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Cardiopoietic Stem Cell Therapy in Heart Failure

The C-CURE (Cardiopoietic stem Cell therapy in heart failURE) Multicenter Randomized Trial With Lineage-Specified Biologics

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Objectives This study sought to evaluate the feasibility and safety of autologous bone marrow–derived and cardiogenically oriented mesenchymal stem cell therapy and to probe for signs of efficacy in patients with chronic heart failure.

Background In pre-clinical heart failure models, cardiopoietic stem cell therapy improves left ventricular function and blunts pathological remodeling.

Methods The C-CURE (Cardiopoietic stem Cell therapy in heart failURE) trial, a prospective, multicenter, randomized trial, was conducted in patients with heart failure of ischemic origin who received standard of care or standard of care plus lineage-specified stem cells. In the cell therapy arm, bone marrow was harvested and isolated mesenchymal stem cells were exposed to a cardiogenic cocktail. Derived cardiopoietic stem cells, meeting release criteria under Good Manufacturing Practice, were delivered by endomyocardial injections guided by left ventricular electromechanical mapping. Data acquisition and analysis were performed in blinded fashion. The primary endpoint was feasibility/safety at 2-year follow-up. Secondary endpoints included cardiac structure/function and measures of global clinical performance 6 months post-therapy.

Results Mesenchymal stem cell cocktail–based priming was achieved for each patient with the dose attained in 75% and delivery without complications in 100% of cases. There was no evidence of increased cardiac or systemic toxicity induced by cardiopoietic cell therapy. Left ventricular ejection fraction was improved by cell therapy (from 27.5 ± 1.0% to 34.5 ± 1.1%) versus standard of care alone (from 27.8 ± 2.0% to 28.0 ± 1.8%, $p < 0.0001$) and was associated with a reduction in left ventricular end-systolic volume (−24.8 ± 3.0 ml vs. −8.8 ± 3.9 ml, $p < 0.001$). Cell therapy also improved the 6-min walk distance (+62 ± 18 m vs. −15 ± 20 m, $p < 0.01$) and provided a superior composite clinical score encompassing cardiac parameters in tandem with New York Heart Association functional class, quality of life, physical performance, hospitalization, and event-free survival.

Conclusions The C-CURE trial implements the paradigm of lineage guidance in cell therapy. Cardiopoietic stem cell therapy was found feasible and safe with signs of benefit in chronic heart failure, meriting definitive clinical evaluation. (C-Cure Clinical Trial; NCT00810238) (J Am Coll Cardiol 2013;61:2329–38) © 2013 by the American College of Cardiology Foundation

Acute management of myocardial infarction has reduced early mortality, precipitating the unintended consequence of increased prevalence of chronic heart failure among survivors

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Abbreviations and Acronyms

CI = confidence interval

ESV = end-systolic volume

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

(1,2). As the myocardium has a limited intrinsic capacity to restore organ function after ischemic injury (3–5), multimodal treatments are used to alleviate symptoms and improve clinical status in heart failure. Current therapies target impaired contractility and hemodynamic decompensation without, however, treating the parenchymal loss that underlies the development and progression of disease (6). To address this unmet need, stem cell therapy is increasingly considered as a potential means to fortify innate mechanisms of regeneration (7–11). Stem cells traditionally isolated from bone marrow, a readily used source, demonstrate excellent safety in the clinical testing, yet patient-to-patient variability in repair outcome remains a recognized limitation necessitating further optimization (12–18).

By processing myocardial tissue excised during cardiac surgery or obtained by endovascular biopsy, it is now possible to derive resident stem cell populations (19,20). This advance provides the prospect of anatomically matching the regenerative cell source with the target organ. Such an approach is, however, hampered by the invasive nature of heart tissue sampling and the limited quantity of starting material. Orienting bone marrow stem cells for cardiac repair would eliminate the need for the patient to undergo myocardial harvest, rendering this accessible and renewable compartment an alternative to heart tissue. Recently, hallmark traits of cardiac development were successfully triggered within bone marrow–derived mesenchymal stem cells, establishing the first human scalable lineage-specified phenotype derived without heart tissue harvest (21–24). Pre-clinical testing demonstrated that cardiopoietic stem cells reliably repair the failing myocardium, providing the foundation for clinical translation (22).

The ensuing C-CURE clinical trial addressed the feasibility and safety of autologous bone marrow–derived cardiopoietic stem cell therapy and assessed the signs of efficacy in patients with ischemic cardiomyopathy. This first-in-class biotherapeutics introduces a new strategy to optimize regenerative intervention in heart failure.

Methods

Study design and patient population. The multicenter C-CURE clinical trial was approved by competent authorities and ethics committees as a prospective, randomized, open, and parallel 2-arm study in a stable heart failure population with a history of myocardial infarction (Fig. 1). The primary study endpoint was feasibility and safety at 2-year follow-up. Secondary endpoints, assessed at 6 months, included cardiac structure and function in tandem with measures of global clinical performance. The defining inclusion criterion was chronic heart failure of ischemic origin with impaired left ventricular ejection fraction (LVEF) (15% to 40%) (Online Table 1). Key inclusion criteria were age (18 years of age and older and younger than 75 years of age), ischemic heart disease, and management according to guidelines. Patients with an ischemic event at least 2 months before recruitment were eligible. At least 2 months before enrollment, patients needed to be optimally managed and revascularized. If patients were not already fitted with an implantable cardioverter-defibrillator (ICD), one was provided. Major exclusion criteria were previous cell therapy, myocardial infarction or revascularization within 2 months before enrollment, ventricular aneurysm, and left ventricular wall thickness <5 mm in the target territory documented by echocardiography after patient consent and before randomization (Online Table 1). Patients with moderate to severe aortic valve disease or left ventricular thrombus were excluded, as were patients who received a biventricular pacemaker within 6 months. Patients having a biventricular pacemaker for >6 months and under stable pacing were permitted to join the study. Patients (N = 319) were screened at 9 clinical sites in Europe (Belgium, Serbia, and Switzerland). The trial was conducted from January 2009 to January 2012.

Randomization. In total, 48 patients were randomized through a site-independent centralized process after exclusion of 271 patients (of whom 249 did not meet inclusion/exclusion criteria, 17 refused to participate, and 5 provided consent after the recruitment cutoff date). Baseline data demonstrated similar distribution of age, sex, body mass index, prevalence of cardiovascular risk factors, and cardiac disease history in study groups (Table 1). No difference in medications or hemodynamics was observed. At the time of consent, 1 patient refused participation, and on randomization, 2 patients were excluded because they did not meet clinical inclusion criteria and no bone marrow was harvested, 2 were excluded because they did not meet bone marrow inclusion criteria and declined repeat bone marrow harvest, and 7 were excluded as quality control inclusion criteria were not met and declined repeat bone marrow harvest (Fig. 1). Patients in the control arm received standard of care comprising a beta-blocker, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a diuretic with

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