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Human Clinical Article

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Abstract

Patients with heart failure experience limitations in daily activity and poor quality-of-life. Prospective surveillance of health-related quality-of-life supplemented traditional death and hospitalization outcomes in the multinational, randomized, double-blinded CHART-1 clinical trial that assessed cardiopoiesis-guided cell therapy in ischemic heart failure patients with reduced left ventricular ejection fraction. The Minnesota Living with Heart Failure Questionnaire (MLHFQ), a Food and Drug Administration qualified instrument for evaluating therapeutic effectiveness, was applied through the 1-year follow-up. Cell treated (n = 109) and sham procedure (n = 140) cohorts reported improved MLHFQ scores comparable between the 2 study arms (mean treatment difference with baseline adjustment −3.2 points, P = .107). Superiority of cell treatment over sham in betterment of the MLHFQ score was demonstrated in patients with pre-existing advanced left ventricular enlargement (baseline-adjusted mean treatment difference −6.4 points, P = .009). In this highly responsive subpopulation, benefit on the MLHFQ score paralleled reduction in death and hospitalization post-cell therapy (adjusted Mann-Whitney odds 1.43, 95% CI, 1.01-2.01; P = .039). The potential of cell therapy in addressing the quality-of-life dimension of heart failure requires further evaluation for disease relief.

Key words: cardiopoiesis; clinical development; efficacy; health-related quality-of-life; ischemic heart failure; Minnesota Living with Heart Failure Questionnaire; patient perspective; symptom; trial endpoint.

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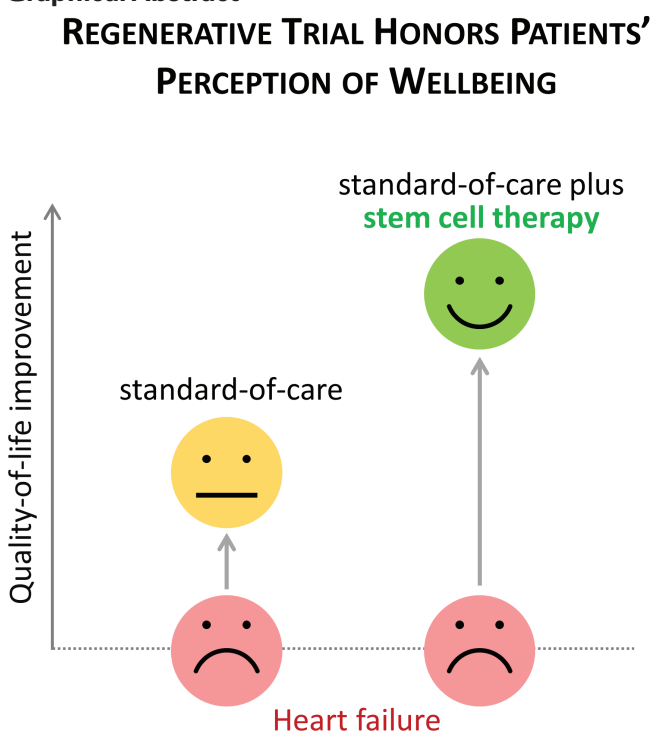
Graphical Abstract



Benefit afforded by regenerative biotherapy is typically assessed using physician-reported outcomes, such as functional recovery, hospitalization, and mortality. In the setting of a phase III clinical trial for heart failure, this study integrates the patients' perception of disease burden on daily living documenting that stem cell therapy, delivered as an adjunct to standard-of-care, significantly improved health-related quality-of-life.

Significance Statement

Patients with advanced heart failure are handicapped in day-to-day life. The present study quantified the activity and behavior of heart failure patients, documenting a sustained improvement in health-related quality-of-life in response to cell therapy. The reported benefit exemplifies patient-centric evaluation of regenerative therapy in heart failure management.

Lessons Learned

- Patients with advanced heart failure suffer from limitations in daily activity and poor quality-of-life. Whether cell therapy can impact the patients' perception of wellbeing was assessed in the present study.
- Patients were surveyed for their daily activity and behavior during a 1-year follow-up in one of the largest cell therapy trials for heart failure. Three hundred fifteen patients, on standard-of-care, were randomized to sham procedure or endocardial delivery of autologous mesenchymal cells conditioned for cardiac repair.
- Cell treatment significantly improved health-related quality-of-life and reduced death and hospitalization in heart failure patients presenting with a cardiac chamber enlargement.
- The present study integrates patient-reported outcomes in a stem cell clinical trial, advancing patient-centric evaluation of biotherapy in the context of chronic disease.
- Further studies are required to validate the reach of regenerative therapy in improving quality-of-life.

Introduction

Patients with heart failure experience a heavy burden of debilitating symptoms, functional disability, and psychosocial compromise.[1] With progression of disease, patients value interventions that improve quality-of-life.[2] This whole person perspective pinpoints a recognized priority in ensuring patient-centric development of new therapies.[3-6]

Regenerative biotherapies are considered for refractory heart failure.[7] Cell therapy assessment focuses on compromised cardiac function and structure.[8,9] These objective measures of organ health, predictive of poor outcome, do not necessarily reflect the wellbeing of an individual.[10] Building on the experience in feasibility, safety, and efficacy, clinical trials in regenerative medicine are primed to integrate patient-reported daily suffering.

Here, the largest regenerative clinical trial for ischemic heart failure provided an opportunity to survey the long-term impact of cell therapy on quality-of-life. The CHART-1 trial (Congestive Heart failure cArdiopoietic Regenerative Therapy) assessed a single-dose autologous

cardiopoiesis-guided mesenchymal cell (coded C3BS-CQR-1) intervention in patients with symptomatic heart failure as an adjunct to guideline-directed medical therapy.[11] Mesenchymal cells offer a safe autologous source yet demonstrate heterogeneous restorative capacity. Preimplantation primed patient-derived cells, C3BS-CQR-1, exemplify a biotherapeutics optimized for heart failure patients.[11] Here, sustained benefit over a 1-year follow-up on quality-of-life scores over sham was observed, preeminent in patients with pre-existing advanced left ventricular remodeling. This study expands the scope of targetable endpoints for cell therapy in suitable heart failure candidates to honor the patients' perception of their health status.

Materials and Methods

Patient Population

Registered with clinicaltrials.gov (NCT01768702) and EudraCT (2011-001117-13) and approved by regulatory bodies and ethics committees at participating sites, the phase III CHART-1 trial was conducted across 39 hospitals in 10 countries to test long-term outcomes of C3BS-CQR-1 therapy in chronic ischemic heart failure.[12] All study participants had chronic heart failure due to ischemic heart disease or previous myocardial infarction. Within the last 12 months, participants were in New York Heart Association (NYHA) functional class III or IV or Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) class 4, 5, 6, or 7 (Table 1). At time of inclusion, subjects were in NYHA class II or greater with left ventricular ejection fraction ≤35% and had an episode of worsening symptoms in the past 12 months despite optimal medical and revascularization therapy.[11] Participants gave written informed consent. Previous reports focused on traditional objective endpoints (ie, mortality, heart failure hospitalization, and echocardiography) and clinician-rated performance (6-minutes walk test).[13-16] The present study integrates the patient's perception, enabling comprehensive evaluation of cardiac cell therapy.

Study Intervention

This prospective, randomized, double-blinded study included: (1) recruitment and screening, (2) bone marrow harvest, (3) randomization, (4) C3BS-CQR-1 manufacturing, (5) intervention, and (6) follow-up (Supplementary Fig. S1). Upon successful expansion of bone marrow to yield 24×10^6 mesenchymal cells, participants were randomized 1:1 to cell (C3BS-CQR-1) delivery or sham procedure (Supplementary Methods). C3BS-CQR-1 were generated in a centralized Good Manufacturing Practice facility from patient-derived mesenchymal cells under a cardiopoiesis guiding protocol utilizing recombinant factors, namely TGF-β, BMP-4,

Table 1. Study eligibility.

	Inclusion criteria	Exclusion criteria
Age	18 to 80 years old	
Heart failure		
Stage	Chronic heart failure	
Class	At the time of inclusion: NYHA ≥II	
	Within 12 months: NYHA III or IV or INTERMACS 4, 5, 6, or 7	
Etiology	Ischemic heart failure (without need for additional revascularization)	Valvular disease (moderate to severe, prosthetic mitral or aortic valve)
Episodes	Hear failure worsening[a] within 12 months	ACS or VT/VF within 90 days
Treatment	At least 1 month of stable medical regimen[b] plus optimal revascularization therapy	Heart transplant PCI within 90 days CABG or CRT within 180 days
LVEF	≤35%	
MLHFQ	Total score >30	
6MWT	100 to 400 m	Inability to perform
Cardiac structural eligibility		LV thrombus, LV wall thinning
Non-cardiac conditions	Willing and able to give informed consent	Pregnancy BMI < 19 or > 45 kg/m^2 Immunosuppressive therapy Chronic infection, Active malignancy Renal dysfunction, Anemia Allergies to agents for procedures Life expectancy less than 2 years Prior cell therapy Angiogenic therapy within 60 days

[a]Indicates worsening heart failure that required hospital admission or outpatient treatment with intravenous vasoactive medication or diuretic.
[b]Includes angiotensin-converting-enzyme inhibitor and/or angiotensin receptor blocker, beta blocker, aldosterone blocker, and diuretic.
Abbreviations: ACS: acute coronary syndrome; BMI: body mass index; CABG: coronary artery bypass grafting; CRT: cardiac resynchronization therapy; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support class; LV: left ventricle; LVEF: left ventricular ejection fraction; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association functional class; PCI: percutaneous coronary intervention; VT/VF: sustain ventricular tachycardia/ventricular fibrillation; 6MWT: 6-minutes walk test.

Activin-A, IGF-1, IL-6, FGF-2, thrombin, and retinoic acid.[13] Patients assigned to cell treatment underwent endomyocardial injections of C3BS-CQR-1 (up to 600 × 10^6 cells) using a retention enhanced catheter,[17] while patients in sham control experienced the process of cardiac catheterization and catheter manipulation without endomyocardial injections (see Supplementary Methods).

Patient-Reported Outcomes

Health-related quality-of-life was assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) prior to, and at the 26-, 39-, and 52-week timepoints postintervention in accordance with a predeclared schedule (Supplementary Fig. S1).[11] The MLHFQ consists of 21 items,[18] each rated from 0 (none) to 5 (very much). The total score ranges from 0 (best) to 105 (worst) comprising physical (8 items with 0 to 40 score) and emotional (5 items with 0 to 25 score) domains plus additional 8 items (score 0 to 40). At times of scheduled follow-up, participants received instructions and filled out the questionnaire based on their feeling and functionality in daily life during the past 4 weeks. The MLHFQ was available in original English version, as well as in Bulgarian, Dutch, Flemish, French, Greek, Hebrew, Hungarian, Italian, Polish, Serbian, and Spanish, covering native languages of participants.

Randomization and Blinding

A web-based randomization system (Sealed Envelope, London, UK), according to a central randomization scheme stratified for each study center, was used. Patients (= MLHFQ answerers) and investigators who performed non-procedural study visits, including recruitment and follow-up assessments with MLHFQ evaluation, were blinded to treatment arms. The study design required endocardial injection in the cell treatment but not in the sham procedure. The interventional team (who provided sham or cell treatment) was not involved in follow-up visits or evaluation. Before study launch, each site identified the blinded assessment team and the unblinded interventional team.

Statistical Analysis

Changes in the MLHFQ scores were compared between groups using mixed models for repeated measures (MMRM) with treatment and treatment by time interaction. Results adjusted for baseline score were examined with the addition of baseline score and the baseline by time interaction to the model. Two-sided *P*-values <.05 without adjustment for multiple comparisons were considered significant. *P*-values for categorized changes in MLHFQ score were calculated based on Kruskal-Wallis test. Subpopulation Treatment Effect Pattern Plots were used to explore the potential effect of left ventricular end-diastolic volume, a disease severity marker, on therapeutic outcome.[11] The CHART-1 trial also measured mortality, worsening heart failure, 6-minute walk test, left ventricular end-systolic volume, and ejection fraction.[11] A hierarchical composite score was evaluated using the Cochran-Mantel-Haenszel Chi-square test with modified ridit scores with the treatment effect presented as the Mann-Whitney odds. Data are presented as mean ± SD or mean (SE). SAS 9.4 (SAS Institute Inc., Cary, NC) was employed for statistical analysis.

Results

The CHART-1 trial randomized 315 patients with ischemic heart failure to the C3BS-CQR-1 therapy (n = 157) and sham control (n = 158) arms (Supplementary Fig. S1).[14] At baseline, patients displayed symptomatic heart failure with reduced left ventricular ejection fraction (27.9 ± 7.0%), a high incidence (85%) of hospitalization within the past 12 months, and severely limited activity (78% stratified as New York Heart Association class III or IV).[15] All patients were on guidelines-directed medical therapy for heart failure, namely pharmacotherapy/cardiac implantable electrical devices (ie, 93% on an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker, 90% on a beta-adrenoceptor blocker, 76% on a mineralocorticoid receptor blocker, 85% on a loop diuretic, 40% with an implantable cardioverter-defibrillator, and 19% on cardiac resynchronization therapy).[14] Between randomization and intervention, 44 patients withdrew from the study (16 deaths, 7 procedural contraindications, 3 consent withdrawals, and 18 who did not meet C3BS-CQR-1 release specifications; Supplementary Fig. S1). A total of 271 patients underwent either the cell therapy (C3BS-CQR-1, n = 120) or sham (n = 151) procedure to which they were randomized. Cell-treated and sham groups were indistinguishable at baseline across demographics, heart failure history, comorbidities, medications, vital signs, 6-minute walk test, biomarkers, and left ventricular parameters on echocardiography (Supplementary Table S1).[15] There was no difference in baseline MLHFQ scores between those randomized to cell therapy versus sham. Specifically, in sham and cell-treated cohorts, total scores preintervention were 49.1 ± 15.1 and 52.6 ± 15.7, respectively. Similarly, physical domain scores were 21.3 ± 7.1 and 23.3 ± 7.2, and emotional domain scores were 9.7 ± 4.9 and 10.8 ± 5.7, respectively.

A total of 236 patients (104 out of 120 in the cell treatment, 132 out of 151 in the sham control) completed the 52-week follow-up (Supplementary Fig. S1). Premature termination (16 or 13.3% in the cell treatment, 19 or 12.6% in the sham control) was largely due to death or left ventricular assist device implantation (34 out of 35 or 97.1%). Throughout the 1-year follow-up, cell- and sham-treated cohorts reported lower (ie, favorable) MLHFQ score trends (Fig. 1). Mean MLHFQ total scores decreases (ie, improvement) from baseline in sham- and cell-treated patients were −10.4 (1.4, n = 140) and −15.9 (1.6, n = 109) at 26 weeks; −11.0 (1.5, n = 136) and −14.9 (1.7, n = 108) at 39 weeks; −11.5 (1.6, n = 132) and −15.6 (1.8, n = 104) at 52 weeks, respectively (Fig. 1A). Across 1-year follow-up, mean treatment difference between the 2 arms was −4.6 points (ie, favoring cell therapy, P = .027; Fig. 1A). The baseline-adjusted mean treatment difference was −3.2 points in MLHFQ total scores (P = .107; Fig. 1B), −0.8 points in MLHFQ physical domain (P = .384), and −1.0 points in MLHFQ emotional domain (P = .088). Cardiovascular events that could, in principle, affect MLHFQ score values were comparable in cell- and sham-treated cohorts.[14,15]

Furthermore, the impact of disease severity on patient-reported outcomes was analyzed. A significant enlargement of the left ventricle (left ventricular end-diastolic volume between 200 and 370 mL) defined patients with advanced cardiac remodeling.[16] At baseline, advanced left ventricular enlargement was documented in 162 enrolled patients (of which 66 received cell treatment and 96 sham procedure).

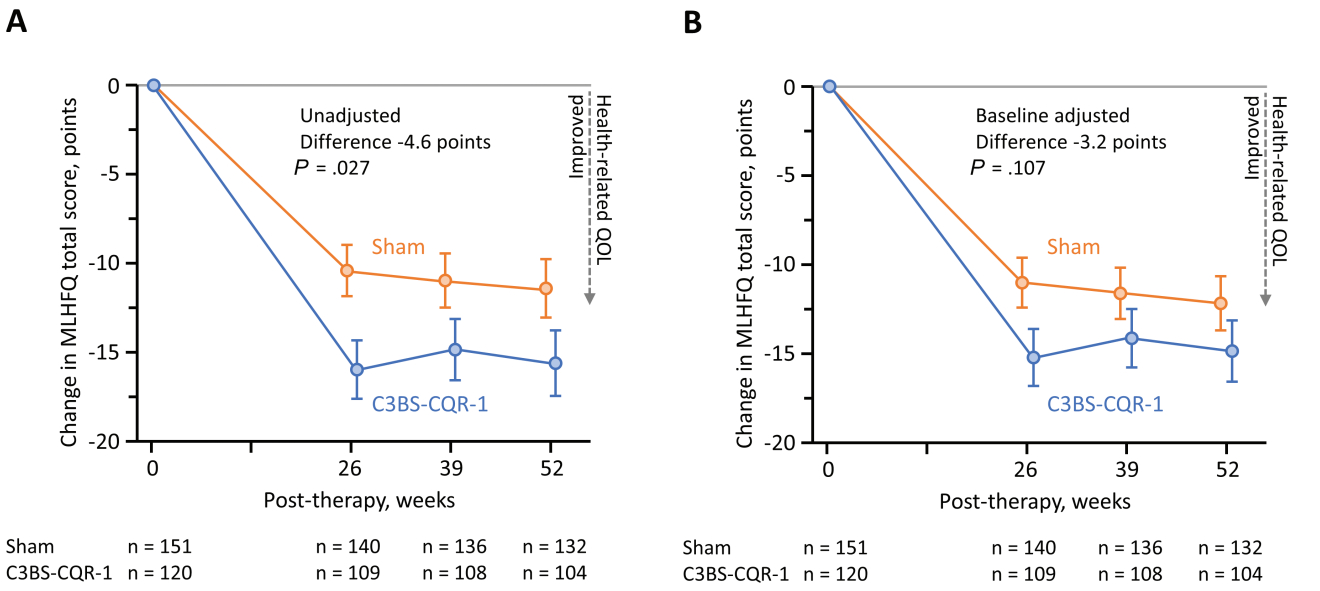


Figure 1. Patient-reported quality-of-life (QOL) for the entire study cohort through follow-up. Symptoms and signs of heart failure, recognized in the past 4 weeks, were assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) prior to (baseline), at 26-, 39-, and 52-week timepoints postintervention in accordance with a predeclared schedule.[11] Throughout the prospective 1-year follow-up, patients treated with cardiopoiesis-guided mesenchymal cell (coded C3BS-CQR-1) and sham control (sham) counterparts reported lower (ie, favorable) MLHFQ score trends. (**A**) The mean decrease (ie, improvement) in MLHFQ total scores at 52-weeks, without baseline score adjustment, was −11.5 (1.6) in sham procedure and −15.6 (1.8) in C3BS-CQR-1 treatment, respectively. The unadjusted mean treatment difference, between study arms, across the 1-year follow-up was −4.6 points (ie, favoring C3BS-CQR-1 treatment; $P = .027$). (**B**) Baseline score adjusted mean decrease in MLHFQ total scores at 52-weeks were −12.2 (1.5) in sham procedure and −14.8 (1.7) in C3BS-CQR-1 treatment. The adjusted mean treatment difference was −3.2 points in MLHFQ total scores ($P = .107$) with −0.8 points in MLHFQ physical domain ($P = .384$) and −1.0 points in MLHFQ emotional domain ($P = .088$). Data are presented as mean (SE).

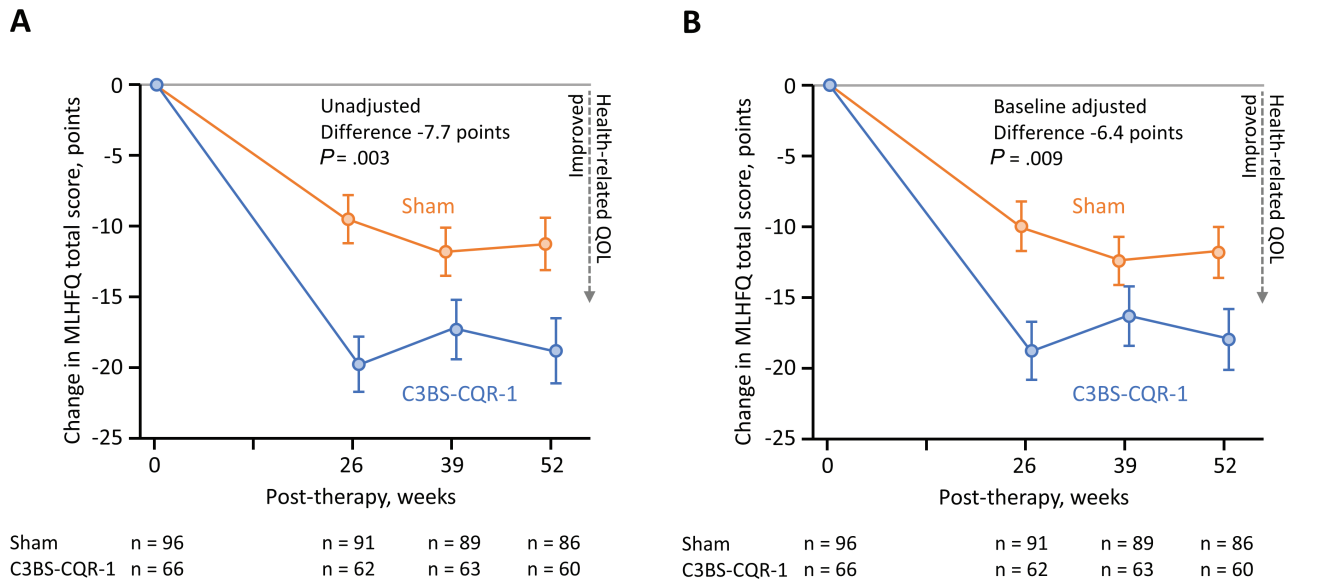


Figure 2. Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores for patients with advanced left ventricular enlargement at baseline. Advanced ventricular enlargement was defined as pretherapy left ventricular end-diastolic volume (LVEDV) between 200 and 370 mL. While pretreatment total MLHFQ scores were equivalently poor in both study arms, total MLHFQ score was significantly lower (more favorable) in patients treated with cardiopoiesis-guided cell (C3BS-CQR-1), compared to those that received sham procedure. In subpopulations with baseline LVEDV 200-370 mL, the mean treatment difference in MLHFQ total scores, between the 2 treatment groups, across the 1-year follow-up was −7.7 points (ie, favoring C3BS-CQR-1 therapy) without baseline adjustment ($P = .003$) (**A**) and −6.4 points with baseline adjustment ($P = .009$) (**B**). Data are presented as mean (SE).

The MLHFQ scores improved throughout follow-up in both groups yet were consistently more favorable in the cell treatment group (Fig. 2). In this subpopulation, the baseline-adjusted mean treatment difference in MLHFQ total scores was −6.4 points ($P = .009$; Fig. 2B), which differed significantly from the effect in patients outside this subpopulation (interaction $P = .038$), detecting superiority of cell therapy over sham in patients with advanced disease. As per trial design, health-related quality-of-life was graded into 3 categories, namely: (1) improved (decline ≥10 points in

MLHFQ total score); (2) no meaningful change (change between –10 and 10 points); and (3) deteriorated (increase ≥10 points).[11] In the subpopulation with advanced left ventricular remodeling, improved heart failure signs and symptoms were reported in three-quarters (77%) of patients receiving cell therapy versus half (52%) of those receiving the sham procedure (baseline-adjusted Mann-Whitney odds 1.45, 95% confidence interval (CI), 1.06-1.99, $P = .018$; Table 2). The response to intervention was similar according to age, sex, and NYHA class at baseline.

Paralleling improved health-related quality-of-life in response to cell therapy, patients with left ventricular end-diastolic volume between 200 and 370 mL also benefitted across the hard endpoints of death and heart failure worsening with hospitalization (adjusted Mann-Whitney odds 1.43, 95% CI, 1.01-2.01; $P = .039$; Table 3). The benefit observed in this subpopulation contrasted the neutral outcome recorded for the entire patient cohort (adjusted Mann-Whitney odds 1.02, 95% CI, 0.79-1.32; $P = .900$; Table 3). Thus, patient stratification by disease severity identified potentially suitable candidates for cardiac cell therapy.

Discussion

Cardiopoiesis offers a conditioning regimen aimed at promoting the cardioreparative capacity of autologous adult cells prior to delivery into failing hearts.[19] Here, the benefit of cardiopoiesis-guided cell (C3BS-CQR-1) therapy on health-related quality-of-life was documented. This patient-reported outcome complements reduction in death or heart failure hospitalization in target patient subpopulations.[15,16,19] C3BS-CQR-1 therapy thus achieves goals set in the regulatory guidance for new drug development for heart failure.[3]

The present regenerative medicine clinical trial uses disease signs and symptoms to incorporate the patients' perspective in evaluating biotherapy for heart failure. The Minnesota Living with Heart Failure Questionnaire (MLHFQ), employed to quantify quality-of-life in this study, is one of the Food and Drug Administration (FDA) approved scoring system qualified to determine the effectiveness of a heart failure treatment.[18] Available in over 30 languages, the MLHFQ assesses sickness perception specific to heart failure in a culturally unbiased manner.[20] The MLHFQ measures the degree of organ decompensation and reflects disease-imposed suffering in daily living. This consideration embeds the empathy for patients' needs. Moreover, the gravity of individual presentation varies among patients and is not necessarily captured on clinical examination, laboratory testing, or by imaging during hospital visits.[18,21] The salient symptoms of dyspnea, fatigue, and exertional intolerance are typically related to deteriorating hemodynamics leading to reduced heart reserve. Introduction of patient-reported outcomes fills a gap in decision-making, traditionally relying on cardiac functional and structural endpoints, hospitalization, and survival rates.[22]

Here, patients in both study arms reported, at baseline, high MLHFQ scores reflecting life-limiting symptomatic heart failure despite receiving optimal standard-of-care. In guiding the evaluation of effectiveness for new therapies, a 5-point change in the MLHFQ total score is considered clinically meaningful.[20] Case in point, the commonly used angiotensin converting inhibitor enalapril showed a 5-point improvement in the MLHFQ total score.[23] Similarly, the efficacy of device-based cardiac resynchronization therapy was documented by a 6-point superiority over standard-of-care in patients

Table 2. Benefit of cardiopoietic cell therapy over sham procedure on health-related quality-of-life measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

	Treatment arms	
Study populations	**Sham control**	**C3BS-CQR-1**
Entire cohort		
Baseline, *n*	151	120
Total MLHFQ score 52 weeks post-therapy versus baseline		
≥10-point improvement (decrease), *n* (%)	72 (54.5)	68 (65.4)
No meaningful change, *n* (%)	50 (37.9)	21 (20.2)
≥10-point deterioration (increase), *n* (%)	10 (7.6)	15 (14.4)
Mann-Whitney odds (95% CI), *P* value		
Unadjusted		1.15 (0.88-1.50), .297
Adjusted for baseline total MLHFQ score		1.07 (0.82-1.38), .629
Subpopulation (LVEDV 200-370 mL)		
Baseline, *n*	96	66
Total MLHFQ score 52 weeks post-therapy versus baseline		
≥10-point improvement (decrease), *n* (%)	45 (52.3)	46 (76.7)
No meaningful change, *n* (%)	34 (39.5)	9 (15.0)
≥10-point deterioration (increase), *n* (%)	7 (8.1)	5 (8.3)
Mann-Whitney odds (95% CI), *P* value		
Unadjusted		1.57 (1.13-2.19), .008
Adjusted for baseline total MLHFQ score		1.45 (1.06-1.99), .018

A Mann-Whitney odds >1.0 favors cell therapy.
Abbreviations: CI: confidence interval; LVEDV: left ventricular end-diastolic volume; n: cohort size.

Table 3. The composite hierarchical score integrates mortality, heart failure worsening (hospitalization), and health-related quality-of-life (Minnesota Living with Heart Failure Questionnaire, MLHFQ).

Study populations	Treatment arms	
	Sham control	C3BS-CQR-1
Entire cohort		
Baseline, *n*	151	120
Outcome at 52 weeks post-therapy		
1) Cardiovascular death, *n* (%)	16 (10.6)	15 (12.5)
2) Heart failure hospitalization ≥2 times, *n* (%)	4 (2.6)	6 (5.0)
3) Heart failure hospitalization once, *n* (%)	10 (6.6)	10 (8.3)
4) MLHFQ total score did not improve ≥10 points or died of non-cardiovascular cause, *n* (%)	53 (35.1)	29 (24.2)
5) MLHFQ total score improved ≥10 points	68 (45.0)	60 (50.0)
Mann-Whitney odds (95% CI), *P* value		1.02 (0.79-1.32), .900
Subpopulation (LVEDV 200-370 mL)		
Baseline, *n*	96	66
Outcome at 52 weeks post-therapy		
1) Cardiovascular death, *n* (%)	9 (9.4)	5 (7.6)
2) Heart failure hospitalization ≥2 times, *n* (%)	4 (4.2)	4 (6.1)
3) Heart failure hospitalization once, *n* (%)	8 (8.3)	4 (6.1)
4) MLHFQ total score did not improve ≥10 points or died of non-cardiovascular cause, *n* (%)	34 (35.4)	11 (16.7)
5) MLHFQ total score improved ≥10 points	41 (42.7)	42 (63.6)
Mann-Whitney odds (95% CI), *P* value		1.43 (1.01-2.01), .039

A Mann-Whitney odds >1.0 favors cell therapy.
Abbreviations: CI: confidence interval; LVEDV: left ventricular end-diastolic volume; n: cohort size.

with advanced heart failure.[24] Cell therapy afforded, in the present study, a comparable magnitude of improvement in the MLFHQ total score. Importantly, the observed benefit was achieved in patients already on optimal therapy. Cell therapy in this trial setting is thus of possible additive value to heart failure management above that attained with standard-of-care alone.

Realizing disease burden reduction in daily life has been attempted with distinct cell types used in treating heart failure of diverse etiologies,[25,26] in line with a presumed utility of regenerative interventions.[27] Here, through post hoc analysis, a major quality-of-life improvement was documented in patients with left ventricular enlargement (end-diastolic volume between 200 and 370 mL). Corroborating reversal in cardiac remodeling and decline in death/hospitalization,[15,16,19] this study supports the notion of enhanced responsiveness in defined patient populations. The present investigation addresses the patient's dimension of disease perception, extending the evaluation of regenerative biotherapy.

The interpretation of outcome in clinical trials is often hindered by heterogeneous responses among participants. Indeed, in the era of evidence-based medicine, next steps when pre-specified primary outcomes do not achieve the 5% level of significance are a major challenge.[28] Over half of phase II/III clinical trials fail, raising concerns that potentially innovative agents are prematurely withdrawn in clinical testing partially due to trial failure to identify the right patient population.[29] In this regard, subgroup analysis, which evaluates treatment effects based on baseline characteristics, provides information in identifying best candidates for therapy.[30] Left ventricular ejection fraction is the gold standard used to classify heart failure phenotypes and advise guideline-directed medical therapy.[31,32] However, increasing evidence points to cardiac structural remodeling, quantified by chamber volume, as a determinant of responsiveness to device/surgical therapy for patients considered refractory to pharmacological approaches.[33,34] More recently, the importance of left ventricular size in predicting outcome has been also documented in the setting of cell therapy.[15,16,34-36] Subgroup analysis carries the risk of false-positive findings, especially in studies with a small sample size, a single endpoint, and non-independence of data points. The present study represents one of the largest cell therapy trials for heart failure to date. Improvement was documented not only with quality-of-life scoring but also using a hierarchical composite constructed from independent endpoints. Deaths or consent withdrawals between randomization and intervention timepoints were not statistically different between sham- versus cell-treated cohorts. This equivalency suggests that efforts to minimize selection bias, including similar baseline characteristics among randomized arms, were put in place. Outcomes based on post hoc analysis are exploratory and hypothesis generating thus need further validation in clinical trials and across diverse populations. The Subpopulation Treatment Effect Pattern Plots explored, without prior assumptions, homogeneity/heterogeneity in treatment effects within the patient population but was not designed to determine cutoff values.[37,38] While a provisional consideration,[39] ischemic cardiomyopathy with left ventricular end-diastolic volume between 200 and 370 mL covers patient populations that suffer from advanced chronic heart failure and are refractory to standard-of-care. New therapeutic options aim to target presumed residual myocardial viability.[40-43] Accordingly, the FDA has granted "Fast Track" designation to C3BS-CQR-1 therapy for reduction in mortality, decrease in hospitalization, and improvement in quality-of-life for ischemic heart

failure patients with left ventricular end-diastolic volume between 200 and 370 mL.[12,19]

Conclusion

Results from the CHART-1 clinical trial suggest that cell therapy has the potential to improve quantity and quality-of-life in patients with advanced ischemic heart failure. Independent clinical investigation is needed for validation.

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Conflict of interest

S.Y., A.B., and A.T. are co-inventors on regenerative sciences-related intellectual property disclosed to Mayo Clinic. Mayo Clinic has administered former research grants from Celyad. Mayo Clinic, A.B., and A.T. have interests in Rion LLC. J.B., M.V., and W.W. disclose prior affiliation to an institutional co-founder of Celyad. T.J.P. reports research funding from CSL Behring, IntraCellular Therapies, and Xylocor Therapeutics, Inc., and consulting fees from Recardio, Eli Lilly, and Novo Nordisk. G.C., B.A.D., and C.E. are employees of Momentum Research, Inc. which has received grants from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics Inc., Corteria Pharmaceuticals, Roche Diagnostics Inc., Sanofi, Windtree Therapeutics Inc., and XyloCor Therapeutics, Inc. M.M. reports personal fees from Vifor Pharma, Amgen, AstraZeneca, Abbott Vascular Inc., Bayer, Servier, Edwards Therapeutics, Actelion, LivaNova, and Windtree Therapeutics, Inc. G.S.F. reports personal fees from Servier, Novartis, and Boehringer Ingelheim. W.W. reports institutional research grants from Terumo, MiCell, and MicroPort; honoraria from MicroPort; and serving as medical advisor of Rede Optimus Research; and cofounder of Argonauts, an innovation accelerator.

Author Contributions

S.Y.: conception and design, financial support, data analysis and interpretation, manuscript writing, final approval of manuscript; J.B.: conception and design, financial support, administrative support, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; T.J.P., G.C., B.A.D., C.E., A.B., M.M., G.S.F.: conception and design, data analysis and interpretation, final approval of manuscript; M.V.: collection and assembly of data, final approval of manuscript; W.W.: conception and design, administrative support, final approval of manuscript; A.T.: conception and design, financial support, administrative support, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript.

Data Availability

The authors declare that all data supporting the findings of this study are available within the article.

Supplementary Material

Supplementary material is available at *Stem Cells Translational Medicine* online.

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