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EDITORIAL COMMENT

Mesenchymal Cell Therapy for Dilated Cardiomyopathy

Time to Test the Water*

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Following more than a decade of preclinical testing, stem cell-based interventions in the mammalian heart have emerged as a promising treatment for heart disease. Today, we have unanimity that cardiomyogenesis—the generation of new heart muscle cells—is rather unlikely in the absence of long-term engraftment and robust transdifferentiation, at least as a result of adult stem cell transfer. Myocardial repair after severe myocardial infarction and in chronic heart failure (HF) is likely mediated via paracrine signaling pathways (1). Among candidate cell types, mesenchymal stem cells (MSC) derived from bone marrow and, more recently, cardiac-derived cells expanded from myocardial biopsies feature prominently because they are capable of enhancing angiogenesis, mitigating inflammation and apoptotic cell death, and reducing scar remodeling and myocardial fibrosis via immune-modulatory and cytoprotective cytokines (**Figure 1**) (2–4).

Moreover, MSCs have a documented immune-privileged status because they lack major histocompatibility class II and costimulatory molecules; plus, they have a reassuring safety profile and a promising therapeutic potential in selected patients with ischemic cardiomyopathy (5,6). However, major limitations of using autologous cells include the requirement for a long and costly cell expansion procedure as well as a risk of impaired stem cell functionality in older patients with significant comorbidities. To circumvent these limitations, more recent clinical developments have focused on allogeneic mesenchymal precursor cells or cardiac-derived cells, as in the ongoing phase III DREAM-HF (Efficacy and Safety of Allogeneic Mesenchymal Precursor Cells (Rexlemestrocel-L) for the Treatment of Heart Failure; NCT02032004) and ALLSTAR (Allogeneic Heart Stem Cells to Achieve Myocardial Regeneration; NCT01458405) trials.

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In this issue of the *Journal*, Hare et al. (7) expand the concept of allogeneic MSC therapy in chronic HF patients by focusing on 2 new important features. First, the authors exclusively targeted patients with nonischemic dilated cardiomyopathy (NIDCM), an important cohort of HF patients with a high unmet clinical need (8). Second, they introduced a randomized comparison between autologous and allogeneic MSCs. The carefully executed POSEIDON-DCM (Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis in Dilated Cardiomyopathy) trial recruited 37 patients with stable HF of nonischemic origin over 3.5 years to test the safety and feasibility of transendocardial injections of autologous versus allogeneic MSCs. The primary safety endpoint in this small pilot trial was met in all 34 patients who received a total of 10 NOGA-guided transendocardial injections with no treatment-emergent serious adverse events within 30 days in either group, a reassuring finding of such an invasive therapeutic intervention.

All patients were subsequently followed for up to 12 months with serial immune surveillance, endothelial function analysis, and multimodal cardiac imaging of functional and structural remodeling. By design, the study lacked a control group, which cautions against definitive conclusions on efficacy. Evaluation of functional status, quality of life, and

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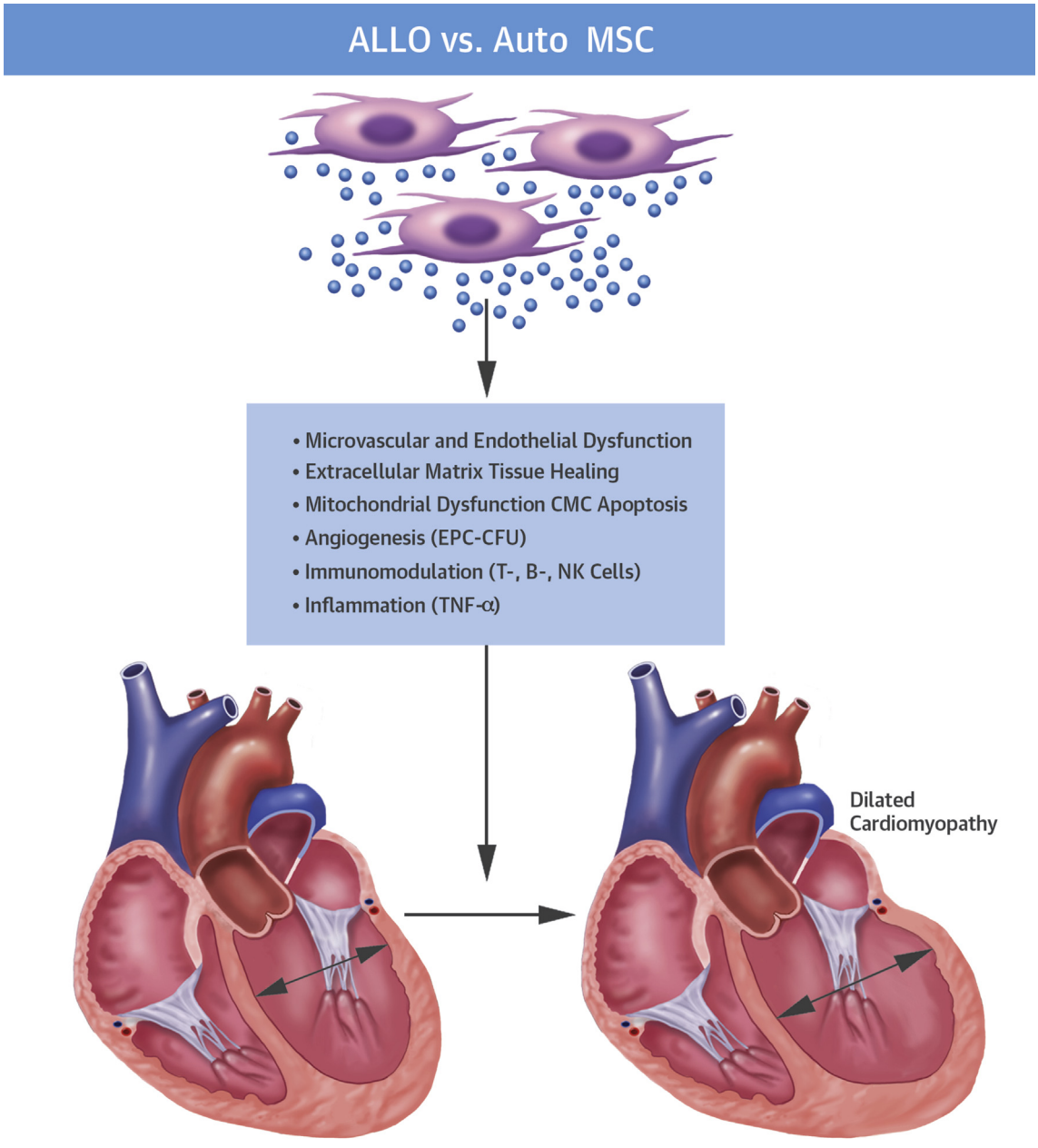
FIGURE 1 Drivers of Left Ventricular Dilation in NIDCM



Proposed mechanisms whereby allogeneic (ALLO) and autologous (Auto) mesenchymal stem cells (MSCs) can modulate the progression of left ventricular dilation in nonischemic dilated cardiomyopathy (NIDCM). MSCs exert paracrine effects resulting in reduced cardiac myocyte (CMC) mitochondrial dysfunction and apoptosis; reduced matrix remodeling and collagen synthesis; improved microvascular and endothelial cell function, measured via flow-mediated vasodilation; enhanced angiogenesis and endothelial progenitor cell colony formation units (EPC-CFU); reduced inflammation; and modulated adaptive and innate immune responses. NK = natural killer; TNF = tumor necrosis factor.

remodeling parameters collected at follow-up visits showed encouraging signals for some of the between-group comparisons in favor of allogeneic transfer but requires confirmation in adequately powered, controlled trials.

One of the major challenges in NIDCM is the complex and heterogeneous etiology of the disease, including genetic, toxic, inflammatory, infectious, and unknown causes of the dilated phenotype (**Figure 1**) (9). Careful identification of which NIDCM

patients best respond to transendocardial MSC injection is mandatory. The authors have performed a laudable effort in the POSEIDON-DCM study to garner mechanistic insights into the cells' mode of action, which is important in view of the fact that the observed variability in left ventricular function changes with time. Approximately one-quarter of patients randomized to allogenic cell transfer experienced impaired or unchanged global systolic function after 1 year, whereas others showed a dramatic improvement. The reason for such variability, which was not observed in patients randomized to autologous MSC therapy, remains unclear. One of the caveats of allogeneic therapies is the inherent risk of sensitization against donor-cell-specific human leukocyte antigens, especially in a relatively young population with advanced NIDCM, many of whom will ultimately require listing for transplantation.

The authors have diligently performed immune surveillance of different T-cell populations and monitored critical inflammatory cytokines, including tumor necrosis factor (TNF)-α. On aggregate, the reported immune phenotype suggested that allogeneic MSCs favorably altered several immunologic markers typically activated in chronic inflammation, as well as circulating TNF-α levels at 6 months. This was consistent with previously reported clinical benefits in left ventricular assist device patients who received intramyocardial injections of mesenchymal precursor cells and showed better tolerance of weaning from circulatory support (10). Yet in the POSEIDON-DCM study, calculated panel reactive antibody monitoring indicated that 4 of 15 patients (27%) treated with allogeneic MSCs developed a moderate antibody response, whereas 1 patient (7%) developed a high response that would compromise future transplantation or repetitive injections.

Repeated stem cell administration in chronic disease states is an emerging concept that has been successfully tested in ischemic cardiomyopathy (11). NIDCM is a steadily progressing disease that requires lifelong HF treatment, but because homing signals that direct injected stem cells to the site of myocardial injury are lacking in NIDCM, repeated injections might be a prerequisite for cell therapy to be effective. Although moderate calculated panel reactive antibody responses might not harm or affect the clinical course of patients in the short term, they definitely require careful monitoring in view of the likelihood of repeat dosing of MSCs in chronic HF.

Where does the POSEIDON-DCM study lead us from here? We need a better understanding of drivers of disease progression in NIDCM (inflammation, microvascular dysfunction, radical stress with impaired mitochondrial function, apoptotic cell death or ongoing matrix remodeling, and impaired collagen homeostasis) and on the different mechanisms of allogeneic versus autologous MSCs. The data from this pilot trial represent an important and necessary step on a developmental path towards better targeted cell therapies for nonischemic HF and should facilitate future efforts to optimally match stem cell modes of action with drivers of disease.

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