Long-lasting gene therapy benefits advanced heart failure patients

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Researchers from the Cardiovascular Research Center at Icahn School of Medicine at Mount Sinai reported the long-term benefits of a single dose of their gene therapy AAV1/SERCA2a in advanced heart failure patients on Nov. 19 at the American Heart Association Scientific Sessions 2013.

The new long-term follow-up results from their initial Calcium Up-Regulation by Percutaneous Administration of Gene Therapy In Cardiac Disease (CUPID 1) clinical trial found a one-time, high-dose injection of the AAV1/SERCA2a gene therapy results in the presence of the delivered SERCA2a gene up to 31 months in the cardiac tissue of heart failure patients.

In addition, study results show clinical event rates in gene therapy patients are significantly lower three years later compared to those patients receiving placebo. Also, patients experienced no negative side effects following gene therapy delivery at three-year follow-up.

"This study shows AAV1/SERCA2a gene therapy has long-lasting and beneficial effects for congestive heart failure patients allowing us to block the downward spiral of patients with severe heart failure, " says principal investigator Roger J. Hajjar, MD, Director of the Cardiovascular Research Center and the Arthur & Janet C. Ross Professor of Medicine at Icahn School of Medicine at Mount Sinai, who developed the gene therapy approach.

The gene therapy uses a modified adeno-associated viral-vector derived from a parvovirus. The one-time gene therapy is injected through the coronary arteries of heart failure patients using catheters. It works by introducing healthy SERCA2a genes into cells. The delivery of the SERCA2a gene produces SERCA2a enzymes, which helps heart cells restore their proper use of calcium.

SERCA2a is an enzyme critical for proper pumping of calcium in calcium compartments within cells. SERCA2a dysfunction or reduced expression occurs in patients with heart failure. When SERCA2a is down-regulated, calcium stays longer in the cells than it should, and it induces pathways that lead to overgrowth of new and enlarged cells. This contributes to an enlarged heart in heart failure patients.

Previously, CUPID 1 study results showed the gene therapy to be clinically safe and effective for over 12 months with improved heart function status and left ventricular function, along with a significant decrease in recurrent cardiovascular events. CUPID 1 was the first-in human clinical gene therapy randomized, double-blind study which enrolled 39 patients with advanced heart failure.

"AAV1/SERCA2a gene therapy has been proven to be a safe and effective therapeutic intervention for advanced heart failure," says Dr. Hajjar. "Our long-term results support the potential use of AAV1/SERCA2a gene therapy as a new important additional tool for treating and managing advanced heart failure patients."

This study was presented as an Oral Session (Abstract 10667): Long Term Follow-up of Patients with Advanced Heart Failure Following a Single Intracoronary Infusion of AAV1/SERCA2a.

In addition, on Nov. 19 Dr. Hajjar also presented at the AHA Scientific Sessions 2013 a Plenary talk entitled, "How the Postgenome Era Will

Change the Practice of Cardiology" and discussed his work on targeted gene therapy for human heart failure.

In his Plenary talk, Dr Hajjar presented his new findings just published in the journal *Science Translational Medicine* on Nov. 13 that show delivery of small ubiquitin-related modifier 1 (SUMO-1), an important regulator of SERCA2a, in preclinical heart failure models improves cardiac contractility and prevents left ventricular dilatation—two major aspects of heart failure. According to Dr. Hajjar, the transition of this SUMO-1 gene therapy from pigs to humans seems likely in the short-term. Also, Dr. Hajjar revealed that development of novel cardiotropic vectors may render cardiovascular gene therapy easier and less-invasive in the near future.

Provided by The Mount Sinai Hospital