Clinical Experience With Regenerative Therapy in Heart Failure

Advancing Care With Cardiopoietic Stem Cell Interventions

Jozef Bartunek, Andre Terzic, Atta Behfar, William Wijns

Adoption of regenerative strategies for heart failure is challenged by mixed outcomes in clinical trials. Ongoing development plans strive to improve biotherapeutic potency, optimize delivery, standardize dosing, and target responsive patient populations. The CHART (Congestive Heart Failure Cardiopoietic Regenerative Therapy) program offers advanced experience in clinical development of next-generation regenerative therapies.

Patients with cardiac remodeling and ventricular chamber dilation are at risk to progress into pump failure refractory to standard of care. Innovative treatments are needed to alter disease course, avert end-stage organ deterioration, and delay/avoid destination assist device implantation or transplantation.

Targeting tissue restoration, cell-based therapies are potentially paradigm-shifting interventions. However, clinical trials are confounded by intertrial and interpatient variability underscoring the complexity in translating promising biotherapies into viable solutions. Inconsistent efficacy is ascribed to an unpredictable potency of cell products, limited retention after delivery, and disease heterogeneity.[1] Calls for transnational cooperation have been issued to ensure that translational and clinical readiness of regenerative therapies is pursued in a systematic manner.[2]

The CHART development program draws from multinational public–private collaborations. This science-driven discovery–development–delivery pathway leverages an optimizing approach of guided cardiopoiesis to mitigate variability inherent to cell products/patients and integrates a quality system to certify regenerative proficiency of a biotherapy candidate.[3] Cardiopoiesis imposes lineage-specifying instructions on stem cells to promote cardioreparative proclivity (Figure). Accordingly, a cardiopoietic index which uses gene expression profiling was developed to assess the regenerative quotient of patient-derived stem cells.[4] This quality standard allows pre-assessment of repair potential.

The cardiopoietic cell phenotype demonstrated promise in proof-of-concept preclinical studies, both in small[5] and large[6] animal models, providing the foundation for clinical exploration. The first-in-man C-CURE trial (Cardiopoietic Stem Cell Therapy in Heart Failure) evaluated feasibility and safety of the cardiopoiesis technology in 48 randomized patients with chronic ischemic heart failure.[7] Cardiopoietic stem cells (dose range: $605–1168\times10^6$ cells extrapolated from preclinical experience) were endomyocardially delivered under electromechanical guidance on average ≈48 months after myocardial infarction. There was no evidence of cardiac or systemic toxicity. The C-CURE trial documented signs of efficacy including improved left ventricular (LV) ejection fraction and reduction in LV end-systolic volume. Favorable impact on global parameters, such as the 6-minute walk distance test, was noted along with benefit in a composite clinical score encompassing cardiac and general wellness end points.[7]

In the ensuing clinical development step, and to address limited cell retention, the CHART program relied on a novel delivery device that yields improved cell retention.[8] On the basis of modeling of tissue and injection needle physical interaction, a curved nitinol needle containing side holes was incorporated into a deflectable delivery tip (Figure). The CHART program leveraged these advances in the largest cardiovascular regenerative medicine clinical trial to date. The CHART-1 trial was conducted across 39 hospitals in 351 randomized ischemic heart failure patients on optimal guidelines-directed standard of care.[9] Similar to the C-CURE trial, patients had a history of myocardial infarction yet inclusion did not require documentation of ongoing ischemia. Trial design incorporated a sham-controlled procedure with double-blinded analysis. The single dose of up to 600×10^6 cardiopoietic cells reflected regulatory advice relying on preclinical testing and was delivered endomyocardially leveraging the new cell retention–enhanced catheter. In the overall study population, the trial was neutral on the primary end point consisting of a hierarchical composite of mortality, worsening heart failure, Minnesota Living with Heart Failure Questionnaire score, 6-minute walk test, LV end-systolic volume, and LV ejection fraction at 9-month follow-up.[9] CHART-1 demonstrated a safe profile. Although interventionalists-reported unblinded procedural events were higher in the active group, the incidence of overall blinded events—reported by clinicians responsible for patient care—was similar between groups. Notable insights relevant for further evaluation of regenerative interventions were obtained (Figure).

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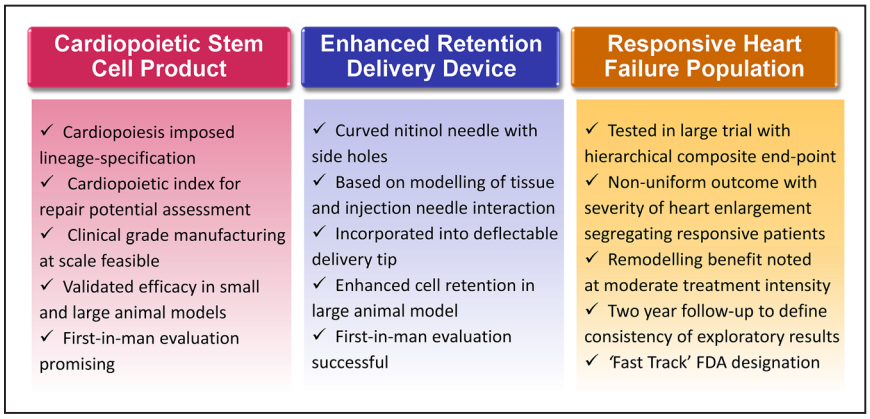

Figure. The Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART) program has provided relevant learnings pertinent to an optimized biotherapeutics, an enhanced delivery system, and scoping of responsive individuals in the setting of the largest cardiopoietic stem cell therapy clinical trial to date. FDA indicates Food and Drug Administration.

First, the CHART-1 trial set a standard in the design of cardiac regenerative clinical studies. In contrast to conventional clinical criteria-driven randomization, CHART-1 used a scheme where randomization followed initial stem cell expansion. This approach aims to mitigate inherent variance in baseline stem cell function. CHART-1 is also the first large randomized cell therapy trial that applied a hierarchical composite end points.[10] In addition, the double-blind design was implemented in the setting of a sham-controlled procedure congruent with stringent protocols. Ethical considerations circumvented potential procedural risk related to placebo injections in a vulnerable population. Rigorous implementation of double-blinded reporting of postprocedural events, in tandem with core laboratory assessments, ensured unbiased evaluation of end points. It should be noted that the clinical development path may vary depending on the product or target population. In this regard, the methodology of sham controls versus placebo injections differs from the recent ixCELL-DCM trial[11] but is comparable to the ongoing DREAM-HF trial (Efficacy and Safety of Allogeneic Mesenchymal Precursor Cells [Rexlemestrocel-L] for the Treatment of Heart Failure).[12] CHART-1 likewise differs in cell dosing reflecting the nature of respective biological products and insights from (pre)clinical testing. Similar to CHART-1, modern studies increasingly use composite end points to comprehensively gauge efficacy. We submit that the used design and methodology are justified as they facilitate timely and adequate readout of clinical status, and as such provide a blueprint for studies that are to follow.

Second, exploration of the CHART-1 trial primary composite end point according to heart failure severity at baseline prospectively revealed a clinically relevant patient population that significantly benefited from cardiopoietic cell therapy.[9] This target population, representing 60% of the whole study cohort, was identified by the severity of heart enlargement, namely a baseline LV end-diastolic volume (LVEDV) between 200 and 370 mL.[9] The effect was sustained at 52 weeks (Bartunek et al, unpublished data, 2017). Patients displaying a lower (<200 mL) or greater (>370 mL) LVEDV did not seem to respond to cell therapy beyond standard of care.[9] This observation is consistent with previously reported modifying effect of baseline LV enlargement influencing outcomes in revascularization, interventions targeting mitral regurgitation or with cardiac resynchronization therapy. The CHART-1 finding of a responsive patient population defined by baseline LVEDV documents for the first time the significance of disease severity in defining outcome of a cell-based therapy.[9] This observation is relevant to streamline patient-tailored designs of future trials and potential clinical applications of cell therapy targeting individuals with the highest likelihood of response.

Third, besides defining the responsive LVEDV range, predefined longitudinal echocardiographic analysis through 52 weeks demonstrated benefit of cardiopoietic cells on LV volumes reduction.[13] It is notable that the extent of volume reduction achieved on top of optimal care was comparable to established medical or device-based interventions associated with improved long-term outcomes.[13] These encouraging insights with cardiopoietic cell therapy should be considered in light of the prognostic value of LV reverse remodeling in predicting improved outcomes in patients with advanced heart failure.[14]

Fourth, LV volumes substantially improved in patients treated with ≤19 injections compared with sham controls or those treated with more injections.[13] The inverse relationship between number of injections and improved LV volumes is consistent with a ceiling effect observed in several studies using autologous or allogeneic cell preparations.[15] A ceiling-like effect observed in the CHART-1 trial does not seem related to the rise in postprocedural troponin. Troponin T levels, as assessed by the central core laboratory at 6 and 24 hours postprocedure, were similar across the range of injections. Rather, it may relate to superior retention of delivered cells because of the optimized needle–myocardial relationship achieved with the used catheter. Here, factors related to a saturation effect in relation to the extent of eligible segments with 8 mm wall thickness, their distribution, or overcrowding during delivery are to be considered. The size of the CHART-1 population and the scheduled 2-year analyses offer a unique opportunity to obtain insights into the relationship between treatment intensity and clinical outcomes, specifically in patients with severely enlarged LVs identified as potential high responders. In case of projected benefit detectable already at lower dose regimens, such insights would impact future intervention strategies when using refined delivery methods beyond single end-hole delivery catheters or when using superior delivery platforms. Hence, unlike conventional pharmacological studies, the CHART-1 trial underscores that dose dependency in interventional cell biotherapy does not follow classical drug regimens established with small chemicals. Absence of traditional dose-dependent relationships in case of optimized cell

products with optimized delivery platforms, where less is better, implies the need of carefully determining proper posology using tailored approaches that address the integral biotherapy/delivery/patient triad.[15]

Clinical experience generated by the CHART program informed the decision of the Food and Drug Administration to grant Fast Track designation to cardiopoietic stem cell therapy for reduction in mortality, hospitalization, and improvement in quality of life for patients with chronic heart failure secondary to ischemic cardiomyopathy with baseline LVEDV between 200 and 370 mL. The Food and Drug Administration Fast Track Development Program provision is intended to facilitate development and expedite review of drugs to treat serious and life-threatening conditions so that an approved product can reach patients expeditiously.

Cardiopoietic stem cell therapy has now reached advanced clinical trial testing. Exploratory analyses of treatment intensity on clinical end points including cardiovascular morbidity and mortality may further refine optimal cardiopoietic cell regimens in target patient populations with cardiac enlargement. The overall clinical experience with the upcoming 2-year-long follow-up will be decisive to determine the consistency of early findings and their clinical implications.

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