The ABCD (Autologous Bone Marrow Cells in Dilated Cardiomyopathy) Trial: A Long-Term Follow-Up Study
Sandeep Seth, Balram Bhargava, Rajiv Narang, Ruma Ray, Sujata Mohanty, Gurpreet Gulati, Lalit Kumar, Balram Airan, Panangipalli Venugopal, for the AIIMS Stem Cell Study Group

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To the Editor: We reported the short-term results (6-month follow-up) of a pilot study of the role of stem cell therapy in ischemic cardiomyopathy (1). We now present the final long-term (3-year follow-up) results of the trial. The study included patients between 15 and 70 years of age with idiopathic dilated cardiomyopathy with normal coronary arteries, an ejection fraction (EF) of <40%, and no other severe comorbidities (e.g., chronic renal failure). The study design was an open-label, randomized trial in which 85 patients were enrolled. The end points of the study were 1) change in New York Heart Association (NYHA) functional class, 2) change in quality of life per the Kansas City Cardiomyopathy Questionnaire (KCCQ), 3) change in left ventricular function (Vivid 7TM, Wipro GE Healthcare, offline analysis using Simpson’s method), and 4) mortality. An endomyocardial biopsy was performed in 8 patients. After administering local anesthesia, bone marrow (60 ml) was aspirated from the iliac crest using a sterile bone marrow aspiration needle, and mononuclear bone marrow stem cells were separated using the Ficoll density separation method. A mean volume of 59 ± 2 ml of bone marrow was removed. This contained 168 ± 96 million cells, of which 2.7 ± 1.5 million cells were CD34+ cells and showed 92% viability. During stem cell injection, the coronary sinus ostium was cannulated with a 6-F Swan–Ganz catheter (Arrow International, Reading, Pennsylvania) with a reverse loop within the right atrium. The balloon was inflated, ensuring that the distal pressure did not increase to more than the diastolic pressure (this slowed the flow of blood from the coronary sinus, possibly allowing a longer time for cell migration and homing). Subsequently, the left coronary was hooked, and two-thirds of the stem cell concentrate was injected slowly. The entire procedure was repeated for the right coronary artery. Clinical and echo-cardiographic follow-up was performed.

Eighty-five patients with similar demographics, left ventricular volumes and function, and functional status score (KCCQ) were studied in 2 groups (treatment arm and control arm). The mean follow-up period was 28 ± 9 months. Two patients in the treatment arm were lost to follow-up, and another 2 patients underwent biventricular pacing. Among the remaining 41 patients, 10 (24.4%) patients died within 3 years. There were 12 NYHA functional class IV patients, and of them, 6 died during the follow-up period and 5 patients showed improvement (1 patient to class I, 1 patient to class III, and the remaining 3 patients to class II). Mortality was not significantly different between the treatment and control arms. The EF improved in the treatment arm by 5.9% with a reduction in end-systolic volumes and no change in end-diastolic volumes. Both NYHA functional class III and IV groups in the treatment arm showed improvement, although the effect on the NYHA functional class III patients (EF: 23.6 ± 10.6% to 30.1 ± 11%) was greater than that on the NYHA functional class IV patients (EF: 20.1 ± 9% to 24 ± 13.8%). There was no significant improvement in the EF in the control patients (Table 1). There was a significant improvement in quality of life as assessed by KCCQ and functional status on long-term follow-up in the treatment group (Table 1). Endomyocardial biopsies showed a trend toward improvement in vascularity with no definite evidence of transdifferentiation (1). This was in the form of significantly increased capillary density with no increase in the supporting pericytes. No new myocardial cells or any immature cells were seen.

Recently, the results of a few small trials were reported that suggest a beneficial role of stem cell therapy in nonischemic dilated cardiomyopathy (2–4). Kalil et al. (2) showed intramyocardial transplantation of bone marrow stem cells in dilated cardiomyopathy patients with improvement in functional class without improvement in left ventricular function. Wang et al. (3) also found similar results after intracoronary infusion of autologous mesenchymal stem cells. Kaparthi et al. (4) showed improvement in functional status and left ventricular function after intracoronary autologous bone marrow mononuclear cells infusion. Large randomized trials are ongoing in Brazil, Europe, and India.

In the initial 6 months of the ABCD (Autologous Bone Marrow Cells in Dilated Cardiomyopathy) trial (1), we found that 76% of our patients who were NYHA functional class III showed an improvement in EF by 5.4%. This improvement manifested after 1 month, which is too early to be explained by formation of fresh myocytes. This benefit was predominantly due to improvement in end-systolic volumes while the end-diastolic volumes remained the same. This is similar to a number of other studies that also showed an improvement in EF of about 4% to 6%, and also with no change in end-diastolic volumes. This would suggest that stem cells do not cause any change in the remodeling process but improve myocardial cell function. In animal models of dilated cardiomyopathy, direct injection of mesenchymal stem cells has been shown to significantly increase capillary density and decrease the collagen volume fraction in the myocardium, resulting in decreased left ventricular end-diastolic pressure and increased left ventricular systolic function. This is similar to our histopathological data showing a trend toward increasing vascularity (1).

In summary, the clinical follow-up results of a first-in-man pilot study of stem cell therapy in patients with dilated cardiomyopathy at the completion of 3 years of follow-up demonstrate that the benefit is sustained and without any long-term side effects. The effect is less in patients with more severely damaged myocardium. This study establishes the long-term safety and long-term efficacy of this therapy in dilated cardiomyopathy.
3 years for treatment group. †p

NYHA functional class for dyspnea

I 0 22 (54) 14 (35) 10 (25)
II 29 (71) 6 (15) 12 (30) 18 (45)
III 12 (29) 9 (22) 14 (35) 12 (30)

Mortality

Functional status score 51.19 ± 19.90 67.02 ± 21.8* 51.52 ± 18.12 52.74 ± 18.8†
Clinical summary score 59.81 ± 20.27 75.22 ± 18.31* 59.95 ± 18.44 61.17 ± 19†

Echocardiography data

End-systolic volume, ml 137.3 ± 62.6 120 ± 52* 145.7 ± 74.7 147.8 ± 79.9†
End-diastolic volume, ml 176.7 ± 76.40 166.5 ± 65.5 184.9 ± 94.6 187.7 ± 98.8†
Ejection fraction, % 22.5 ± 8.3 28.4 ± 11.8* 20.8 ± 9.3 21.2 ± 9.2†

Treatment at 3 yrs

ACE inhibitor or ARB (ramipril equivalent), % taking drug 41 (100) 40 (100)
Dose, mg 7.5 ± 1.2 7.4 ± 1.7
Beta-blocker (carvedilol equivalent), % taking drug 29 (70) 29 (72)
Dose, mg 12.5 ± 5 12.1 ± 3

References


LETTERS TO THE EDITOR

Statins and Heart Failure

Cleland et al. (1) report that patients with less severe heart failure (HF) due to ischemic heart disease (IHD), as indicated by lower levels of N-terminal pro-B-type natriuretic peptide (lower tertile, \(<103\) pmol/l [868 pg/ml]), had a greater clinical benefit from rosuvastatin (hazard ratio [HR]: 0.65; 95% confidence interval [CI]: 0.47 to 0.88, p = 0.005), despite the lower absolute event rate, contrary to the results of the original study (2).

We reported that treatment with atorvastatin (mean dose 23 mg/day) of 800 IHD patients resulted in a reduction of 50% (HR: 0.50; 95% CI: 0.27 to 0.94, p = 0.021) in new cases or worsening cases of HF requiring hospitalization versus 800 IHD patients...
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