shown to differentiate into endothelial cells, smooth muscle cells, and new myocytes, and most of these cells fuse their nuclei with reversibly injured murine myocytes in a SCID mouse model of myocardial infarction.11-13 This was initially thought to be an important mechanism and sparked much of the early enthusiasm in the field, but generation of new heart muscle cells was found to occur at a relatively low level. Like Losordo et al,1 others have shown that CD34+ cells exert paracrine effects.14 Thus, although CD34+ cells exert multiple beneficial effects on the injured heart, the ability to differentiate into functional myocardial cells is fairly small, only a handful of similarly sized trials have been published.2-4
heart, their major contribution to enhance ventricular function in the SCID mouse experimental model is through improvement of coronary blood flow.\textsuperscript{11}

One of the more difficult challenges in developing clinical stem cell trials has been the selection of appropriate end points. The traditional end points that have been used may not be the best ones for evaluating the effects of cell therapy. There has been a general lack of uniformity and consistency in the use of end points, due in part to the limited understanding of the mechanistic aspects of the therapy. To date, most cell therapy studies have not been powered to examine the most important clinical end points (ie, mortality and major adverse cardiovascular and cerebral events), and many investigators have compromised by using soft end points, such as the use of angina in the present study. This approach allows investigators to present more positive results, but the lack of objective end points limits the robustness and applicability of the findings. On the other hand, the use of surrogate and even exploratory end points must continue, because our understanding of the effects of biological therapies is incomplete.

It is not clear why the lower dose of CD34\textsuperscript{+} cells in the study by Losordo et al\textsuperscript{1} was more effective than the larger dose, but as the authors indicate, the same phenomenon has been noted previously in stem cell studies.\textsuperscript{13,14} Moreover, it may be that larger doses of cells are not necessarily more beneficial in cell therapy. Once a threshold dose is reached (as suggested by engraftment studies in bone marrow transplantation\textsuperscript{15}), other issues such as nutrient availability may favor the survival of a smaller number of cells. However, the topic is controversial, and an optimal dosing approach has not been identified.

At this point, the question is what other studies are necessary to enable adult human CD34\textsuperscript{+} stem cell therapy to become a therapeutic option for similar patients in the future? Additional studies are needed to confirm these results. Furthermore, it would be useful to obtain direct comparisons of the effects of CD34\textsuperscript{+} stem cells, mesenchymal-type cells, and ALDH\textsuperscript{+} cells on coronary blood flow, regional left ventricular function, symptom relief, and exercise capacity. Other future studies of interest include determining whether combinations of these stem cells may be more effective than single-cell therapy and assessing the benefits of repeated therapy with 1 or more cell types.

As stated above, this contribution by Losordo et al\textsuperscript{1} is important and, if confirmed by additional studies, offers an alternative treatment for patients who are severely limited by angina and for whom there are few, if any, other attractive therapies. As we continue to add to the knowledge base for stem cell therapy, we move closer to implementing this innovative therapy into clinical medicine. Stem cell investigators have taken by the horns the daunting task of applying biological therapies in the arena of cardiac disease. The rodeo is far from over, but at least we have begun the ride.

Disclosures

None.

References


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