Study Shows Stem Cell Therapy Dosing Matters in Ischemic Cardiomyopathy

Results of the Dose Comparison Study of Allogeneic Mesenchymal Stem Cells in Patients with Ischemic Cardiomyopathy (TRIDENT Study) are being simultaneously released online September 18 by the journal Circulation Research and at the Heart Failure Society of America Annual Scientific Meeting in Dallas. The study is part of the growing evidence suggesting that direct delivery of allogeneic human mesenchymal stem cells into the heart of people with ischemic cardiomyopathy holds promise to regenerate areas of damaged heart muscle. Left untreated, the hearts of people with this condition become weaker following a heart attack or as a result of coronary artery disease.

Joshua M. Hare, M.D., in the laboratory.

One unknown, however, remains the optimal dose of the stem cells. Now the Phase II TRIDENT study led by Joshua M. Hare,
M.D., and colleagues at the University of Miami Miller School of Medicine offers new insight. The investigators found that a dose of 100 million allogeneic human mesenchymal stem cells, versus 20 million, was more effective in decreasing scar tissue and restoring left ventricular ejection fraction in study of 30 people with ischemic cardiomyopathy (ICM).

“These results continue to support the fact that therapy with mesenchymal stem cells can dramatically reduce scar in patients who suffer from ICM. This is precedent setting,” said Hare, Louis Lemberg Professor of Medicine and director of the Interdisciplinary Stem Cell Institute at the University of Miami. “No other therapy available to modern medicine can do this. The amount of scar is an extremely important predictor of bad health outcomes — such as death, heart failure or arrhythmias.”

“With the right dose, mesenchymal stem cells can improve a patient’s ejection fraction as well,” Hare said. Left ventricular ejection fraction is a measure of the heart’s ability to pump blood.

“The results confirmed our hypothesis that dose matters,” Hare said. The 15 patients randomized to the 100 million stem cell dosing group had a similar reduction in scar size, 6.1 g, compared to a 6.4 decrease in the 15 patients randomized to the 20 million dose group. However, ejection fraction only improved in the higher dose group, by 3.7 units. At the same time, increases in pro-BNP, a marker of worsening heart disease, increased only in the lower dose group by 20 m, further supporting the superior effectiveness of the higher dose.
Hare and colleagues also evaluated the safety of this therapeutic strategy. They found no treatment-emergent serious adverse events at 30 days after treatment or any treatment-related serious adverse events at 12 months. Major cardiac event rate was 20 percent in the lower dose group, versus 13.3 percent in the higher dose group. The rates of re-admission to the hospital from worsening heart failure and improvements in NYHA classification also favored the 100 million stem cell group.

This Phase II research advances the field of allogeneic stem cell therapy for ICM by helping to clarify some inconsistencies on dosing in previous studies in the literature, Hare said.

In terms of next steps, the findings also form the foundation for future investigations to evaluate a wider range of doses to further fine-tune this innovative therapeutic approach. The results could help researchers pick the correct dosing range in Phase III studies, which could make the difference between a positive or negative trial outcome, Hare said. Importantly, the findings also hold the potential to allow more precise and effective dosing for patients with ICM.

“If the therapy is approved, the dosing would be crucial to the clinical outcome,” said Hare.

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