

Abstract

Congestive heart failure (CHF) is the only cardiovascular disease that is increasing in prevalence. The outlook for a patient with dilated CHF remains dismal despite recent advances in therapy. The key abnormality associated with CHF of diverse etiologies is depressed cardiac contractility. We have shown that the amount of adenylyl cyclase type VI (AC_{VI}) – a dominant AC isoform in mammalian cardiac myocytes – sets a limit on cAMP production.² We then showed that cardiac-directed expression of AC_{VI} increases cardiac contractile function in transgenic mice.³ When AC_{VI} is expressed in the background of Gq-associated cardiomyopathy, cardiac function and survival are improved.^{4,5} We then showed the global LV function and responsiveness can be changed by gene transfer of AC_{VI} in a manner that can be applied clinically – intracoronary delivery of an adenovirus encoding AC_{VI} (Ad5. AC_{VI}).⁶ Finally, we found that intracoronary delivery of Ad5.AC_{VI} improves heart function and geometry in the setting of heart failure.

We propose gene transfer of AC_{VI} for the treatment of clinical CHF, using intracoronary delivery of Ad5.AC_{VI} for the treatment of dilated Class III/IV CHF.

Hypotheses: *Intracoronary delivery of an adenovirus encoding adenylyl cyclase AC_{VI} will improve heart function and reduce symptoms in patients with Class III/IV congestive heart failure.*

We propose to conduct a Phase 1 / Phase 2 clinical trial. The clinical trial design will be a randomized, double-blinded, placebo-controlled, single-dose study to evaluate the safety, tolerability and clinical effectiveness of ascending doses of human adenovirus-5 (E1/E3-deleted, replication incompetent) encoding human adenylyl cyclase type VI in patients with congestive heart failure. The vector will be delivered by intracoronary injection with nitroprusside to increase gene transfer efficiency. We will also evaluate the effects of Ad5.AC_{VI} on exercise tolerance, symptom severity and hemodynamics measured by right heart catheterization.

Two elements justify the use of human subjects in these experiments. First, the adenovirus vector and method of delivery proposed have been used already in Phase 1 / Phase 2 placebo-controlled randomized and double-blinded clinical trials in patients with angina,^{8,9} and was found to be safe and a dose was identified that appeared to be effective, albeit with an adenovirus containing a different transgene in the treatment of a different cardiovascular disease than that proposed here. Second, patients with severe heart failure have a poor long-term outcome on optimal medical therapies, with 50% of patients dying within 3 years of the onset of severe symptoms.