Cardiac repair in patients with ischemic heart disease. Since the turn of the century, several forms of cell therapy have been evaluated in clinical trials, including skeletal myoblasts, bone marrow mononuclear cells, mesenchymal stem cells, and cardiac stem cells (CSCs). Cell therapy, in its various forms, has generally been efficacious, providing modest improvements in cardiac structure and function in patients with acute myocardial infarction (MI), as well as chronic ischemic heart disease. Although bone marrow cells are relatively easy to harvest and deliver, these are not natural residents of cardiac tissue, and their ability to regenerate lost myocardium remains controversial. In the absence of an obvious choice, the search for newer cellular substrates has continued.

In 2003, Beltrami et al described the existence of c-kit⁺ cells in the heart, which were reported to be self-replicating, clonogenic, and multipotent, giving rise to cardiomyocytes, smooth muscle cells, and new blood vessels in ischemic rat hearts. Subsequent demonstration of heart repair with intravascular delivery of c-kit⁺ CSCs paved the way for clinical translation using intracoronary delivery. Intense research in this area quickly resulted in the discovery of several additional types of cardiac progenitors, including cardiospherederived cells (CDCs), Sca-1⁺ cells, cardiac side population cells, Isl1⁺ cells, and epicardial progenitors, among others. Of these, c-kit⁺ CSCs and CDCs have already been tested in randomized controlled trials in humans. Intracoronary injection of culture-expanded autologous c-kit⁺ CSCs into hearts of ischemic cardiomyopathy patients improved left ventricular ejection fraction (LVEF) and reduced infarct size in the Stem Cell Infusion in Patients With Ischemic cardiomyopathy (SCIPIO) trial. Injection of autologous CDCs into the infarct-related artery reduced scar mass and increased regional contractility with a nonsignificant increase in LVEF in the Cardiosphere-Derived Autologous Stem Cells to reverse Ventricular Dysfunction (CADUCEUS) trial. Despite these early successes of CSC therapy in humans, efficacy has been questioned. In view of this raging controversy, it is both important and useful to critically evaluate the preclinical evidence underlying clinical translation.

In this issue of Circulation Research, Zwetsloot et al present the first systematic review and meta-analysis of placebo-controlled animal studies of CSC therapy for cardiac repair after MI. The authors must be commended for painstakingly compiling detailed information from 80 eligible studies and generating valuable insights. In the combined analysis, CSCs improved LVEF by 10.7% compared with controls, indicating a robust positive impact on cardiac function. The improvement in LVEF was largely independent of cell source, although CDCs produced greater improvement compared with Sca-1⁺ cells in small animals. The benefits on cardiac function were not significantly influenced by cell source, comorbidities, use of immunosuppression, cell culture methodologies, and disease models. Overall, the results of this meta-analysis of cumulative data from diverse experimental conditions provide strong and consistent preclinical evidence in support of the efficacy of cardiac progenitors for heart repair.

These results also unravel several translationally relevant findings. The comparable ability of allogeneic cells to improve LVEF is particularly encouraging. One of the fundamental challenges to widespread CSC use in humans is the mandatory waiting period required for expansion of autologous CSCs, the frequency of which is low in cardiac tissue. For example, CSCs were injected at a mean of 113 days after harvest in SCIPIO and at 1.5 to 3 months after MI in CADUCEUS. This unavoidable delay also precludes autologous CSC injection at earlier time points after acute MI. However, several animal studies have tested the efficacy of allogeneic or even xenogeneic CSCs in immunocompetent recipients without immunosuppression. In the study by Malliaras et al, injection of syngeneic and allogeneic CDCs both reduced infarct size and improved EF in rats after MI. The current observations by Zwetsloot et al are consistent with these findings. Importantly, meta-analysis of pooled data revealed that improvements in LVEF with xenogeneic cells were also similar to those with syngeneic and allogeneic CSCs. These results bode well for potential use of off-the-shelf CSC products with minimal delay after MI in humans.

Another important finding is the comparable improvement in LVEF with CSC therapy in models of permanent coronary occlusion and ischemia/reperfusion. Although most patients with acute MI currently undergo prompt revascularization, healthcare access varies widely across the globe. Moreover, many patients experience clinically unrecognized MIs. If CSCs are able to restore cardiac function in patients with chronically occluded arteries and ischemic cardiomyopathy, larger number effects on LVEF are anticipated in the future.
of patients may potentially benefit. However, nearly all large animal studies of CSC therapy thus far have used ischemia/reperfusion, although cells were injected after several weeks in most studies. The efficacy of CSCs to improve cardiac parameters in patients with cardiomyopathies resulting from reperfusion as well as nonreperfused MIs at various stages of remodeling remains to be further examined in clinical trials.

The differences in outcomes of CSC therapy between small and large animal studies identified by Zwetsloot et al. are also important from a translational viewpoint. The improvement in LVEF with CSC therapy was significantly greater in small animals (11.5%) compared with large animals (5.2%). The reduction in infarct size expressed as percentage of LV was also significantly different between small and large animal studies. CSC therapy led to ≥10% reduction in infarct size in small animals, whereas large animal studies documented small and nonsignificant decrease compared with controls. Infarct size expressed as percentage of area at risk was provided only in small animal studies, and the 10.85% reduction with CSC therapy mirrored the above data on infarct size as percentage of LV. Intriguingly, these infarct size data from large animals do not corroborate the results from SCIPIO and CADUCEUS. The SCIPIO trial reported a 22.7% reduction in infarct size at 4 months and a 30.2% reduction at 12 months. The CADUCEUS trial showed an 11.1% reduction in scar size at 1 year after CDC injection. Together, these data from well-conducted separate clinical trials underscore, on a positive note, that even large animal preclinical data may not always accurately predict the outcomes in clinical trials.

How do we explain these differences in observations based on animal size? In their extensive analysis, Zwetsloot et al. highlighted a significant difference between the qualities of large and small animal studies, with large animal studies emerging superior to their counterparts. There was also evidence of potential publication bias in small animal studies, although the overall effect size was reduced only by 0.1% in EF difference, following correction. The numerically smaller effect size in large animal studies offers another potential explanation for this difference. However, the likely influence of study quality was further supported by the indication of attrition bias, particularly evident in small animal studies. Although 8 of 9 large animal studies were considered low risk for attrition bias, only 21 of 71 studies in small animals appeared to be at low risk. In the majority of the small animal studies, the authors failed to report the number of animals excluded from the study and the reasons behind their exclusion. This attrition bias in small animal studies might have a sizable impact on the measured outcomes and could possibly explain the differences in observations between small and large animal studies. Collectively, these observations emphasize the critical importance of honest and accurate reporting of all experimental data in preclinical research.

Although meta-analyses of animal studies are considerably less frequent compared with clinical ones, the importance of such endeavors is paramount, especially in this era of rapid translation of basic discoveries. Although CSC therapy has shown tremendous promise in early clinical trials, many questions remain unanswered with regard to mechanisms as well as the ideal cell type, timing, route, cell number, and other relevant details of study design, some of which are addressed in this meta-analysis by Zwetsloot et al. Meta-analysis of preclinical data can also be helpful to identify the influence of bias in the published literature. In this regard, when the authors stratified the analysis after removing the heterogeneity introduced by cell types, the publication bias became extensive with the majority of cell types. This is a key finding that can be unmasked only by careful meta-analysis of pooled preclinical data.

In closing, it is reassuring to find that infarct repair with CSC therapy has actually been better in humans than in large animals. This is consistent with the notion that as bona fide tissue-resident cardiac precursors, CSCs are able to reconstitute functional myocardium that was once considered lost forever. However, these early benefits of CSC therapy from smaller trials need to be tested and further substantiated in the current multicenter randomized controlled trials that are being performed using the most stringent methodologies. The cumulative preclinical data demonstrate that these ongoing clinical trials with cardiac progenitors are based on solid foundations, and provide reason for much optimism in the field of cardiac cell therapy.

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Disclosures

None.

References


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