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New Era: Mavacamten for Obstructive Hypertrophic Cardiomyopathy

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Abstract

Obstructive hypertrophic cardiomyopathy results from asymmetric septal hypertrophy, which eventually obstructs the outflow of the left ventricle. Obstructive hypertrophic cardiomyopathy is linked to mutations in genes that encode for sarcomere proteins, including actin, β-myosin heavy chain, titin, and troponin. The mutations lead to structural abnormalities in myocytes and myofibrils, causing conduction irregularities and abnormal force generation. Obstructive hypertrophic cardiomyopathy is a chronic disease that worsens over time, and patients become at higher risk of developing atrial fibrillation, heart failure, and stroke. Up until recently, there were no disease-specific medications for obstructive hypertrophic cardiomyopathy. Nevertheless, the US Food and Drug Administration approved mavacamten on April 28, 2022, for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (New York Heart Association class II to III) in adults to improve functional capacity and symptoms. Its approval was based on data from EXPLORER-HCM and EXPLORER-LTE (NCT03723655). Mavacamten is a novel, first-in-class, orally active, allosteric inhibitor of cardiac myosin ATPase, which decreases the formation of actin-myosin cross-bridges, and thus, it reduces myocardial contractility, and it improves myocardial energetics. It represents a paradigm-shifting pharmacological treatment of obstructive hypertrophic cardiomyopathy. In this review, we describe its chemical and mechanistic aspects as well as its pharmacokinetics, adverse effects and warnings, potential drug-drug interactions, and contraindications.

Keywords

Cardiomyopathy; mavacamten; heart failure; actin-myosin cross-bridge; stenosis; hypertrophy

1. INTRODUCTION

1.1. Obstructive Hypertro-phic Cardiomyopathy (OHCM)

Obstructive hypertrophic cardiomyopathy (OHCM) is also known as idiopathic hypertrophic subaortic stenosis. It results from asymmetric septal hypertrophy, which eventually obstructs

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CONFLICT OF INTEREST

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the outflow of the left ventricle. Although hypertrophy can happen in any part of the left ventricle, it is often in the interventricular septum (Fig. 1A). Such hypertrophy obstructs the blood flow from the left ventricle to the rest of the body. It impacts individuals from all races and equally affects both women and men [1-4].

HOCM is a genetic chronic disease that is linked to problems in several genes causing septal hypertrophy. HOCM is generally asymptomatic in children, and it may first appear with a sudden loss of life in adolescents and teenagers. In other words, HOCM is difficult to diagnose, and unfortunately, it is not detected until a serious cardiac event occurs. HOCM is a major cause of sudden cardiac death in young individuals, including those who are well-trained athletes [1-4].

HOCM familial form is a genetically transmitted and autosomal dominant disorder. However, it can also be attributed to *de novo* mutations. Specifically, HOCM results from a mutation in genes that encode for sarcomere proteins including actin, β-myosin heavy chain, titin, and troponin. The mutations lead to structural abnormalities in myocytes and myofibril causing conduction irregularities and abnormal force generation. Other causes of HOCM include excessive sympathetic stimulation because of decreased catecholamine uptake or increased catecholamine release, atypical microcirculation that disrupts the myofibrils' normal contractile function, and thickened coronary arteries that leads to myocardial ischemia and eventually ventricular fibrosis and compensatory hypertrophy [5-8].

Symptoms and signs of OHCM include chest pain, shortness of breath, fatigue, arrhythmias, fainting, lightheadedness, dizziness, and swelling in the veins of the neck, abdomen, legs, feet, and ankles. OHCM is a chronic disease that becomes worse over time, and patients become at a higher risk of developing atrial fibrillation, stroke, and heart failure. It can also lead to sudden cardiac arrest. Importantly, OHCM has been regarded as the most common cause of sudden cardiac death in young people and competitive athletes in North America [9, 10].

2. STATE-OF-THE-ART BEFORE THE CURRENT APPROVAL

Up until recently, there were no approved therapeutics for OHCM. For asymptomatic patients, life changes and medications to treat cardiovascular diseases are used. For those with symptoms, disease management can be achieved using medications and procedures. Diuretics, β-blockers, and calcium channel blockers offer varying levels of symptom relief. A variety of medical procedures have been adopted to treat HCM, some of them are surgical such as septal myectomy, while other are not surgical such as alcohol septal ablation. On the one hand, septal myectomy is an open-heart surgery for patients with severely symptomatic OHCM. In this surgery, the thickened septum that is protruding into the left ventricle is removed. This typically enhances the blood flow in the heart and the outgoing blood flow to the body. On the other hand, alcohol septal ablation is a nonsurgical procedure in which ethanol is injected into the diseased area of the heart muscle. The alcohol kills the cells in this area, and the thickened, diseased tissue eventually dwindles to a smaller size [11-13].

Surgically implanted devices can also be used to improve cardiac function. They include an implantable cardioverter defibrillator which assists in maintaining a normal heartbeat by mitigating the irregular heartbeat by sending an electrical shock to the heart. Pacemakers can also be used to send electrical pulses to help the heart beats at a normal rate. Cardiac resynchronization therapy devices can be used to coordinate the functions of the two ventricles of the heart. Lastly, in the advanced end-stage of OHCM, heart transplantation may be essential. Mortality rate for HOCM has improved, however it still ranges from 1 to 6% [11-13].

3. MAVACAMTEN

3.1. Chemistry and Mechanism of Action

Mavacamten (MYK-461) is an orally active, small molecule drug that is chemically known as 3-(1-methylethyl)-6-[[(*1S*)-1-phenylethyl]amino]- 2,4(*1H,3H*)-pyrimidinedione (Fig. 1B). MYK-461 was identified to reduce contractility by reducing the adenosine triphosphatase activity of the cardiac myosin heavy chain. Chronic administration of MYK-461 was found to suppress the development of ventricular hypertrophy, myocardial fibrosis, and cardiomyocyte disarray and to decrease profibrotic and hypertrophic gene expression in mice with heterozygous human mutations in myosin heavy chain [14]. The drug also acutely relieved the obstruction of the left ventricular outflow in feline hypertrophic cardiomyopathy [15]

Specifically, mavacamten is a reversible, allosteric inhibitor selective for cardiac myosin. It modifies the number of myosin heads that can enter “on actin” states (power-generating), thus decreasing the likelihood of force-producing (systolic) and residual (diastolic) cross-bridge formation (Fig. 2). Dysregulation of the super-relaxed state and excessive myosin actin cross-bridge formation are the hallmarks of OHCM. Thus, mavacamten shifts the overall myosin population towards a super-relaxed, energy-sparing state. In OHCM patients, mavacamten improves cardiac filling pressure and decreases dynamic LOVT obstruction [16, 17]. The drug is available in 2.5 mg, 5 mg, 10 mg, and 15 mg capsules. The drug was initially developed by MyoKardia, Inc., which was subsequently acquired by Bristol Myers Squibb [18, 19].

3.2. Clinical Trials and Approved Use

Mavacamten was approved by FDA on April 28, 2022, for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (New York Heart Association (NYHA) class II to III) in adults to improve functional capacity and symptoms. The approval was based on data from EXPLORER-HCM and EXPLORER-LTE trials of adults with symptomatic NYHA class II to III OHCM. In EXPLORER-HCM, treatment with the drug over 30 weeks resulted in substantial improvement in exercise capacity, LVOT, NYHA functional class, and health status [20]. The safety and efficacy findings were seen at the end of the blinded, randomized, initial 30-week phase of EXPLORER-LTE maintained in patients who continued treatment for a median of about 62 weeks [21].

3.3. Pharmacokinetics

Pharmacokinetic studies indicated that mavacamten does not inhibit CYP enzymes, nevertheless at elevated concentrations, it induces CYP3A4 and CYP2B6 enzymes *in vitro*. Mavacamten exhibited elevated permeability and low efflux transport across Caco-2 cell membranes. Mavacamten was not a substrate for organic-anion-transporting polypeptides (OATPs), organic cationic transporters (OCTs), or sodium taurocholate co-transporting polypeptides (NTCPs), in human hepatocytes. Therefore, it was determined that the drug has limited drug-drug interaction risk [22].

In vitro mavacamten metabolite profiles included phase I- and phase II-mediated metabolism cross-species. Predominant metabolizing enzymes were CYPs 2C19 (74%), 3A4 (18%), and 2C9 (8%). Major pathways included aromatic hydroxylation (M1), aliphatic hydroxylation (M2), *N*-dealkylation (M6), and glucuronidation of the M1-metabolite (M4) (Fig. 3). Overall, mavacamten demonstrated excellent oral bioavailability, long terminal elimination half-life, high volume of distribution, and low clearance cross-species. Simple four-species allometric scaling was found to predict the volume of distribution, plasma clearance, and half-life in humans, which were found to be 9.5 L/kg, 0.51 mL/min/kg, and 9 days, respectively [22].

Furthermore, mavacamten has an estimated oral bioavailability of >85% and T_{max} (time to maximum concentration) of 1 hour. No clinically relevant pharmacokinetic differences were observed following mavacamten administration with a high-fat meal. Plasma protein binding of mavacamten is 97-98%. Following a single dose of 25 mg radiolabeled mavacamten, 85% of the dose was recovered in urine (3% unchanged) and <10% of the dose was recovered in feces (1% unchanged). Age, sex, race, ethnicity, or mild to moderate renal impairment had no clinically significant effects on the pharmacokinetics of mavacamten. The effects of severe renal impairment and kidney failure are unknown. No dosage adjustment has been recommended in patients with mild to moderate hepatic impairment, although mavacamten exposures were increased up to 2.2-fold. The effect of a severe hepatic impairment is unknown [19].

Since the main metabolizing enzyme is the polymorphic CYP2C19, pharmacogenomics has a role to play. A person with two normally functioning alleles is considered a normal metabolizer. A person with two nonfunctional alleles is considered a poor metabolizer. About 2% of persons with European ancestry, 4% of persons of African ancestry, and 14% of East Asians are poor metabolizers. Following a single dose of 15 mg, mavacamten exposure increased by 241%, and C_{max} (maximum concentration) increased by 47% in CYP2C19 poor metabolizers compared to normal metabolizers. The mean half-life is prolonged in poor metabolizers (23 days) compared to normal ones (6 - 9 days) [19].

3.4. Adverse Effects

The drug has US Boxed Warning. The warning indicates that mavacamten decreases left ventricular ejection fraction (LVEF) and can cause heart failure due to systolic dysfunction. Echocardiogram assessments of LVEF are required before and during treatment with mavacamten. Starting mavacamten in patients with LVEF <55% is not advised. Mavacamten

should be discontinued if LVEF is <50% at any visit or if the patient starts to experience worsening of his/her clinical status or the symptoms of heart failure [18, 19].

In the EXPLORER-HCM trial, dizziness (27% *vs*. 18%) and syncope (6% *vs* 2%) were the adverse reactions that occurred in >5% of patients and more common in the mavacamten group than in the placebo group. According to the trial's results, the drug can be associated with reversible reduction in LVEF. Furthermore, based on animal studies, the drug may cause fetal toxicity when administered to pregnant patients. Therefore, the absence of pregnancy should be confirmed before the treatment and the patients to be advised to use effective contraception during treatment with mavacamten and for 4 months after the last dose. Mavacamten may decrease the effectiveness of combined hormonal contraceptives [18, 19].

Importantly, mavacamten was not genotoxic in a bacterial reverse mutation test, a rat *in vivo* micronucleus assay, or a human *in vitro* lymphocyte clastogenicity assay. There was no evidence of carcinogenicity seen in a 6-month rasH2 transgenic mouse study at mavacamten doses of up to 3.0 mg/kg/day in females and 2.0 mg/kg/day in males. In reproductive toxicity studies, there was no evidence of mavacamten affecting the fertility and mating in female or male rats at doses up to 1.2 mg/kg/day, or the fertility and viability of offspring of dams dosed up to 1.5 mg/kg/day [19]. The safety of mavacamten was orally assessed in dogs and rats at dose levels within the range of 0.06-10 mg/kg/day. Echocardiographic findings, cardiac dilation, reduction in systolic function, and death, as well as increased heart weight in rats, were in line with the drug's pharmacological mechanism. Other toxicities included QTc prolongation in dogs and cardiac osseous metaplasia in rats [19].

3.5. Contraindications

Discontinuation of certain CYP450 inducers or simultaneous use of mavacamten with certain CYP450 inhibitors can elevate the heart failure risk attributed to systolic dysfunction. Therefore, the use of mavacamten is contraindicated with strong CYP3A4 inhibitors (erythromycin, clarithromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, grapefruit, and goldenseal) or strong CYP3A4 inducers (carbamazepine, enzalutamide, phenobarbital, rifampin, phenytoin, and St. John's Wort) as well as with moderate to strong CYP2C19 inhibitors (amitriptyline, clomipramine, fluconazole, fluvoxamine, imipramine, and ticlopidine/- eslicarbazepine, esomeprazole, fluoxetine, moclobemide, omeprazole, and voriconazole) or inducers (rifampin). Given the risk of heart failure, mavacamten is available only *via* a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called CAMZYOS REMS PROGRAM [18, 19].

CONCLUSION

Mavacamten is a novel, first-in-class, orally active, allosteric inhibitor of cardiac myosin ATPase, which decreases actin-myosin cross-bridge formation, and thus, it reduces myocardial contractility, and it improves myocardial energetic consumption in OHCM pathology. Mavacamten was recently approved by FDA, and it represents a paradigm-shifting pharmacological treatment of OHCM [23-26].

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LIST OF ABBREVIATIONS

NYHA	New York Heart Association
OATPs	Organic-Anion-Transporting Polypeptides
OCTs	Organic Cationic Transporters
OHCM	Obstructive Hypertrophic Cardiomyopathy

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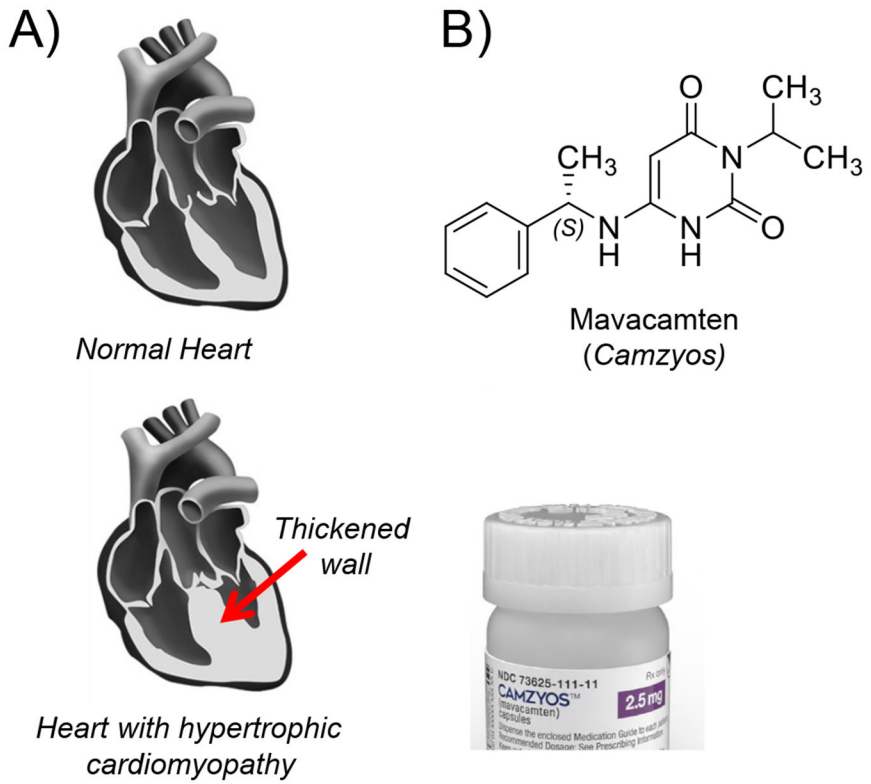

Fig. (1).

(A). Illustration of normal and hypertrophic hearts. (**B**) The chemical structure of mavacamten, along with the representation of its pharmaceutical container.

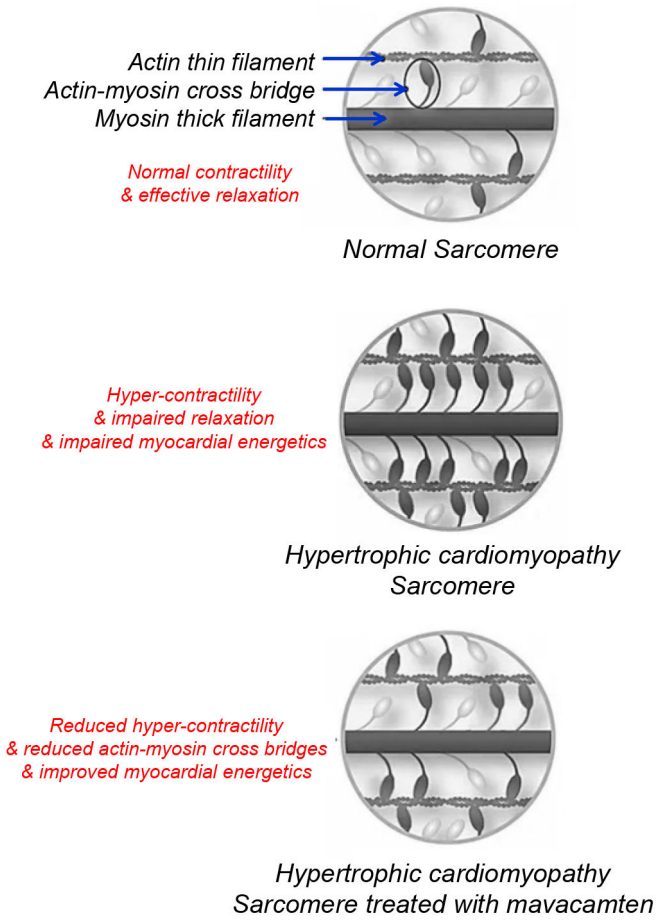

Fig. (2).

Mechanism of action of mavacamten. It reduces the number of actin-myosin cross bridges and diminishes excessive contractility characteristic of hypertrophic cardiomyopathy. In OHCM, mavacamten improves LVOT, physical functioning, and quality of life.

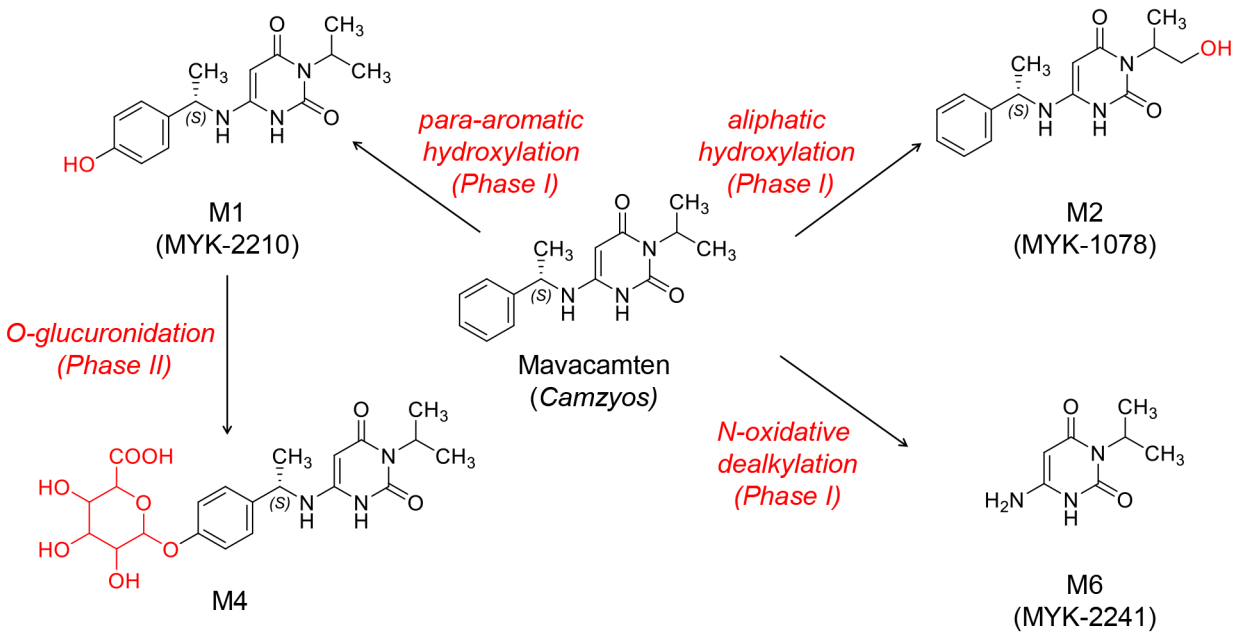

Fig. (3).
In vitro hepatic metabolism of mavacamten.