Transcoronary Infusion of Cardiac Progenitor Cells in Pediatric Dilated Cardiomyopathy

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Study design and outcome measures

The clinical study was registered as NCT03129568 (ClinicalTrials.gov). The TICAP-DCM (Transcoronary Infusion of Cardiac Progenitor Cells in Pediatric Dilated Cardiomyopathy) phase 1, open-label trial was conducted at Okayama University Hospital between July 24th, 2017, and September 17th, 2018. The study design and protocol were approved by the Ethics Committee of Okayama University (01F1701003) and followed the Guidelines on Clinical Research Using Human Stem Cells issued by the Ministry of Health, Labour and Welfare, Japan. This trial was performed in accordance with the Declaration of Helsinki with written consent from all parents of eligible patients.

Children aged less than 18 years with a diagnosis of DCM based on clinical and echocardiographic findings were screened and the study enrollment required evidence of LV dilation with reduced EF defined as less than 40% (*1*). Although neuromuscular, mitochondrial, syndromic, and metabolic causes were considered to be further validated by genetic screening, sarcomeric mutation analysis was not performed in patients with cardiomyopathy with either isolated or LVNC phenotype. Exclusion criteria included cardiogenic shock, intractable arrhythmias, repeated infections, advanced renal or hepatic dysfunction, and manifested cancer diseases. Mixed hypertrophic or restrictive cardiomyopathy phenotypes were also excluded. Every eligible participant was subjected to endomyocardial biopsies to obtain sufficient specimens for pathological diagnosis and CDC culture. Patients classified as secondary DCM, such as inflammation, toxic exposure, metabolic disorders, and structural heart disease, were not enrolled in this trial.

The TICAP-DCM prospective, open-label, phase 1 trial comprised of a phase 1a study (n=5, prespecified as 7 but limited to 5 patients available for recruitment due to the disease severity and rarity) to evaluate procedural safety during intracoronary delivery of CDCs (3.0×10^5/kg) using nonocclusive approach, and a phase 1b study (n=24, in a 1:1 randomization) to assess the therapeutic benefits. The sample size was determined based on a power of 85% to detect a difference of 4.5% in the cardiac function, assuming that the common standard deviation is 3.5% between controls and CDC-treated groups using a 2-group *t* test at 2-sided. Study participants were assessed at baseline, 6, and 12 months of follow-up. The primary safety endpoint was adverse events occurring in the treatment arm including ventricular fibrillation, ventricular tachycardia, heart failure, myocardial infarction, advanced infection, and tumor formation after CDC infusion (*2*). The secondary endpoint was to assess the functional improvement of the global cardiac function and heart failure status from baseline to 6 months of follow-up, as described previously (*3*). The study participants were closely monitored by an independent data monitoring committee at the Center for Innovative Clinical Medicine. Data management board at Translational Research Center for Medical Innovation (Kobe) has verified and vouched for the accuracy, completeness, and fidelity of the clinical data.

Statistical analysis

Descriptive data are presented as absolute numbers and percentages or means and SDs. Significance of differences between two treatment groups was assessed using Student's *t*-test. Paired *t*-test was used to determine the significance between baseline and an endpoint within a group. For multiple comparisons of continuous measures between groups, the Kruskal-Wallis test was used if normality could not be established. When the variables were distributed normally, one-way analysis of variance (ANOVA) was performed and Tukey post hoc test was

applied to determine the statistical significance between groups. Categorical variables presented by the number of observations between the groups were compared using Fisher exact test. Individual comparisons at baseline to 6 and 12 months of follow-up were analyzed by one-way ANOVA with repeated measures followed by Dunn–Bonferroni post hoc correction according to the data normality. The Friedman test was used to analyze the heart failure status in CDC-treated patients from baseline to 12 months of follow-up and Wilcoxon signed-rank test with Dunn–Bonferroni post hoc correction was applied to compare the changes from baseline. Linear regression analysis using Pearson's correlation coefficient was applied to evaluate the relationship between absolute changes in the extent of myocardial fibrosis from baseline to 12 months of follow up and the expressions of CDCex-derived miRNAs, and *r* values were presented as Pearson product-moment correlation coefficient. A *P* value less than 0.05 was considered to be significant. Analyses were conducted using SPSS software (version 26, IBM Corporation, Armonk, NY).

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