Journal of the American Heart Association

EDITORIAL

Can't Patch Everything: Personalized Medicine for Cell Therapy in Dilated Cardiomyopathy

Andrew Sundin, MD; Wayne Balkan, PhD; Joshua M. Hare, MD

Among incident cases of heart failure with reduced ejection fraction, non-ischemic dilated cardiomyopathy (NIDCM) represents the etiologic basis in approximately 36% patients.[1,2] Unlike ischemic cardiomyopathy which arises from ventricular remodeling driven by an underlying infarct scar, fibrosis in NIDCM is present to variable degrees and is patchy and interstitial.[3,4] Although there is no known cure for NIDCM,[5] cell therapy has shown promise in early stage clinical trials.[6] A clear and emerging trend is that there is broad variability in patient responsiveness to these therapies.

See Article by Domae et al.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Domae et al demonstrate 2 distinct groups of stem cell-responsiveness relationships.[7] Patients with New York Heart Association classification II–IV NIDCM were implanted with autologous, scaffold-free skeletal cell patches. This product that has been approved for use in Japan under the Japanese Pharmaceuticals and Medical Devices Agency conditional approval pathway, a development that was not universally endorsed by the academic community.[9] Previous phase I clinical trials for ischemic[10] and dilated[11] cardiomyopathy demonstrated feasibility, safety and efficacy of the skeletal cell patches, and in the current study the primary study end point was the combination of major adverse cardiovascular events and incidence of heart failure, defined as admission according to the Framingham heart failure diagnostic criteria.[12]

Of the 24 patients with dilated cardiomyopathy receiving the cell patch; 13 were classified as responders, defined as those in whom "symptoms, exercise capacity and cardiac performance were improved postoperatively"; and 11 were classified as non-responders , those not exhibiting such improvements. Responders also exhibited decreased serum BNP (brain natriuretic peptide), stabilized pulmonary capillary wedge pressure, and had an elevated level of the epigenetic marker human H3K4me3 (histone H3 lysine 4 trimethylation) and less fibrosis detected in the myocardium preoperatively.[7]

In addition to the above, responders baseline characteristics included a statistically more favorable clinical profile in terms of BNP (23.3±4.5 versus 56.1±10.0 pg/mL), pulmonary capillary wedge pressure (8.5±1.2 versus 15.5±2.1 mm Hg), and New York Heart Association classification II (7 of 13, 53.8% versus 1 of 11, 9.1%) compared with non-responders. Multivariate analysis indicated that responders and non-responders clinical response could be partially predicted using BNP, pulmonary capillary wedge pressure, and H3K4me3; however, no cutoff values were offered. These findings suggest that the severity of disease can alter patient response to patch therapy. At a minimum these findings can be viewed as hypothesis generating and could assist in patient selection for future trials.

Key Words: Editorials ■ cardiac remodeling ■ cell transplantation ■ genetics ■ nonischemic cardiomyopathy ■ regeneration

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: Joshua M. Hare, MD, University of Miami Miller School of Medicine, Miami, FL 33136. E-mail: jhare@med.miami.edu

For Sources of Funding and Disclosures, see page 3.

JAHA is available at: www.ahajournals.org/journal/jaha

Previous in vitro studies implicate diminished expression of H3k4me3 along with additional epigenetic changes of favorable histone complexes in heart failure.[13] These findings were supported by a clinical study that looked at preoperative and postoperative cardiac biopsies in patients with a left ventricular assist device. Postoperative findings produced an improved histologic profile and upregulated several favorable histone complexes, which in turn correlated with decreased cardiomyocyte size and ANP (atrial natriuretic peptide) and BNP levels.[14] Although H3k4me3 allowed patient stratification predictive of the success of cellular transplant, in the present study without repeat cardiac biopsy, it is unclear if the cell graft induced a more favorable histologic profile.

Fibrosis is implicated in the pathogenesis of nonischemic cardiomyopathy[4] and is present in all end-stage heart failure, with the distribution differing with etiology. As collagen deposition increases, ventricular function deteriorates contributing to diastolic dysfunction.[3] One of the key mechanisms of action underlying the efficacy of the skeletal patch is an anti-fibrotic effect, and in this regard the patch is reported to secrete hepatocyte growth factor, vascular endothelial growth factor, and stromal cell-derived factor-1,[15] cytokines that reduce fibrosis, increase angiogenesis, and augment migration of cardiac stem cells, respectively[15] (Figure).

Preclinical studies in rats identified that secretion of these cytokines correlated with decreased fibrosis, increased cellularity and decreased pulmonary artery pressures.[15,16] Additionally, the surgical placement of a sheet lattice over cardiac tissue was postulated to provide structural integrity to the cardiac tissue providing mechanical support to the heart and reducing stress while the grafted cells enact their paracrine activity.[15] Cardiac remodeling with a reduction in fibrosis would decrease left ventricular stiffness, allowing for improved relaxation of cardiac tissue, and thus a reduction of pulmonary capillary wedge pressure without necessarily changing ejection fraction, consistent with their results. These findings provide additional support for the growing appreciation that cell-based therapies exert clinically beneficial effects without engrafting and promote endogenous remuscularization.[17] Similar to the epigenetic changes discussed, the effect of the patch system on fibrosis can only be surmised, as no follow-up cardiac biopsy was performed. This gap could be addressed in the future by using delayed enhancement gadolinium magnetic resonance imaging to non-invasively quantify cardiac fibrosis.[3]

Another crucial consideration in patients with NIDCM is the contribution of genetics. Among cases of dilated cardiomyopathy, 20% to 50% are attributable to a familial origin, with variable expression and inheritance patterns.[18] The relationship between genotype and responsiveness to cell therapy was first assessed by Rieger and colleagues who evaluated the role of genetic variants in a pre-specified analysis of patients from the POSEIDON-DCM (Percutaneous Stem Cell Injection Delivery Effects On Neomyogenesis in Dilated Cardiomyopathy) clinical trial,[19] which compared the effectiveness of allogenic- and autologous-bone

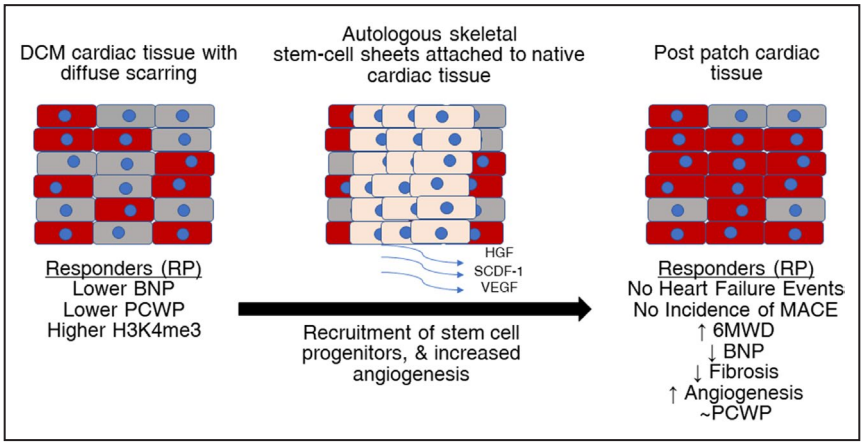

Figure 1. Potential mechanism by which autologous skeletal stem-cell sheets improve the status of patients with non-ischemic dilated cardiomyopathy.
Autologous skeletal stem cell sheets secrete a variety of growth factors[15] that likely mediate the improvements in responsive patients following implantation. 6MWD indicates 6-minute walk distance; BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy; H3K4me3, histone H3 lysine 4 trimethylation; HGF, hepatocyte growth factor; MACE, major adverse cardiovascular event; PCWP, pulmonary capillary wedge pressure; SCDF-1, stem cell-derived factor-1; and VEGF, vascular endothelial growth factor.

marrow-derived mesenchymal stromal/stem cells.[5] Genetic sequencing of these patients using a 104 gene cardiomyopathy panel allowed classification of patients as being negative for any variant (n=6), having a variant of uncertain significance (VUS, n=20), or a pathologic variant (n=8). Interestingly, survival at 1 year was 100%, 85%, and 40% in negative for variant, variant of uncertain significance, and pathologic variant subgroups, respectively, and only the negative for variant, and variant of uncertain significance groups demonstrated a positive change in ejection fraction over this time course, whereas ejection fraction continued to decline in the patients with the pathologic variant. There were no statistically significant differences in baseline characteristics between the 3 groups except for pro-BNP (pro B-type natriuretic peptide), which was markedly elevated in the pathologic variant population. Patients negative for identifiable pathologic variants were more likely to respond to cell delivery as indicated by improved cardiac function, quality of life and survival and reduced major adverse cardiovascular events.[19] The converse was true for patients positive for pathologic variants. This exciting finding forms the hypothesis for a new trial and will be tested in a larger placebo-controlled trial, DCMII (Transendocardial Injection of Allogeneic-Mesenchymal Stem Cells [MSCs] in Patients With Non-Ischemic Dilated Cardiomyopathy), that will stratify patients prospectively (ClinicalTrials.gov #NCT04476901).

An early adage about this new and emerging field was that success would result from "using the right cell in the right patient at the right time and by the correct delivery method". As the current work[7] and that of others[19] (reviewed in Banerjee et al[20]) clearly illustrates, this principle of personalized medicine can contribute to success in correct patient selection. Most importantly, new and emerging concepts need to be prospectively tested in larger, well-powered clinical trials using primary end points supported by earlier trials.

ARTICLE INFORMATION

Affiliations

Interdisciplinary Stem Cell Institute (A.S., W.B., J.M.H.) and Department of Medicine, University of Miami Miller School of Medicine, Miami, FL (W.B., J.M.H.).

Sources of Funding

This work is supported by W81XWH-19-PRMRP-CTA from the Department of Defense. Dr Hare is also supported by 1R01HL134558, 1R01HL137355, and 2R01HL107110 from National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) and the Marcus and the Soffer Family Foundations.

Disclosures

Dr Hare reported having a patent for cardiac cell-based therapy. He holds equity in Vestion Inc. and maintains a professional relationship with Vestion Inc. as a consultant and member of the Board of Directors and Scientific Advisory Board. Dr Hare is the Chief Scientific Officer, a compensated consultant and advisory board member for Longeveron, and holds equity in Longeveron. Dr Hare is also the co-inventor of intellectual property licensed to Longeveron. Dr Hare's relationships are disclosed to the University of Miami, and a management plan is in place. Longeveron LLC and Vestion Inc. did not participate in funding this work. The remaining authors have no disclosures to report.

REFERENCES

1. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol*. 2013;10:531–547. DOI: 10.1038/nrcardio.2013.105.
2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. *Circulation*. 2021;143:e254–e743. DOI: 10.1161/CIR.0000000000000950.
3. Mewton N, Liu CY, Croisille P, Bluemke D, Lima JAC. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2011;57:891–903. DOI: 10.1016/j.jacc.2010.11.013.
4. Hare JM, Walford GD, Hruban RH, Hutchins GM, Deckers JW, Baughman KL. Ischemic cardiomyopathy: endomyocardial biopsy and ventriculographic evaluation of patients with congestive failure, dilated cardiomyopathy and coronary artery disease. *J Am Coll Cardiol*. 1992;20:1318–1325. DOI: 10.1016/0735-1097(92)90243-G.
5. Hare JM, DiFede DL, Rieger AC, Florea V, Landin AM, El-Khorazaty J, Khan A, Mushtaq M, Lowery MH, Byrnes JJ, et al. Randomized Comparison of Allogeneic Versus Autologous Mesenchymal Stem Cells for Nonischemic Dilated Cardiomyopathy: POSEIDON-DCM Trial. *J Am Coll Cardiol*. 2017;69:526–537. DOI: 10.1016/j.jacc.2016.11.009.
6. Poglajen G, Zemljič G, Frljak S, Cerar A, Andročec V, Sever M, Černelč P. Stem cell therapy in patients with chronic nonischemic heart failure. *Stem Cells Int*. 2018;2018:6487812. DOI: 10.1155/2018/6487812.
7. Domae K, Miyagawa S, Yoshikawa Y, Fukushima S, Hata H, Saito S, Kainuma S, Kashiyama N, Iseoka H, Ito E, et al. Clinical outcomes of autologous stem cell-patch implantation for patients with heart failure with nonischemic dilated cardiomyopathy. *J Am Heart Assoc*. 2021;10:e008649. DOI: 10.1161/JAHA.117.008649.
8. Report on the Deliberation Results. Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau. Japan Ministry of Health, Labour and Welfare. September 2, 2015. Available at: https://www.pmda.go.jp/files/000215222.pdf. Accessed May 1, 2021.
9. Yui Y. Concerns on a new therapy for severe heart failure using cell sheets with skeletal muscle or myocardial cells from iPS cells in Japan. *NPJ Regen Med*. 2018;3:7. DOI: 10.1038/s41536-018-0047-2.
10. Sawa Y, Yoshikawa Y, Toda K, Fukushima S, Yamazaki K, Ono M, Sakata Y, Hagiwara N, Kinugawa K, Miyagawa S. Safety and efficacy of autologous skeletal myoblast sheets (TCD-51073) for the treatment of severe chronic heart failure due to ischemic heart disease. *Circ J*. 2015;79:991–999. DOI: 10.1253/circj.CJ-15-0243.
11. Miyagawa S, Domae K, Yoshikawa Y, Fukushima S, Nakamura T, Saito A, Sakata Y, Hamada S, Toda K, Pak K, et al. Phase I clinical trial of autologous stem cell-sheet transplantation therapy for treating cardiomyopathy. *J Am Heart Assoc*. 2017;6:e003918. DOI: 10.1161/JAHA.116.003918.
12. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. *N Engl J Med*. 1971;285:1441–1446. DOI: 10.1056/NEJM197112232852601.
13. Kaneda R, Takada S, Yamashita Y, Choi YL, Nonaka-Sarukawa M, Soda M, Misawa Y, Isomura T, Shimada K, Mano H. Genome-wide histone methylation profile for heart failure. *Genes Cells*. 2009;14:69–77. DOI: 10.1111/j.1365-2443.2008.01252.x.
14. Ito E, Miyagawa S, Fukushima S, Yoshikawa Y, Saito S, Saito T, Harada A, Takeda M, Kashiyama N, Nakamura Y, et al. Histone modification is correlated with reverse left ventricular remodeling in nonischemic dilated cardiomyopathy. *Ann Thorac Surg*. 2017;104:1531–1539. DOI: 10.1016/j.athoracsur.2017.04.046.
15. Kondoh H, Sawa Y, Miyagawa S, Sakakidakitagawa S, Memon I, Kawaguchi N, Matsuura N, Shimizu T, Okano T, Matsuda H. Longer preservation of cardiac performance by sheet-shaped myoblast

implantation in dilated cardiomyopathic hamsters. *Cardiovasc Res*. 2006;69:466–475. DOI: 10.1016/j.cardiores.2005.11.005.
16. Hoashi T, Matsumiya G, Miyagawa S, Ichikawa H, Ueno T, Ono M, Saito A, Shimizu T, Okano T, Kawaguchi N, et al. Skeletal myoblast sheet transplantation improves the diastolic function of a pressure-overloaded right heart. *J Thorac Cardiovasc Surg*. 2009;138:460–467. DOI: 10.1016/j.jtcvs.2009.02.018.
17. Bolli R, Mitrani RD, Hare JM, Pepine CJ, Perin EC, Willerson JT, Traverse JH, Henry TD, Yang PC, Murphy MP, et al. A Phase II study of autologous mesenchymal stromal cells and c-kit positive cardiac cells, alone or in combination, in patients with ischaemic heart failure: the CCTRN CONCERT-HF trial. *Eur J Heart Fail*. 2021;14:69–77. DOI: 10.1002/ejhf.2178.
18. Rosenbaum AN, Agre KE, Pereira NL. Genetics of dilated cardiomyopathy: practical implications for heart failure management. *Nat Rev Cardiol*. 2020;17:286–297. DOI: 10.1038/s41569-019-0284-0.
19. Rieger AC, Myerburg RJ, Florea V, Tompkins BA, Natsumeda M, Premer C, Khan A, Schulman IH, Vidro-Casiano M, DiFede DL, et al. Genetic determinants of responsiveness to mesenchymal stem cell injections in non-ischemic dilated cardiomyopathy. *EBioMedicine*. 2019;48:377–385. DOI: 10.1016/j.ebiom.2019.09.043.
20. Banerjee MN, Bolli R, Hare JM. Clinical studies of cell therapy in cardiovascular medicine: recent developments and future directions. *Circ Res*. 2018;123:266–287. DOI: 10.1161/CIRCRESAHA.118.311217.