Hypertrophic cardiomyopathy: Affects and new therapies

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Hypertrophic cardiomyopathy (HCM) is one of the most common genetic heart diseases worldwide. It affects men and women equally and has been identified in persons of diverse ethnic backgrounds.1-7 HCM is characterized by a thickened, nondilated left ventricle and often causes exertional dyspnea and reduced exercise capacity, which can impair quality of life. Left ventricular outflow tract obstruction, which results from contact of the mitral valve with the ventricular septum during systole, is one of the principal determinants of HCM-related complications and therefore is an important target for therapy.Cardiac hyper contractility, which results from an excessive number of actin–myosin cross-bridges within the cardiac sarcomere, is an important mechanism that promotes outflow obstruction. Other factors include elongation of the mitral valve leaflets, apical displacement of the papillary muscles, and protrusion of the hypertrophied ventricular septum into the left ventricular outflow tract. This impedance to blood flow generates a left ventricular outflow tract pressure gradient, which can be reliably quantified with the use of echocardiography.

Invasive therapies for obstructive HCM, such as surgical myectomy and percutaneous alcohol septal ablation, are effective in relieving left ventricular outflow tract gradients and favorably affect the clinical course, including providing long-term relief of limiting symptoms. However, these interventions are associated with risk, and surgical expertise is confined to select high-volume centers. In addition, established pharmacologic therapies have limited efficacy, including suboptimal reduction of the outflow tract gradient and relief of symptoms.

Moreover, these therapies have not been shown to increase objective measures of exercise capacity and have been associated with side effects that prevent their use in some patients.Therefore, drugs that are safe and reliably improve how patients feel and function with minimal side effects remain an important unmet need in the treatment of this disease. Mavacamten, a recently approved cardiac myosin inhibitor, has been shown to improve exercise capacity and reduce symptoms in patients with obstructive HCM.

Aficamten is a reversible inhibitor of cardiac myosin that reduces left ventricular contractility by decreasing the number of active actin–myosin cross-bridges within the sarcomere. Aficamten was designed to have a shallow dose–response relationship (i.e., small reductions in left ventricular ejection fraction as the dose is increased, indicating a wide therapeutic window) and a plasma half-life that allows for personalized dose adjustments as often as every 2 weeks — features that differentiate it from mavacamten. In a phase 2 trial, treatment with aficamten resulted in significant reductions in left ventricular outflow tract gradients in patients with obstructive HCM. The SEQUOIA-HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM) trial was conducted to evaluate the efficacy and safety of aficamten in adult patients with symptomatic obstructive HCM.

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