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New Drug Update

Mavacamten: a novel avenue towards hypertrophic obstructive cardiomyopathy

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ABSTRACT

Hypertrophic obstructive cardiomyopathy (HCM) is the most common heterogeneous genetic cardiovascular disorder. Its pathophysiology involves left ventricular hypertrophy, increased fibrosis, hypercontractility, and reduced compliance. The symptomatic obstructive HCM presents as dyspnoea, syncope, chest pain, palpitations, arrhythmias, or sudden death, usually after provocative manoeuvres like exercise. Until April 2022, treatment options were disease non-specific like Beta blockers, Cardio-selective Calcium Channel Blockers, Dipyridamole, and Ranolazine. Mavacamten is a first-in-class, FDA-approved drug molecule for HCM. It works by selective and reversible inhibition of the cardiac myosin ATPase thereby decreasing the formation of actin- myosin cross- bridges in systole and diastole. The excessive actin-myosin cross-bridging is the hallmark of disease and is responsible for the compromised functioning of the heart in both the systole and diastole phase due to left ventricular outflow tract (LVOT) obstruction and increased ventricular filling pressure respectively. Mavacamten acts by producing super-relaxed state of heart which is then translated into decreased LVOT obstruction and improved cardiac filling pressures thereby improving the functional capacity and symptoms in patients with New York Heart Association (NYHA) stage II, and III symptomatic or obstructive heart failure. Mavacamten is administered orally 2.5-15 mg per day with titration guided by lab investigations and clinical symptoms. Its bioavailability is 85%, undergoes metabolism by CYP2C19 and CYP3A4 and is excreted mainly in urine. It is also an enzyme inducer and shows considerable drug interactions. Common adverse effects are dizziness and syncope. Sometimes the drug may worsen heart failure or completely block ventricular function. Mavacamten has raised hopes for the possibility of managing this potentially lethal intrigue disorder with medicines alone.

Keywords: Heart failure, Hypertrophic cardiomyopathy, LVOT, Mavacamten, Myosin ATPase, NYHA

INTRODUCTION

Hypertrophic obstructive cardiomyopathy (HCM) is the most common inherited cardiovascular disease present in one in 500 of the general population.[1] In most cases of this genetic disorder, the wall thickness of the left ventricle is increased to ≥15 mm in the absence of any secondary cause explaining it, and left ventricular obstruction becomes ≥30 mm Hg.[2] The less commonly reported causes leading to HCM are increased sympathetic drive and thickened coronary arteries which are responsible for excessive activity dependent and oxygen deprivation mediated hypertrophy of cardiac muscles. HCM affects male and female equally. It remains asymptomatic and hence undiagnosed in a large number of patients. The symptomatic HCM presents as dyspnoea, syncope, chest pain, palpitations, arrhythmias, or sudden death usually following provocative manoeuvres like exercise.[3]

This heterogeneous genetic disorder results from the mutations in either of the genes involved in the encoding of sarcomere-associated proteins. MYH7, MYBPC3, TNNT2, and TNNI3 are the most frequently affected causal genes. The genetic mutation in any of the sarcomere proteins results in the structural abnormalities and the hypertrophy of the cardiac muscle leading to hypercontractility. Thus, the pathophysiology of HCM involves ventricular hypertrophy, increased fibrosis, hypercontractility, and reduced compliance of heart muscle.[4,5] As a consequence of this hypercontractility, dynamic left ventricular outflow tract (LVOT) obstruction is seen, thereby compromising the left ventricle volume ejection during systole responsible for the symptoms like syncope, decreased exercise capacity, exertional dyspnea and/or chest pain. The fibrosis and reduced compliance also interfere with proper relaxation during diastole causing the retrograde collection of blood in periphery and lungs producing congestive symptoms like edema and dyspnoea. As the heart itself receives supply during diastole, improper relaxation in diastole interferes with coronary supply causing subendocardial ischemia presenting as the chest pain.[6,7] The major complications of HCM are arrythmias, heart failure, heart block, endocarditis and sudden death.

Till 2022, a large number of drug-treatment practices for HCM focused on symptomatic control of the disease progression using non-specific medicines like Beta-blockers, Verapamil type-calcium channel antagonists, Antiarrhythmics, Dipyridamole or Ranolazine. Angiotensin-converting enzyme (ACE) inhibitors are relatively contraindicated and require close monitoring during use.[8] These non-disease-specific pharmacological methods were less effective and poorly tolerated. Rather some cardiovascular drugs viz. nitrates, nifedipine type-calcium channel blockers and positive ionotropic drugs such as digitalis are absolutely contraindicated in HCM. For pharmacologic-treatment refractory LVOT obstruction in HCM patients, surgical reduction of the septum by Surgical Myectomy or Percutaneous Alcohol Septal Ablation is done.[9]

Mavacamten is a novel disease-specific drug for the HCM. It has raised hopes for the possibility of managing this potentially lethal intrigue disorder with medicines alone.[10]

MAVACAMTEN

Mavacamten is the first FDA-approved (April 2022) selective and reversible inhibitor of cardiac myosin ATPase. It has been approved for the adults suffering from symptomatic heart failure New York Heart Association (NYHA) Class II and III following HCM to improve their functional capacity and symptoms.[11]

Safety and effectiveness

A total of three clinical trials have been completed till now to analyse the safety, efficacy, and pharmacokinetics of Mavacamten.[12]

The 'MAVERICK HCM' trial was a multicentric, phase II, double-blind and placebo-controlled trial that enrolled 59 adult patients with symptomatic HCM (NHYA functional classes II and III) with ≥55% left-ventricular ejection fraction (LVEF), and ≥300 pg/ml N-terminal Pro-B-type Natriuretic peptide (NT proBNP). They were then randomized in a ratio of approximately 1:1:1 to receive either mavacamten at a pharmacokinetic-adjusted dose to achieve target plasma levels of 200 ng/ml or 500 ng/ml or placebo for 16 weeks. Mavacamten, an innovative myosin inhibitor, was well tolerated by patients suffering from symptomatic HCM. Commonly used biomarkers for cardiac stress -NT proBNP and cTnI (Cardiac Troponin I) were significantly reduced indicating the drop in myocardial-wall stress. These findings laid the groundwork for future research on Mavacamten in this patient population, and used clinical parameters and laboratory investigations including LVEF to guide drug-dosage.[13]

The 'EXPLORER-HCM' was another randomized, double-blind, placebo-controlled clinical study to evaluate Mavacamten (MYK-461) in adults with symptomatic HOCM. The trial was completed on May 6, 2020, and it collected data from 251 study participants. Mavacamten treatment in them improved the exercise capacity, decreased the LVOT obstruction, and NYHA functional class, and benefitted the health status.[14,15] The above pivotal trials highlighted the importance of Mavacamten in disease-specific treatment.

One more open-labeled, parallel-group, single-center phase 1 study evaluating the pharmacokinetics of single-dose Mavacamten in forty-five healthy adults has been completed in February 2022 and the published details are awaited.[16]

Currently, an extended study of 252 weeks, 'MAVA-LTE', is ongoing to assess the long-term safety, efficacy, and appropriate dose guided clinically. MAVA-LTE planned to recruit around 280 patients from those who had completed the EXPLORER–HCM or MAVERICK-HCM (MYK-461-006) trial and submit their willingness to participate in the extended study within 90 days of end of parent study. The three treatment arms in MAVA-LTE received active treatment with Mavacamten to achieve base target trough concentration, higher target trough concentration and dose titrated to achieve desired clinical response. MAVA-LTE data cut-off date analysis showed that patients were on an average 60 years old and 39% were women. The interim analysis to analyze the primary outcome of the trial found that the Mavacamten was well tolerated and no serious and treatment- emergent adverse events were reported.[17] The data collected so far also supported the previous findings of Mavacamten in terms effectiveness by showing that long-term improvement in LVOT gradients, NT-proBNP, and diastolic functions in HOCM patients indicating that Mavacamten can be used in HOCM patients under clinical supervision.[18]

Mechanism of action of Mavacamten

Mavacamten is a selective, reversible inhibitor of the cardiac myosin ATPase enzyme. It acts allosterically to regulate the number and type of active myosin heads available for binding with actin (also, known as "on actin" or power-generating state). As the HCM is known for its mechanistic characteristics, such as excessive myosin actin crossing-bridge formation, Mavacamten acts by inhibiting this cross-bridging helps in decreasing both the force-producing (systolic) and residual (diastolic) cross-bridge formation. Given the fact that excessive actin- myosin interaction in systole causes dynamic LVOT obstruction and this interaction in diastole interferes with ventricular filling, both ultimately leading to decreased cardiac ejection fraction besides other features of disease, Mavacamten shifts myosin populations towards a super-relaxing state that is energy-sparing and recruitable. Hence Mavacamten mediated myosin ATPase inhibition in HCM patients reduces dynamic LVOT obstruction and improves cardiac filling pressures. Mavacamten has been shown to reduce biomarkers for cardiac wall stress in clinical and preclinical research.[19]

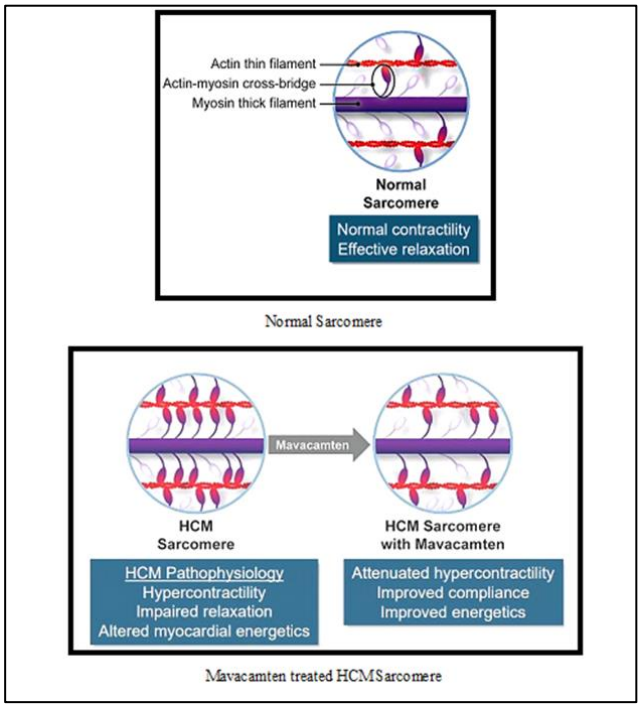

Figure 1: Mechanism of action of Mavacamtem: Attenuation of hypercontractility and improved compliance through myosin ATPase inhibition.[24]

Pharmacokinetic profile

Mavacamten is administered orally to patients suffering from hypertrophic cardiac disease. Its bioavailability is 85% (without any effect of coadministration of food) and the volume of distribution is high (0.51 ml/min/kg). Mavacamten is primarily metabolized by CYP2C19 (74%), CYP3A4 (17%), and excreted in urine (85%) and faeces (7%) The elimination half-life of Mavacamten is eight days. It is not a substrate of OATP, OCT or NTCP in human hepatocytes. Mavacamten is a CYP3A4, CYP2C9, CYP2C19 enzyme inducer and hence shows interactions with drugs metabolized by these enzymes.[20]

Adverse reactions

The augmented effect of Mavacamten can drastically reduce systolic function and can deteriorate or completely block ventricular function. There are reports documenting the decrease in LVEF by up to 10% (normally it should be at least more than 50%). In the phase III 'EXPLORER' trial, dizziness (27%) followed by syncope (6%) were the most frequent adverse effects. Other side effects reported with Mavacamten are acute stress cardiomyopathy, atrial fibrillation, ventricular tachycardia, angina pectoris, headache, dyspnea, chest pain, fatigue, and palpitations.[21]

Drug interaction

Mavacamten is primarily metabolized by CYP2C19 or CYP3A4 enzymes so drugs inhibiting (like ketoconazole, verapamil) and inducing (rifampicin) these enzymes will show drug interactions with it. Mavacamten itself is also an inducer of these and CYP2C9 enzymes further complicating the picture. Infact, as many as 829 drug interactions have been identified so far with this drug. Therefore, it is pertinent to keep the patients informed about possible drug interactions and patients are also required to disclose any concomitant medication they are taking while on Mavacamten including all the over-the-counter medications like omeprazole and esomeprazole.[22]

Indications and dosage

Mavacamten is indicated in adults with symptomatic NYHA class II-III obstructive HCM with LVEF> 55%. It is not initiated in patients with LVEF less than 55% owing to the risk of worsening systolic function.

The recommended starting dose is 5 mg once a day with no consideration of meal timings. Then the patient is re-evaluated clinically as well as through investigations for the subsequent dose titration after 4 weeks. If the LVOT gradient is <20 mm Hg down-titrate to next lower dose i.e. 2.5mg per day; in case between 20-30mm Hg continue with the same dose with recommended re-evaluation at 8 weeks of therapy. The LVOT gradient beyond 30 mm Hg at 4 weeks may require increase in dose to next higher level. 2.5 mg and 15mg are the minimal and maximal daily administered doses. Since Mavacamten can worsen heart failure in some patients, it is important to periodically (every four weeks) assess the LVEF, and the Valsalva left ventricular outflow tract (LVOT) gradient and monitor the patient for heart failure symptoms. Stop the treatment temporarily if the LVEF is below 50% irrespective of dose and duration of treatment and in case LVEF drops below 50% on more than two occasions, permanently withdraw Mavacamten. Withhold the treatment if the LVOT gradient

is less than 20mm Hg and keep the patient on minimum dose and reassess after four weeks for further decision. Any concomitant illness like infection and uncontrolled arrhythmias can also impair systolic functions thereby requiring the postponement of the drug and when restarted it should be from one dose lower than previous dose. If a dose is missed, it should be taken earliest possible, and then continue with the subsequent scheduled dose at the usual time the next day.[23]

CONCLUSION

HCM is the most common genetic disorder associated with left ventricular hypertrophy, fibrosis, hyper contractility, and reduced compliance. Previously, a number of non-disease specific drugs like Beta blockers, Verapamil like calcium channel blockers, Ranolazine and Dipyridamole were being used for the symptomatic control of the disease progression but they were inadequate.

Mavacamten is a first-in-class, disease- specific, FDA-approved drug molecule for the HCM that works by selective and reversible inhibition of the cardiac myosin ATPase. Since excessive cross- bridging is the hall mark of HCM, Mavacamten checks this cross bridging and thereby improves the functional capacity and symptoms in patients with NYHA stage II, III symptomatic or obstructive heart failure (a frequent complication of HCM). Mavacamten is given by oral route in doses of 2.5 to 15 mg once a day, titrated as guided by the LVEF, Valsalva, and LVOT gradient. The common adverse effects reported are dizziness and syncope and a trial 'MAVA-LTE' is undergoing to evaluate long term treatment emergent adverse events. As of now, Mavacamten has raised the hopes to treat this virtually untreatable, potentially lethal intrigue disorder with medicines alone.

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