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Molecular Therapy

Heartening Results: The CUPID Gene Therapy Trial for Heart Failure

Heart failure, which is estimated to affect more than 20 million people throughout Europe and the United States, is one of the leading causes of death worldwide. Despite many advances in the pharmacological management of patients, the prognosis for this condition remains poor. However, the results of the Calcium Up-regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID) gene therapy trial, to be published by Jessup and colleagues in *Circulation*,[1] may provide reason for cautious encouragement among both patients and the gene therapy community. CUPID is a phase II randomized, double-blind, placebo-controlled trial that evaluated the effectiveness of a gene transfer vector based on adeno-associated virus 1 (AAV1) for delivery of SERCA2a complementary DNA in 39 patients with advanced heart failure.

Heart failure is characterized by a progressive reduction in cardiac function such that the heart becomes unable to pump sufficient blood to meet the patient's metabolic needs. More than 50% of patients die within 5 years, from a worsening of the disease or sudden ventricular arrhythmias.[2] Up to 16% of patients are readmitted to the hospital within the first 6 months following their release after diagnosis, rendering this disease the most frequent cause of hospitalization (about 20%) in the population over 65 years of age (in the United States alone, this represents an expenditure of more than $40 billion). Interestingly, current clinical management of heart failure patients is based on the use of drugs such as angiotensin-converting enzyme inhibitors and β-blockers (first introduced into clinical use in the 1970s) and angiotensin II receptor antagonists (the "sartans" drug group, developed in the 1990s), indicating that pharmacological management of heart failure patients has remained largely unchanged over the past 20 years.

The development of heart failure is commonly associated with a series of molecular modifications in the mechanisms controlling cardiac contractility. SERCA2a catalyzes the adenosine triphosphate–dependent movement of calcium ions into the sarcoplasmic reticulum from the cytosol—an activity that is reduced in patients with heart failure, due, at least in part, to lower SERCA2a level. The goal of augmentation of SERCA2a activity is to enhance Ca^{2+} reuptake and thereby improve cardiac contractility via enhanced calcium handling in the myocardium. Recent research from several laboratories has shown that the overexpression of SERCA2a can improve cardiac function in various small- and large-animal heart failure models. Jessup and co-workers, however, are the first to bring this notion forward in the translational setting, showing that the AAV1 vector carrying human SERCA2a, administered to patients through the coronary circulation, has been safe and is potentially effective, especially when considering the group of patients receiving the highest dose of vector.

There are several reassuring points in Jessup and colleagues' data set. One is that this is the first clinical application of AAV vectors for cardiac gene transfer. By virtue of its exquisite and still largely unexplained capacity to transduce postmitotic cells, AAV is currently the vector of choice for cardiac applications. Second, it is interesting to learn that a single intracoronary infusion of the vector has been sufficient to provide a potential therapeutic benefit in a condition where the transgene must be expressed inside the cells and thus where a high efficiency of transduction is required. In this respect, the authors have taken advantage of AAV serotype 1; other serotypes, such as serotype 9, appear to be more efficient for cardiac gene transfer in rodents, but whether this might be applicable to larger animals, including human primates and humans, is still debated. Third, a requisite for efficacy of cardiac gene therapy in treating heart failure is prolonged expression of the transgene—again, a requisite that AAV vectors seem to meet. In the CUPID trial, the frequency of cardiovascular events was monitored over a 12-month period, with a significant decrease of cardiovascular hospitalization in the patients who received the highest of the three doses of vector administered. The dosing regimen also appeared safe. However, one must remain cautious with respect to both safety and efficacy because the groups were small and subject to some differences in baseline characteristics.

Jessup and co-workers report an efficacy signal with the group of patients receiving the highest dose of AAV. This suggests that improvements in vector and delivery method might further improve the efficacy of treatment. However, it is unclear whether more successful SERCA2a delivery might simply serve to slow disease progression—which nonetheless would be a major achievement considering the very poor prognosis of the disease—or whether it might eventually also improve cardiac function over time, overriding other pathological mechanisms underlying the disease. A substantially larger number of patients will be required to address this issue directly. Jessup and colleagues report significant differences in the treated versus control patients when multiple-efficacy domain analysis is applied, which simultaneously takes into consideration a series of clinical and instrumental parameters, but not when ejection fraction alone (a precise measurement of cardiac function) is analyzed. This is a possible indication that treatment at this stage slows progression but does not reverse the condition.

Either way, it is reassuring and satisfying that a gene therapy strategy for heart failure has finally been designed and tested in a small phase II study. The study is by no means a minor achievement, and further clinical studies are eagerly anticipated.

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REFERENCES

1. Jessup, M, Greenberg, B, Mancini, D, Cappola, T, Pauly, DF, Jaski, B *et al.* (2011). CUPID-A Phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca2+ ATPase (SERCA2a) in patients with advanced heart failure. *Circulation.* In press.
2. Lloyd-Jones, D, Adams, RJ, Brown, TM, Carnethon, M, Dai, S, De Simone, G *et al.* (2010). Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* **121**: e46–e215.