GENE THERAPY

Can CUPID rescue the broken hearted?

A small, phase 2 trial—known as CUPID (Calcium Upregulation by Percutaneous administration of gene therapy In cardiac Disease)—has indicated that SERCA2a gene therapy to increase sarcoplasmic reticulum reload with calcium during myocardial relaxation might benefit approximately half of all patients with heart failure.

Of the 509 prescreened patients, 265 were excluded from the study because they had neutralizing antibodies to the viral gene vector (AAV1). After further assessment for eligibility, 39 patients were randomly assigned to receive intracoronary infusion of placebo ($n = 14$) or low-dose (6×10^{11} DNase-resistant particles; $n = 8$), mid-dose (3×10^{12} DNase-resistant particles; $n = 8$), or high-dose (1×10^{13} DNase-resistant particles; $n = 9$) AAV1/SERCA2a therapy.

The high-dose gene therapy was found to be superior to placebo for the functional and left ventricular function/remodelling efficacy domains assessed. Although no

statistically significant improvements were noted for the assessed symptomatic and biomarker efficacy domains, no worsening in these parameters was observed in the patients who received high-dose AAV1/SERCA2a, unlike in those who received placebo. High-dose SERCA2a gene therapy was also associated with shorter duration of cardiovascular hospitalizations than placebo and an 88% reduction in risk of recurrent clinical events by 12 months.

No adverse effects could be attributed to the SERCA2a gene therapy and the CUPID investigators believe that the results “form the basis for advancement of AAV1/SERCA2a into larger pivotal trials.”

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Original article Jessup, M. *et al.* Calcium upregulation by percutaneous administration of gene therapy in cardiac disease (CUPID): a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca^{2+} -ATPase in patients with advanced heart failure. *Circulation* doi:10.1161/CIRCULATIONAHA.111.022889