Intracoronary Administration of Autologous Bone Marrow Mononuclear Cells in Patients with Chronic Ischemic Symptomatic Cardiomyopathy: 5 Years Follow-Up

Alex Blatt MD MSc, Sa'ar Minha MD, Gil Moravsky MD, Zvi Vered MD and Ricardo Krakover MD

Department of Cardiology, Assaf Harofeh Medical Center, Zerifin, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: **Background:** Several studies have demonstrated the short-term safety, feasibility and efficacy of cell transplantation in patients with advanced heart failure. Data on the long-term outcome are lacking.

Objectives: To evaluate the long-term outcome of intracoronary autologous bone marrow administration in patients with stable severe ischemic cardiomyopathy who were not suitable for revascularization.

Methods: We enrolled eight consecutive patients with ischemic cardiomyopathy: all were in NYHA functional class III-IV despite optimal medical treatment. Dobutamine stress echo showed that all had left ventricular ejection fraction ‹ 35% with significant viability or ischemia, or both, in at least two myocardial segments. Based on coronary anatomy none of the patients was suitable for revascularization. Bone marrow was obtained and the cells were injected into all patent conduits after a brief balloon occlusion at a normal coronary segment. Clinical follow-up was performed periodically at the heart failure clinic, and included electrocardiography, laboratory tests and echocardiography.

Results: During 5 years follow-up there were two deaths: one due to leukocytoclastic vasculitis 21 months after intracoronary bone marrow infusion, and the second patient died suddenly during sleep 30 months after the transplant. The other six patients are alive, two of them without any cardiovascular or clinical events. No significant change in systolic and diastolic function was observed on echocardiography.

Conclusions: Despite the small and selected patient group, our long-term follow-up showed a promising outcome for this population of patients suffering from severe cardiac disease. Longer follow-up of a much larger group is needed.

IMAJ 2010; 12: 738–741

KEY WORDS: cell transplantation, autologous intracoronary bone marrow infusion, heart failure, long-term outcome

Despite significant advances in medical and invasive therapy, the prognosis of symptomatic patients with heart failure and chronic ischemic cardiomyopathy remains poor. The 1 and 5 year survival of these patients is around 20% and 50% respectively [1,2], which is higher than for common malignancies such as bladder, breast, prostate and uterus.

Stem cell-based cardiac therapy is a rapidly evolving field of research [3,4]. Numerous preclinical experimental studies [5-7] and pilot safety-feasibility studies [8-11], and some randomized controlled studies [12,13], have yielded non-conclusive but encouraging results [14]. These human studies are characterized by a diverse methodology in almost all aspects: patient population, type of cell investigated, number of injected cells, timing and route of cell injection, follow-up duration, and clinical endpoints [15,16]. The literature on patients with chronic ischemic heart disease as compared to those with acute coronary syndromes treated with cardiac cell regeneration-based therapy is limited. In the meta-analysis published by Abdel-Latif et al. [17] the mean follow-up was relatively short, 4 months (range 3–18 months). A 4 year follow-up after bone marrow mononuclear cell transplantation in patients with acute myocardial infarction was recently published [18].

The purpose of the present study was to evaluate the 5 year outcome of intracoronary autologous bone marrow injection in patients with severe chronic ischemic cardiomyopathy who were not suitable for revascularization.

PATIENTS AND METHODS

The methodology has been described in detail elsewhere [8]. Briefly, patients with ischemic cardiomyopathy, left ventricular ejection fraction < 35%, New York Heart Association functional class III-IV despite optimal medical therapy, were screened. The study had been approved by local and national institutional review boards. After providing written informed consent the patients underwent dobutamine stress echo. Coronary angiography was performed in those with evidence of hibernation and/or ischemia in at least two different myocardial segments. Regional left ventricular function at rest was assessed according to the recommendations of the

American Society of Echocardiography scoring scheme [19] modified by 18 segments (three views: four and two chamber and apical long axis views; six segments in each view) and was scored as follows: 1 = normal, 2 = hypokinetic, and 3 = akinetic contraction (includes dyskinesis and aneurysm). Patients who were not suitable for revascularization, either coronary angioplasty or coronary artery bypass surgery, were screened for inclusion in the study. Exclusion criteria were idiopathic or non-ischemic cardiomyopathy; other etiology for heart failure; history of past or current disease involving bone marrow; patients on dialysis; and positive serologic test for human immunodeficiency virus, hepatitis B or C; and any neoplastic or terminal disease.

One day prior to coronary angiography, bone marrow aspiration was performed and manipulated to the point that a suspension of bone marrow containing only white blood cells was ready for injection. Mild ischemia was induced by 3 minutes inflation of a coronary balloon to nominal pressure in an angiographically normal coronary segment in each patent coronary artery associated with ischemic or viable myocardium on dobutamine stress echo, with baseline TIMI flow of ≥ 2. Thereafter, the bone marrow cell suspension was slowly infused. The mean nucleated cell concentration was greater than 15 x 106/ml. The volume per conduit did not exceed 50 ml and the total suspension volume was less than 180 ml.

Clinical follow-up was performed at 6 month intervals and included assessment of functional class, physical examination, electrocardiography, echocardiography and 24 hour Holter monitoring. The echocardiographic features included ejection fraction, diastolic dysfunction parameters (E/A ratio and W-wave deceleration time), mitral regurgitation, estimated pulmonary pressure (mmHg) and regional wall motion score. We recorded any hospitalization, decompensated heart failure, myocardial infarction and need for interventional procedures. Statistical analysis of average and standard deviation was performed using MS Excel (Microsoft, Seattle, WA, USA).

RESULTS

We enrolled eight patients – including two patients in addition to those described in the previous publication [8]. The 5 year follow-up was completed in all patients as planned. The baseline patient characteristics and 5 year follow-up are presented in Table 1. All the patients were males and their mean age was 64.7 ± 7.2 years. The mean time from their first myocardial infarction was 67.7 ± 43.5 months. The NYHA functional class upon enrolment was III in five patients and IV in the other three. Diabetes mellitus was present in 6 patients (75%) and chronic kidney disease in 5 (62.5%). The first myocardial infarction involved the anterior wall in six patients and in the latter two the inferior wall. The first ischemic episode had been treated percutaneously in five cases and coronary artery bypass graft in three. All patients were treated according to current guidelines.

After 5 years follow-up [Table 2] six patients are alive: in four of them functional class improved at least by one degree. It remained unchanged in one and worsened in one. Of these six patients, two had no cardiovascular or clinically significant events, including hospitalization, while the rest presented one or more. One patient underwent an uneventful percutaneous coronary intervention to a de novo lesion 12 months after the bone marrow infusion. In this patient a cardiac resynchronization therapy defibrillator was implanted 28 months later due to refractory heart failure and chronic hemodialysis was started 58 months after cell therapy. Another patient had an acute coronary syndrome (non-ST elevation myocardial infarction) 11 months after

Table 1. Baseline characteristics

Patient	Age	Gender	NYHA	DM	Cr (mg/dl)	MI location	Months between MI and BM infusion	First revascularization
1	59	M	III	–	–	Anterior	12	PCI
2	56	M	III-IV	+	1.6	Inferior	120	PCI
3	81	M	III-IV	+	–	Anterior	46	PCI
4	56	M	III	+	2.4	Inferior	48	CABG
5	66	M	III	–	2.6	Anterior	96	PCI
6	65	M	III-IV	+	1.8	Anterior	28	PCI
7	64	M	III	+	1.7	Anterior	22	CABG
8	64	M	III	+	–	Anterior	34	CABG

BM = bone marrow, DM = diabetes mellitus, Cr = creatinine, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft

Table 2. Five year clinical events

Patient	NYHA class	Hospitalization	MACE	Devices	Died
1	II	–	–	–	–
2	–	x 3	Pulmonary edema	–	Leukocytoclastic vasculitis (21)
3	II–III	–	–	–	–
4	IV	x 2	NSTEMI, Rt femoral PTA, hemodyalisis, femoral–popliteal bypass	–	–
5	–	–	–	CRT–D	Sudden death (30)
6	II–III	–	–	–	–
7	II–III	–	–	CRT–D	–
8	III	–	PCI, hemodialysis	CRT–D	–

MACE = major adverse cardiac events, NQWMI = non-Q wave myocardial infarction, PTA = peripheral transluminal angioplasty, CRT-D = cardiac resynchronization therapy defibrillator, PCI = percutaneous coronary intervention

NYHA = New York Heart Association

Table 3. Echocardiographic evaluation

	Baseline						5 Year follow up					
Patient	E/A ratio	Desc. time	MR	Pulm. pressure	RWM score	LVEF %	E/A ratio	Desc. time	MR	Pulm. pressure	RWM score	LVEF %
1	1.3	180	Mild	55	41	25	1	205	Mild	25	43	25
3	0.4	>200	Mild	25	39	30	0.95	249	Mild	35	37	25
4	1.3	170	Mild		36	40	1.1	201	Trivial	25	36	40
5	1.3		Mod		38	30		N/A	N/A	N/A	N/A	N/A
7	0.9	>200	Mild	44	44	25	N/A	N/A*	Mild	60	36	45
8	0.6	>160	Trivial	35	40	25	N/A	140	Trivial	25	44	25

*Atrial fibrillation
RWM = regional wall motion, LVEF = left ventricular ejection fraction

the intracoronary bone marrow injection. Coronary angiography was performed without angioplasty. One month later this patient underwent left femoral-popliteal bypass surgery followed by chronic hemodialysis. Finally, 1 year after this last clinical event, yet another vascular procedure was carried out. The fifth patient was hospitalized due to non-cardiac causes (gout and pneumonia) 24, 29 and 54 months after the infusion procedure. In this patient a CRT-D was implanted due to heart failure 20 months after the infusion. The last patient alive underwent successful prostatectomy due to neoplasm 51 months after the bone marrow infusion. One patient died from leukocytoclastic vasculitis 21 months after intracoronary bone marrow infusion. Before this event, he had been hospitalized three times: twice for pulmonary edema and once for acute cholecystitis. The second patient died suddenly during sleep 30 months after the bone marrow transplant, despite an implanted automated cardioverter defibrillator/CRT 8 months after transplantation.

The echocardiographic follow-up [Table 3] of the six patients who are alive did not show any significant change in systolic and diastolic parameters between the baseline and 5 year follow-up echo.

DISCUSSION

Treatment of severe ischemic heart failure is limited. New approaches for improved prognosis and better quality of life are being investigated, among them bone marrow-based therapy which has gained interest in the past decade. The main premise of this therapy assumes the differentiation of the injected cells into viable cardiomyocytes that supposedly will engage in recovery and improvement of cardiac function. In vitro and in vivo trials showed encouraging short-term results but they lack long-term follow-up

Our current study focuses on the 5 year follow-up of eight patients with severe ischemic cardiomyopathy who were not suitable for revascularization. Clearly, our most interesting finding was the unexpectedly low mortality when compared to the expected rate described for these patients. The expected yearly mortality rate in patients with heart failure, NYHA functional class III or higher, ranges between 20 and 30%; in our study, six of eight patients survived for 5 years, a surprising 75% survival rate. Furthermore, only one patient died due to cardiac cause – sudden death, in spite of an ICD/CRT implanted earlier. The other patient died as a result of vasculitis, which cannot be directly related to the procedure. Another message that can be obtained from our results relates to the safety of the procedure, which was previously reported and validated by our current results.

With regard to quality of life measures, NYHA functional class had improved in two patients but deteriorated in one. Analysis of the echocardiographic systolic function (by LVEF and regional quantitative wall motion score) and of diastolic function (by E/A ratio, E-wave deceleration time), as well as the degree of mitral regurgitation and estimated pulmonary pressure, did not demonstrate a significant change over 5 years in the surviving patients. One cannot assume causality between the improvement in objective measures or null effect, related to bone marrow-based therapy for several reasons. First, the study cohort is obviously underpowered by its size; and secondly, many confounders (e.g., ICD/CRT implantation, medical therapy) may have contributed to the different results.

In the present study, follow-up angiography was performed based solely on clear clinical indications. Repeat angiography in two patients failed to identify restenotic lesions as described in previous studies.

In conclusion, although conclusive results cannot be drawn because of the small cohort, our results indicate that intracoronary bone marrow injection for patients with severe ischemic cardiomyopathy is safe and may be related to prolonged survival when compared to expected mortal-

CRT-D = cardiac resynchronization therapy defibrillator

ICD = implantable cardioverter defibrillator
LVEF = left ventricular ejection fraction

ity rates for these patients. Currently, this cell-based cardiac regeneration therapy suggests a nebulous future despite promising animal studies, clinical studies showing feasibility and safety, and initial small-scale studies with long-term outcomes. Further large-scale trials are needed to establish this hypothesis.

Corresponding author:
Dr. A. Blatt
Dept. of Cardiology, Assaf Harofeh Medical Center, Zerifin 70300, Israel
Phone: (972-8) 977-9345
Fax: (972-8) 977-9349
email: alexb@asaf.health.gov.il

References

1. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002; 347: 1397-402.
2. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle heart failure model: prediction of survival in heart failure. *Circulation* 2006; 113: 1424-33.
3. Caspi O, Gepstein L. Regenerating the heart using human embryonic stem cells – from cell to bedside. *IMAJ Isr Med Assoc J* 2006; 8: 208-14.
4. Barbash IM, Leor J. Myocardial regeneration by adult stem cells. *IMAJ Isr Med Assoc J* 2006; 8: 283-7.
5. Taylor DA, Atkins BZ, Hungspreugs P, et al. Regenerating functional myocardium: improve performance after skeletal myoblast transplantation. *Nat Med* 1998; 4: 929-33.
6. Jain M, DerSimonian H, Brenner DA, et al. Cell therapy attenuates deleterious ventricular remodeling and improves cardiac performance after myocardial infarction. *Circulation* 2001; 103: 1920-9.
7. Orlic D, Kajstura J, Chimenti S, et al. Bone marrow cells regenerate myocardium. *Nature* 2001; 410: 701-5.
8. Blatt A, Cotter G, Leitman, et al. Intra-coronary administration of autologous bone marrow mononuclear cells after induction of short ischemia is safe and may improve hibernation and ischemia in patients with ischemic cardiomyopathy. *Am Heart J* 2005; 150: 986e1-7.
9. Perin EC, Dohmann HF, Borojevic R, et al. Improvement in exercise capacity at six months following transendocardial injection of autologous bone marrow mononuclear cells for ischemic cardiomyopathy. *Circulation* 2003; 107: R75-83.
10. Assmus B, Schächinger V, Teupe C, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). *Circulation* 2002; 106: 3009-17.
11. Yao K, Huang R, Sun A, et al. Repeated autologous bone marrow mononuclear cell therapy in patient with large myocardial infarction. *Eur J Heart Fail* 2009; 11: 691-8.
12. Moncini D, Staibano M, Mele L, et al. Autologous bone marrow mononuclear cell transplantation in patients undergoing coronary artery by-pass grafting. *Am Heart J* 2006; 151: 192-7.
13. Wollert KC, Meyer GP, Lotz J, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomized controlled clinical trial. *Lancet* 2004; 364: 141-8.
14. Kang HJ, Kim HS, Zhang SY, et al. Effects of intracoronary infusion of peripheral blood stem-cells mobilized with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis after coronary stenting in myocardial infarction: the MAGIC cell randomized clinical trial. *Lancet* 2004; 363: 751-6.
15. Murry CE, Reinecke H, Pabon LM. Regeneration gaps: observation on stem cells and cardiac repair. *J Am Coll Cardiol* 2006; 47: 1777-85.
16. Beers SL, Bengel FM, Bartunek J, et al. Role of imaging in cardiac stem cell therapy. *J Am Coll Cardiol* 2007; 49: 1137-48.
17. Abdel-Latif A, Bolli R, Tleyjeh IM, et al. Adult bone marrow-derived cells for cardiac repair. *Arch Intern Med* 2007; 167: 989-97.
18. Cao F, Sun D, Li Ch, et al. Long-term myocardial function improvement after autologous bone marrow mononuclear cells transplantation in patients with ST-segment elevation myocardial infarction: 4 years follow-up. *Eur Heart J* 2009; 30: 1986-94.
19. Bourdillon PVD, Broderick TM, Sawada SG, et al. Regional wall motion index for infarcted and noninfarcted regions after reperfusion in acute myocardial infarction: comparison with global wall motion index. *J Am Soc Echocardiogr* 1989; 2: 398-402.