Aptamer Therapy for Heart Failure?

J. David Port, Michael R. Bristow

Autoantibodies (AAbs) to β-adrenergic receptors (β-AR) are common in certain subsets of heart failure, where they have the potential to cause adverse myocardial biological effects.1–7 β-AR AAbs are especially common in peripartum8 and Chagas9,10 cardiomyopathies, but they are also relatively prevalent (≥25%) in dilated cardiomyopathies of both idiopathic and ischemic origins.1,5,11–14 The presence of β1-AR AAbs is also associated with ventricular arrhythmias and an increased prevalence of sudden cardiac death.15 As a functional validation of their putative pathophysiologic role, in animal models anti-β1-AR antibodies have been shown to induce cardiomyopathies.16–18

The prevalence of β1-AR AAbs in heart failure patients is currently being examined prospectively in the Etiology, Titer-Course, and Survival (ETICS) Study.14 ETICS is an ongoing prospective investigation of β1-AR–directed autoimmunity in postmyocarditis and postmyocardial infarction dilated cardiomyopathies, and it also includes an associated retrospective analysis in other types of heart failure. This study should establish the prevalence of β1-AR AAbs in etiologic subsets of heart failure. However, ETICS will not distinguish between AAbs as a heart failure biomarker versus causality in the pathophysiologies of cardiomyopathy or heart failure progression. The latter clinical experiment, ie, a study addressing cause and effect, will depend on the development of a therapy that can specifically and effectively neutralize β1-AR AAbs. To be useful in the clinical setting, such a treatment must be conveniently administered and be relatively free of adverse events. In the current issue of Circulation Research, Haberland et al19 demonstrate that a single-strand DNA aptamer could be such a therapeutic compound.

In small uncontrolled studies, immunophoresis or immunoadsorption of β1-AR AAbs has been shown to reduce myocardial dysfunction and to improve heart failure,20–26 but these therapeutic methods are unwieldy and expensive. Other methods of ameliorating the presence of AAbs in heart failure include the use of competing peptides.27 Based on defined β1-AR epitopes recognized by the AAb, peptide sequences that mimic the epitope can be administered, thereby neutralizing the AAb.27 However, delivery of competing peptides has the potential to elicit an additional immune response.

Aptamers are 15 to 50 nucleotide sequences (DNA or RNA) that are engineered as ligands to bind with high affinity against biological targets such as receptors, bioactive peptides, or, in the case of the study by Haberland et al, antibodies. The first method for generating such aptamers was developed by Gold et al28–31 and termed SELEX, an acronym for systematic evolution of ligands by exponential enrichment. The strength of SELEX and similar aptamer generation methods is that a ligand can be engineered fairly easily against almost any target peptide sequence, but such compounds also suffer from the bioavailability and pharmacokinetic limitations of oligonucleotides. However, chemical modification to stabilize nucleotides (such as 2′-fluoro or 2′-O-methyl) or conjugation with polyethylene glycol to increase molecular weight can, to some extent, mitigate these issues.32,33 SELEX methodology has been used in the development of pegaptanib (Macugen), an anti-vascular endothelial growth factor RNA aptamer approved for the treatment of age-related macular degeneration,34 and therapeutic aptamers are in development for the treatment of myasthenia gravis (to neutralize AAbs against the acetylcholine receptor) and as short-acting anticoagulants against the thrombin receptor.

In the current article, Haberland et al19 use MonoLEX technology,35 a variant of SELEX, to generate aptamers that neutralize and inactivate β1-AR AAbs. Interestingly, the 21 nucleotide DNA sequence investigated, aptamer 110, markedly attenuated β1-AR AAb-mediated increases in heart rate and apoptosis in cultured cardiac myocytes. However, the aptamer had no effect on preventing β-agonist (isoproterenol) increases in heart rate, demonstrating that there was no effect on β-adrenergic ligand binding or on postreceptor signal transduction. This finding is of particular importance in the context of heart failure, in which most patients will be using β-blocker therapy. Based on the mechanism of action of aptamer 110, which is strictly to neutralize β1-AR AAbs, it would be predicted that in heart failure patients in whom β1-AR AAbs are playing a pathophysiologic role, aptamer therapy would be additive with β-blockade and likely other standard medical treatment.

It remains to be seen if aptamer 110 can successfully neutralize β1-AR AAbs and prevent or reverse dilated cardiomyopathy in an in vivo animal model. If successful in the preclinical setting, then the subsequent arduous process of clinical development would remain. The details of chronic treatment, presumably by intravenous or subcutaneous routes of administration, would need to be defined, efficacy would need to be demonstrated, and an acceptable adverse event profile would need to be documented. However, Haberland et al19 should be congratulated for creating this drug developmental opportunity.

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References

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