Cell Therapy for Nonischemic Cardiomyopathy

Current Status and Future Perspectives

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Currently, nonischemic dilated cardiomyopathy (NICM) represents the leading cause of advanced heart failure, accounting for >50% of all heart transplantation procedures. We propose that when compared with patients with ischemic heart failure (IHF), patients with NICM demonstrate a more favorable clinical response to cell therapy, which offers a potential novel promising treatment approach for this patient population.

Chronic heart failure represents one of the most important healthcare problems worldwide. Although survival after diagnosis of heart failure has improved, overall mortality remains high.[1] In the recent years, several novel approaches for heart failure management have been tested in clinical trials, with cell therapy representing one of potentially more promising treatment modalities.

The majority of clinical trials of cell therapy in chronic heart failure have been focusing on patients with IHF. In this cohort, early trials demonstrated clinical benefits and an improvement in left ventricular function after cell therapy; however, subsequent larger trials failed to confirm these findings. Furthermore, a recent meta-analysis of 38 randomized controlled trials in IHF found only low-quality evidence that treatment with bone marrow-derived cells reduces mortality and improves left ventricular ejection fraction (LVEF).[2] Although the reasons for the inconsistent results remain poorly defined, they could be partially explained by the fact that despite the potential beneficial effects on the myocardium, cell therapy does not affect the progression of atherosclerosis, which may limit the clinical efficacy of this approach in patients with IHF.

In the last decade, NICM has become the leading cause of advanced heart failure, accounting for >50% of all heart transplantations.[1] These trends indicate that patients with NICM may represent the largest subpopulation of heart failure patients with a particular need for alternative treatment modalities, including cell therapy. The disease progression in NICM is thought to result from the interactions among specific sarcomeric and cytoskeletal proteins. In addition to alterations in myocytes, patients with NICM also demonstrate defective vascularization and impaired vasculogenesis and angiogenesis.[3] However, when compared with patients with IHF, patients with NICM display significantly lesser amount of myocardial scarring with less transmural involvement.[4] Recent evidence suggests that the underlying disease process in patients with NICM may be reversible, with ≈25% of patients with NICM with recent onset of heart failure having a relatively benign course with spontaneous recovery of left ventricular function.[5] Furthermore, in NICM, the epicardial coronary vessels are normal, and the only target for cell therapy is myocardial dysfunction, which could represent an important underlying mechanism for the differences in clinical response to cell therapy in patients with IHF and NICM.

To date, clinical trials investigating the effects of cell therapy in NICM have been relatively scarce. However, in contrast to the studies in patients with IHF, the results of these trials have been consistently positive, regardless of the choice of study end points, cell types, and modes of cell delivery (Table).

One of the first trials was the TOPCARE-DCM trial (Transplantation of Progenitor Cells and Functional Regeneration Enhancement Pilot Trial in Patients with Nonischemic Dilated Cardiomyopathy),[6] where intracoronary infusion of bone marrow-derived cells was performed in 33 patients with NICM. At 3 months, there was an improvement of regional wall motion of the target area, accompanied by an increase in LVEF. In accordance with these findings, NT-proBNP (N-terminal pro-B-type natriuretic peptide) serum levels decreased significantly within the first year after therapy. The ABCD trial (Autologous Bone Marrow Cells in Dilated Cardiomyopathy)[7] included 85 patients with NICM randomized to either treatment arm, receiving unselected bone marrow-derived cells via coronary sinus, or control arm, treated with medical therapy. During the mean follow-up time of 28 months, there was a significant improvement in LVEF in the treatment arm, with a concomitant reduction in end-systolic volumes. Similar results were found in a study in end-stage NICM[8] where 22 patients randomly underwent either G-CSF (granulocyte-colony stimulating factor) administration or G-CSF stimulation followed by intracoronary infusion of bone marrow-derived cells. At 1 month after therapy, patients who received stem cell infusions showed improvements in LVEF, maximal oxygen consumption, New York Heart Association functional class, and quality of life.

Based on the encouraging results of the pilot trials, our group has performed the first prospective, randomized, open-label trial investigating long-term effects of cell therapy in patients with NICM.[9] We enrolled 110 patients who were randomly allocated

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Table. Clinical Trials of Cell Therapy in Nonischemic Dilated Cardiomyopathy

Study	No. of Patients	Cell Type	Delivery Route	Follow-Up, mo	Primary End Point Reached	LVEF Change, %
TOPCARE-DCM[6]	33	BMC	IC	3	Yes	+3.2
ABCD[7]	85	BMC	IC	28	Yes	+5.9
Bocchi et al[8]	22	BMC	IC	15	Yes	+8.8
Vrtovec et al[9]	110	CD34+	IC	60	Yes	+5.7
Vrtovec et al[10]	40	CD34+	TE, IC	6	Yes	+8.1
REGENERATE-DCM[11]	60	BMC	IC	3	Yes	+5.4
POSEIDON-DCM[12]	37	MSC	TE	12	Yes	+8.0

ABCD indicates autologous bone marrow cells in dilated cardiomyopathy; BMC, bone marrow-derived cells; IC, intracoronary; LVEF, left ventricular ejection fraction; MSC, mesenchymal cells; POSEIDON-DCM, Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis in Dilated Cardiomyopathy; REGENERATE-DCM, Randomized Trial of Combination Cytokine and Adult Autologous Bone Marrow Progenitor Cell Administration in Patients with Non-ischaemic Dilated Cardiomyopathy; TE, transendocardial; and TOPCARE-DCM, Transplantation of Progenitor Cells and Functional Regeneration Enhancement Pilot Trial in Patients with Nonischemic Dilated Cardiomyopathy.

into the stem cell group (n=55) or control group (n=55). In the stem cell group, peripheral blood CD34+ cells were mobilized by G-CSF, collected via apheresis, and injected in the coronary artery supplying target myocardial segments. At 5 years, stem cell therapy was associated with an increase in LVEF, an increase in 6-minute walk distance, and a decrease in NT-proBNP. Because in this trial, the response to intracoronary CD34+ cell therapy was dependent on the degree of myocardial cell retention, we performed a follow-up study investigating whether improving cell retention rates by using transendocardial injection results in superior clinical improvement.[10] Of 40 patients with NICM, 20 were randomized to receive intracoronary injection, and 20 received transendocardial CD34+ cell therapy. At 6 months, LVEF improved in both groups; however, the improvement was more prominent in the transendocardial group. The same pattern was observed for 6-minute walk test distance and NT-proBNP.

In a more recent, randomized, placebo-controlled trial with a combination of G-CSF and intracoronary cell therapy enrolling 60 patients with NICM (REGENERATE-DCM [Randomized Trial of Combination Cytokine and Adult Autologous Bone Marrow Progenitor Cell Administration in Patients with Non-ischaemic Dilated Cardiomyopathy]),[11] they found a significant improvement in cardiac function, symptoms, and biochemical parameters at 3 months after cell therapy. Finally, in a POSEIDON-DCM trial (Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis in Dilated Cardiomyopathy),[12] the authors conducted a randomized comparison of autologous versus allogeneic bone marrow-derived mesenchymal cells in 37 patients with NICM. LVEF increased in both groups with the improvement being more prominent with allogeneic cell therapy. The same was true for changes in exercise capacity and quality of life, suggesting that allogeneic cell therapy may offer a novel opportunity to enhance the potency of cell therapy in NICM.

Collectively, the results of these trials demonstrate that when compared with patients with IHF, the degree of treatment effect with cell therapy in NICM is more pronounced and may persist longer. In contrast with this hypothesis, the results of Ixmyelocel-T trial demonstrated a significant improvement at 12 months after cell therapy in patients with IHF but not with NICM.[13] However, although nonsignificant when compared with the control group, patients with NICM did demonstrate an absolute decrease in New York Heart Association class and increase in exercise capacity after cell therapy, which was comparable with the changes in patients with IHF. This led the authors to conclude that the potential to assess the benefits of ixmyelocel-T in the NICM group may have been limited because of the significant improvements in the control group.

Although less bulky than the data in IHF, these findings suggest that cell therapy may represent a potentially beneficial treatment modality in NICM and that future, larger studies in the field should focus more on this subpopulation of patients with chronic heart failure. Interestingly, recent studies in NICM have also demonstrated that cell therapy may affect diastolic properties[14] and lead to improved right ventricular function.[15] Taken together, these data suggest that a treatment effect of cell therapy in NICM may reach beyond the sole change in LVEF, which has been repeatedly questioned as a valid end point in stem cell studies. Thus, to better understand the impact of cell therapy in NICM, several combined end points should be analyzed in the future.

Despite the challenges, it seems that cell therapy offers a promising treatment strategy for a growing population of patients with NICM who are currently facing relatively limited therapeutic options. The results of ongoing and future clinical trials will provide more insights into the mechanisms of disease progression and better define whether or not the effects of cell therapy in NICM may be further enhanced by the use of more potent stem cell types or repetitive dosing strategies.

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None.

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