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Effect of Aging on Human Mesenchymal Stem Cell Therapy in Ischemic Cardiomyopathy Patients

Samuel Golpanian, MD,* Jill El-Khorazaty, BS,† Adam Mendizabal, PhD,† Darcy L. DiFede, RN, BSN,* Viky Y. Suncion, MD,* Vasileios Karantalis, MD,* Joel E. Fishman, MD,‡ Eduard Ghersin, MD,‡ Wayne Balkan, PhD,* Joshua M. Hare, MD*

ABSTRACT

BACKGROUND The role of patient age in the efficacy of mesenchymal stem cell (MSC) therapy in ischemic cardiomyopathy (ICM) is controversial.

OBJECTIVES This study sought to determine whether the therapeutic effect of culture-expanded MSCs persists, even in older subjects.

METHODS Patients with ICM who received MSCs via transendocardial stem cell injection (TESI) as part of the TAC-HFT (Transendocardial Autologous Cells in Ischemic Heart Failure) (n = 19) and POSEIDON (Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis) (n = 30) clinical trials were divided into 2 age groups: younger than 60 and 60 years of age and older. Functional capacity was measured by 6-min walk distance (6MWD) and quality of life using the Minnesota Living With Heart Failure Questionnaire (MLHFQ) score, measured at baseline, 6 months, and 1 year post-TESI. Various cardiac imaging parameters, including absolute scar size, were compared at baseline and 1 year post-TESI.

RESULTS The mean 6MWD was similar at baseline and increased at 1 year post-TESI in both groups: 48.5 ± 14.6 m ($p = 0.001$) for the younger and 35.9 ± 18.3 m ($p = 0.038$) for the older participants (p = NS between groups). The older group exhibited a significant reduction in MLHFQ score (−7.04 ± 3.54; $p = 0.022$), whereas the younger than 60 age group had a borderline significant reduction (−11.22 ± 5.24; $p = 0.058$) from baseline (p = NS between groups). Although there were significant reductions in absolute scar size from baseline to 1 year post-TESI, the effect did not differ by age.

CONCLUSIONS MSC therapy with TESI in ICM patients improves 6MWD and MLHFQ score and reduces myocardial infarction size. Importantly, older individuals did not have an impaired response to MSC therapy. (J Am Coll Cardiol 2015;65:125–32) © 2015 by the American College of Cardiology Foundation.

Based on pre-clinical studies and clinical trials, bone marrow-derived mesenchymal stem cells (MSCs) (1-3) have been shown to mitigate left ventricular (LV) remodeling associated with acute myocardial infarction (MI) (2,4,5) and chronic (1,6-8) ischemic cardiomyopathy (ICM). Although the data are encouraging, evidence suggesting a deleterious effect of aging on autologous MSC transplantation has been highly controversial (9). Telomere length and shortening play crucial roles in the cellular molecular aging process (10,11), and there is a strong correlation between human mesenchymal stem cell (hMSC) proliferative capacity and telomere length in culture and with donor age (12). In addition to their diminished proliferative potential, aging hMSCs tend to have a compromised homing capability

From the *Interdisciplinary Stem Cell Institute, University of Miami Miller School of Medicine, Miami, Florida; †EMMES Corporation, Rockville, Maryland; and the ‡Department of Radiology, University of Miami Miller School of Medicine, Miami, Florida.
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ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

CI = confidence interval

EDV = end-diastolic volume

EF = ejection fraction

ESV = end-systolic volume

hMSC = human mesenchymal stem cell

ICM = ischemic cardiomyopathy

LV = left ventricular

MI = myocardial infarction

MLHFQ = Minnesota Living With Heart Failure Questionnaire

MSC = mesenchymal stem cell

TESI = transendocardial stem cell injection

(13–16). Accordingly, these age-related impairments suggest that MSC therapy might produce a reduced effect when the cells are derived from older individuals.

SEE PAGE 148

Although some proponents believe that advanced stem cell donor age results in diminished function (17–21), other studies raise a clinically relevant issue as to whether *recipient* age is a crucial factor limiting the response to cell therapy (22–24). This has led to the notion that MSC therapy outcome depends not only on stem cell age, and thus function, but also recipient age and comorbidities (9,22). Indeed, reduced responsiveness as a function of donor age would be a major limitation to the emerging development of cell therapy for heart disease, given the increasing incidence and morbidity of heart disease with age (25). Here, we tested the hypothesis that improvements in functional capacity, quality of life, and reverse remodeling by transendocardial injection of hMSCs in patients with ICM is actually preserved with recipient age. Our data here derive from the phase I/II randomized trials of TAC-HFT (Transendocardial Autologous Cells in Ischemic Heart Failure) (26) and POSEIDON (Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis) (27) trials.

TABLE 1 Baseline Characteristics

	Age Group		
	<60 yrs (n = 23)	≥60 yrs (n = 26)	p Value
Age at transplantation, yrs	51.95 ± 7.33	68.86 ± 4.51	<0.0001
Time from MI to therapy, yrs	6.26 ± 6.42	15.43 ± 9.23	0.0002
Sex			1.000
Male	21 (42.9)	23 (46.9)	
Female	2 (4.1)	3 (6.1)	
Race			0.1547
White	12 (24.5)	19 (38.8)	
European	0 (0.0)	1 (2.0)	
White North American	3 (6.1)	1 (2.0)	
Western European	0 (0.0)	1 (2.0)	
Black	2 (4.1)	0 (0.0)	
Indian/South Asian	0 (0.0)	1 (2.0)	
Filipino (Pilipino)	1 (2.0)	0 (0.0)	
Native American	0 (0.0)	1 (2.0)	
White Caribbean	5 (10.2)	2 (4.1)	
Ethnicity			0.0629
Hispanic or Latino	9 (18.4)	4 (8.2)	
Not Hispanic or Latino	14 (28.6)	20 (40.8)	
Unknown	0 (0.0)	2 (4.1)	
6MWD	418.30 ± 71.57	372.12 ± 93.01	0.0561
MLHFQ total score	42.33 ± 28.84	31.58 ± 27.81	0.2013
Scar size as absolute value	26.93 ± 15.35	21.47 ± 13.29	0.2080
Scar size as % of LV mass	22.09 ± 13.55	11.79 ± 6.06	0.0041
EF	31.96 ± 6.22	29.49 ± 12.65	0.3945
EDV	289.36 ± 81.65	274.40 ± 86.66	0.5525
ESV	199.50 ± 68.53	199.29 ± 86.15	0.9930
SI	0.50 ± 0.07	0.47 ± 0.11	0.3077

Values are mean ± SD or n (%).

6MWD = 6-min walk distance; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; MI = myocardial infarction; MLHFQ = Minnesota Living With Heart Failure Questionnaire.

METHODS

Data from the TAC-HFT and POSEIDON trials were collected in a similar fashion in a central electronic data system. All ICM patients who received hMSCs from these trials were pooled together and dichotomized into 2 age groups, younger than 60 years of age and 60 years of age and older. The associations between age and both clinical and imaging parameters were assessed. Values of $p < 0.05$ were considered significant. Comprehensive statistical methods can be found in the Online Appendix.

RESULTS

A total of 49 patients who received hMSCs from both trials are included in this analysis. Thirty patients received hMSCs in the POSEIDON trial, of whom 11 patients (36.7%) were younger than 60 years of age and 19 patients (63.3%) were 60 years of age and older. In the TAC-HFT trial, a total of 19 patients received hMSCs, with 12 (63.2%) younger than 60 years of age and 7 patients (36.8%) were 60 years of age and older. The average age at transplantation was 51.95 ± 7.33 years (range: 32.48 to 59.91 years) in the younger than 60 years age group and 68.86 ± 4.51 years (range: 62.84 to 79.01 years) in the older group. The mean time from MI to cell therapy was 6.26 ± 6.42 years for younger patients and 15.43 ± 9.23 years for the older group ($p = 0.0002$).

Baseline characteristics are shown and compared between age groups in Table 1. The majority of the cohort was male (89.8%). A borderline statistically significant difference was observed between age groups for the baseline 6MWD test ($p = 0.0561$). Scar size as a percentage of LV mass was significantly different between age groups at baseline ($p = 0.0041$). No other statistically significant differences were observed for demographic characteristics, Minnesota Living with Heart Failure Questionnaire (MLHFQ), or other cardiac imaging parameters.

There was a statistical trend toward reduced functional capacity at baseline in the older age