doi:10.1038/mt.2015.158

Molecular Therapy

Gene Therapy for Heart Failure: Back to the Bench

Gene therapy for heart failure hit another bump on the road to clinical translation with the announcement by Celladon that its lead product Mydicar—adeno-associated viral vector 1 (AAV1)-expressing sarcoplasmic reticulum calcium ATPase (SERCA2a)—had failed in the phase IIb CUPID2 trial.[1] SERCA2a's role in heart failure was validated in the 1990s but proved to be an elusive target for therapeutic intervention using traditional drug discovery methods. It is well established that SERCA2a, which is critical to calcium homeostasis in the myocardium, is downregulated in failing heart, making it an important target for therapy. Mydicar represents enzyme-replacement gene therapy that aims to increase the content of this calcium transporter in cardiomyocytes. All primary, secondary, and exploratory efficacy end points were negative in this phase IIb trial, which was unexpected following the encouraging findings in phases I and IIa.[2] The results send gene therapy for heart failure on a familiar path back to the bench, and the field must now strive to understand and overcome the factors contributing to this late-stage failure.

Heart failure is an important target for the development of new therapies because it is the leading cause of frequent hospitalizations in United States and European Union, and, given a rapidly aging population, its incidence is likely to rise even further in the near future. The CUPID2 trial was a double-blind, randomized, placebo-controlled, multicenter study that evaluated the effects of a single intracoronary infusion of AAV1/SERCA2a versus placebo in 250 patients with severe heart failure. The primary objective of the trial was to determine the efficacy of an intracoronary infusion of Mydicar compared with placebo, in conjunction with maximal optimized heart failure therapy, in reducing the frequency of and/or delaying heart failure–related hospitalizations in patients with systolic heart failure who are at increased risk of terminal events based on elevated levels of natriuretic peptides or a recent heart failure–related hospitalization. A secondary end point was time to the first terminal event, defined as all-cause mortality, heart transplant, or need for a mechanical circulatory support device. Exploratory efficacy end points included a 6-minute walking test and quality of life. A total of 243 of the patients were eligible for a modified intent-to-treat analysis, and, remarkably, all these end points were inconsistent with a treatment effect.

Why did Mydicar fail? The usual causes of failure at such a stage include a suboptimal vector dose, an inefficient vector and expression cassette, insufficient duration of gene expression, and/or inefficient gene delivery. An AAV1 vector delivered at the applied dose (10^{13} vg) has been shown to transduce cardiomyocyte in the preclinical setting, and the cytomegalovirus promoter–driven expression cassette is fairly strong in cardiomyocytes. No data are available on the duration of gene expression in the study, but in other human trials AAV has consistently expressed over several weeks or months. Therefore, these factors are less likely to be responsible for the failure. The most likely reason for the poor outcome is inefficient gene delivery into the fairly large myocardial tissue mass after a single intracoronary injection. Most AAVs bind avidly to the heparan sulfate–rich glycocalyx glycoprotein polysaccharide present on the vascular endothelium, and AAV does not pass efficiently through the intact endothelium into the myocardium.[3] In addition, rapid blood flow in the coronary arteries quickly removes vector from the heart. At this time, the most efficient delivery method into the myocardium appears to be direct intramyocardial injection. Retrograde injection via the coronary sinus may also be an efficient method of delivery, but it is a much more difficult procedure and less practical for standard clinical therapy. In the CUPID2 trial, intracoronary delivery was probably chosen partly because it is a relatively easy procedure to apply in the clinic.

It has also been suggested that the very sick patient population contributed to the poor outcome and that some toxic mechanisms in the microenvironment of the failing heart might have inactivated SERCA2a via posttranslational modifications such as oxidation or acetylation. However, only severe heart failure patients would eventually be eligible

for gene therapy and as such any intended therapy should be effective under these conditions. Celladon had initially announced that they would examine patient subgroups that might have benefited from the therapy, but apparently this has not been successful. While further research is clearly warranted to explore the potential of SERCA2a in the treatment of heart failure, to most investigators in the field, the CUPID2 trial represents just another example of failed gene delivery into the large myocardium.

Although this chapter of the CUPID1 and 2 trials is now closed, heart failure is still a very valid target for the development of new therapies, due to the large unmet clinical need. Alternative therapeutic transgenes include phospholamban, which also affects calcium handling in cardiomyocytes, protein phosphatase-1 inhibitor, calcium sensor S100A1, and adenylyl cyclase type 6. S100A1 was recently taken forward by Bristol-Myers Squibb after being licensed from uniQure for the treatment of congestive heart failure. Additional important targets in the pathogenesis of the failing heart are excess fibrosis, which renders the heart very rigid and unable to contract efficiently; heart-chamber remodeling; and apoptosis and unfavorable changes in cardiomyocyte energy metabolism, which might yield more clues for the development of new therapies. Thus, we can expect further developments in both therapeutic targets and the development of more efficient targeted vectors and delivery methods in the field to help identify more efficient therapies for patients with severe heart failure.

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