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Mavacamten – new drug for the treatment of hypertrophic cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is a complex condition characterized by thickening of the left ventricular wall, often caused by genetic mutations. While treatment options traditionally included medications, invasive procedures, and devices like implantable cardioverter-defibrillators (ICDs), the approval of mavacamten by the European Medicine Agency (EMA) in June 2023 marked a significant development. This novel drug, the first of its kind, targets the underlying pathophysiology of HCM by inhibiting cardiac myosin. Its effectiveness in reducing ventricular hypertrophy and improving cardiac function has garnered attention. However, cautious consideration is warranted, especially concerning its use in pregnant or lactating women due to potential fetal toxicity. Further studies are necessary to evaluate its long-term efficacy and safety profile. *(Farm Współ 2024; 17: 165-172) doi: 10.53139/FW.20241716*

Keywords: mavacamten, hypertrophic cardiomyopathy, HCM

Introduction

Mavacamten is the first allosteric, reversible cardiac myosin inhibitor that acts on the primary pathophysiology of HCM. It was released and approved for treatment after the results of the Phase III EXPLORER-HCM and VALOR-HCM clinical trials, which evaluated its safety and efficacy.

Hypertrophic cardiomyopathy

Etiology

HCM is a condition involving an increase in the thickness of the left ventricular wall of the heart of ≥15 mm, which occurs through changes other than variations in left ventricular muscle loading conditions [1]. Gene alterations in cardiomyocyte sarcomeric proteins are responsible for the development of HCM. 60% of patients with HCM present a familial form, the remaining part a non-familial form. In most of them – the cause of HCM remains unclear. This proportion of patients represents approximately 25-30% of individuals. Gene mutations most commonly affect β-myosin heavy chain (MYH7), cardiac myosin-binding protein C (MYBPC3), and cardiac troponin T (TNNT2) [2]. Other causes of this disease include metabolic diseases, mitochondrial cardiomyopathies, neuromuscular junction diseases, congenital malformation syndromes, infiltrative or inflammatory diseases, endocrinopathies, and drugs. Among the metabolic diseases that cause HCM are disorders of amino acid metabolism (tyrosinemia type I), carbohydrate metabolism (Pompe disease, Cori-Forbes disease, Danon disease, cardiac phosphorylase kinase deficiency, congenital glycosylation disorder type Ia), fatty acid metabolism (dehydrogenase deficiencies). Lysosomal storage diseases (mucolipidosis type II alpha/beta, mucopolysaccharidosis type VII – Sly syndrome, gangliosidosis type I) and mitochondrial disorders (MELAS[1], MERRF[2], Kearns-Sayre syndrome) are also responsible for HCM. Mitochondrial cardiomyopathies originate from mutations in genes

[1] MELAS – an acronym for the first letters of the symptoms of mitochondrial disease in English, caused by a mutation in the gene encoding the tRNA for leucine, i.e.: mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes.
[2] MERF – myoclonic epilepsy with ragged-red fibers – caused by mitochondrial mutations, manifested by myoclonias, seizures, cerebellar ataxia, dementia, myopathy, optic nerve atrophy, peripheral neuropathy, and lipomas.

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responsible for components of the electron transport chain. Neuromuscular diseases include Friedreich's ataxia [3]. Congenital defects that accompany HCM include Noonan syndrome, LEOPARD[3], and Costello [4-7]. Subsequently, the causes of HCM can include non-genetically determined factors. An example is inflammatory infiltrative diseases, which include light chain amyloidosis and familial transthyretin amyloidosis. Endocrine disorders leading to HCM include pheochromocytoma and acromegaly; moreover, children of women with diabetes are particularly at risk of developing HCM [3]. Long-term intake of anabolic steroid drugs, hydroxychloroquine, or tacrolimus predisposes to enlargement of left ventricular wall thickness [8-10].

Epidemiology

HCM occurs with similar frequency among all racial groups. Research papers conducted in North America, Asia, Europe, and Africa show left ventricular muscle thickening of 0.02-0.23%, which has not been explained but may correspond to HCM. The prevalence of the condition indicates age-related onset, with a significantly lower percentage of patients diagnosed before the age of 25 [11-17]. HCM in the pediatric population is diagnosed with a frequency of 0.3-0.5/100,000 cases per year [18].

Pathophysiology

In most cases, HCM, that is, left ventricular hypertrophy, is accompanied by a disruption of the structure of myofibrils and the appearance of myofibrillar fibrosis, resulting in impaired ventricular diastolic function. The cause of these abnormalities is malfunction of the cardiovascular system, which leads to prolonged and uneven ventricular relaxation, loss of ventricular blood suction capacity, reduction of ventricular elasticity and abnormal calcium uptake into the cell [19]. A dynamic obstruction in the left ventricular outflow tract (LVOT) is a stenosis in this area, which is referred to as the LVOT gradient. It results from hypertrophy of the interventricular septum (IVS) or abnormalities in the structure of the subvalvular apparatus of the mitral valve, leading to abnormal turbulent blood flow [20]. When considering the pressure gradient in the left ventricular outflow tract, it is possible to differentiate between a form with stenosis (hypertrophic obstructive cardiomyopathy, HOCM) and a form without outflow tract stenosis (hypertrophic nonobstructive cardiomyopathy, HNCM). Stenosis with a pressure gradient between the left ventricle and aorta is associated with the prolapse of one or both bicuspid valve leaflets. The leaflets move toward the IVS, sometimes so that the leaflet temporarily adheres to the septum – SAM (systolic anterior motion – systolic movement of the anterior mitral valve leaflet) [21]. It is worth noting that LVOT stenosis in HCM may vary depending on day-to-day variability, blood volume, pharmacotherapy taken, autonomic system effects, physical activity, general anesthesia used, local anesthesia, and other factors that affect the cardiovascular system. The stenosis may change even during a single diagnostic assessment [22]. In the case of HCM, when LVOT stenosis is not marked, the prognosis is usually beneficial, and symptoms are mainly a result of diastolic dysfunction. Studies have shown or indicated that the survival time of patients with HCM without outflow tract stenosis is similar to that of individuals of similar age and sex; however, there is one unique form, called „burned-out" HCM in which the clinical pattern changes to dilated cardiomyopathy, with a characteristic increase in the dimension of the heart cavity, myocardial thinning, impaired contraction and the presence of secondary pulmonary vascular pressure problems, which is associated with a worse prognosis for the patient [20]. The pathophysiology of HCM is shown in Figure 1.

Symptoms

The variability of symptoms depends on the severity of pressure gradient changes. It happens that HCM in some patients presents no symptoms, while in others, the symptoms that prompt the patient to consult a doctor are complex ventricular arrhythmias. Left undiagnosed, these usually lead to sudden cardiac death [23]. Other clinical manifestations include exertional chest pain, shortness of breath, fainting, palpitations, and vertigo [24].

[3] A congenital syndrome caused by mutation of PTPN11 responsible for tyrosine phosphatase. The name is derived from the first letters of the symptoms: lentiginosis – lentiginous-like patches on the skin, ECG – ECG abnormalities, ocular hypertelorism, pulmonary stenosis – stenosis of the pulmonary outflow, abnormal genitalia – abnormalities of the external genitalia, growth retardation, deafness.

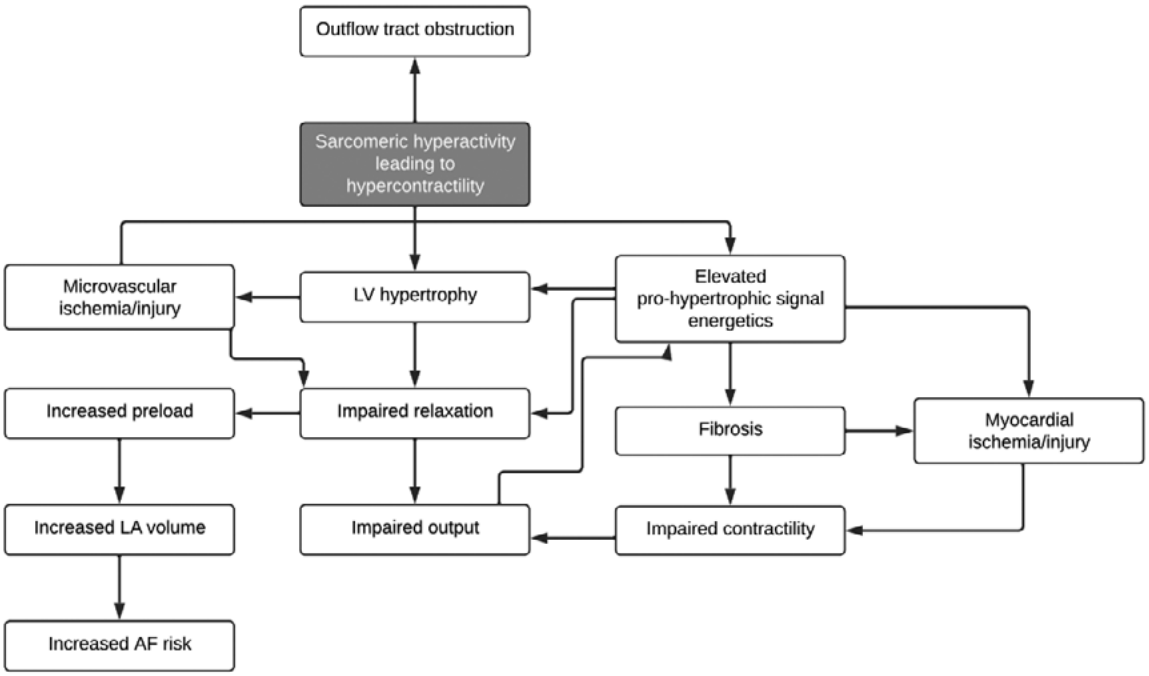

Figure 1. Proposed integrated model of HCM clinical pathophysiology. AF – atrial fibrillation, LA – left atrial, LV – left ventricular

Current treatment guidelines for hypertrophic cardiomyopathy

Depending on the symptoms or complications, the best pharmacological and non-pharmacological treatment for the patient is chosen. Non-pharmacologic, invasive treatment includes myectomy[4] IVS, biventricular cardiac electrostimulation, alcohol IVS ablation, ICD (implantable cardioverter-defibrillator) implantation, or heart transplant. In patients diagnosed with HCM who present no symptoms, similar to those with genetic changes devoid of visible HCM features, treatment is unnecessary.

The HCM Risk-SCD scale, developed through a long-term cohort study, may help assess sudden cardiac death (SCD). The term sudden cardiac death is used to describe death occurring within one hour, which occurs as a result of unexpected cardiac arrest in a person who did not present symptoms indicating a life-threatening condition. The scale takes into account variables whose presence is correlated with an increased risk of sudden death. These variables include left ventricular wall thickness, left atrial size, left ventricular outflow tract gradient, family history of sudden cardiac death in the past, occurrence of nonsustained ventricular tachycardia, and syncope that has not been explained. The patient's age is also essential when clinically assessing the above factors. The risk of sudden cardiac death over the next 5 years is determined based on the presence or absence of the above components. With this scale, it is possible to determine the degree of necessity for ICD implantation (ICD not indicated/ICD indicated). The HCM SCD – Risk calculator is therefore used to assess the absolute risk of SCD. Although it assesses absolute rather than relative risk, it has several limitations. It should not be used to assess SCD in patients under 16 years of age, professional athletes, those with HCM of metabolic origin and congenital malformation syndromes, and patients undergoing ICD implantation for secondary prevention [25].

At the end of June 2023, the European Medicine Agency (EMA) approved the use of a new drug, mavacamten, to treat HOCM [26].

[4] Procedure involving surgical removal of part of the ventricular septum

The drug is the first and only allosteric reversible inhibitor of cardiac myosin (it shows specific inhibitory activity against cardiac myosin) being also a reversible inhibitor of cardiac myosin [27]. It is the only registered drug acting on the primary pathophysiology of HCM. In situations of failure of drug treatment, lack of effect, severity of symptoms, or intolerance of treatment by the patient, invasive treatment is implemented. Methods to reduce the thickness of IVS are percutaneous alcohol ablation of IVS (dedicated to people of advanced age, suffering from severe concomitant diseases or manifesting a solid aversion to surgery) or surgical myectomy – the Morrow procedure used for the rest of the population [28]. Both methods have a comparable effect. They are proposed in patients who present a resting or exercise maximum momentary gradient in LVOT ≥ 50 mmHg. Permanent biventricular stimulation should be opted for in patients in sinus rhythm and when resistance to drug therapy is present when myectomy or IVS alcohol ablation cannot be safely performed, or when there is a reasonable suspicion that these procedures will induce AV block. Implantation of permanent dual-chamber stimulation is also performed to allow intensification of treatment with β-blockers or verapamil [3,29]. The insertion of an ICD is used as a preventive treatment for sudden cardiac death [29,30]. Heart transplantation is recommended in patients without LVOTO, in cases where treatment of ventricular arrhythmias or end-stage heart failure is unsuccessful [3,29,30].

Mavacamten – mechanism of activity

Mavacamten (MYK-461) is an inhibitor of myosin ATPase [31,32]. Myosin is a protein made up of two bases. ATP hydrolysis occurs on each head, which, in cooperation with actin, leads to shortening of the sarcomere [33]. Sometimes, ATP hydrolysis occurs only on one of the myosin heads [34].

Mavacamten inhibits the myosin ATPase cycle four times, increases Km two times, and causes biochemical stabilization of autoinhibition of double-headed cardiac myosin but has no such effect against single-headed S1 myosin [35]. The drug's action is primarily associated with a reduction in the number of heads available for interaction with actin [36].

Mavacamten, through its action, inhibits the development of ventricular hypertrophy and, to some extent, can also reverse this hypertrophy. In addition, it inhibits cardiomyocyte dysfunction and myocardial fibrosis and attenuates the expression of hypertrophic and profibrotic genes [31]. These effects are made possible by weakening the enhanced contractility caused by mutations in beta-myosin [37] and myosin-binding protein C [37,38]. These mutations are responsible for

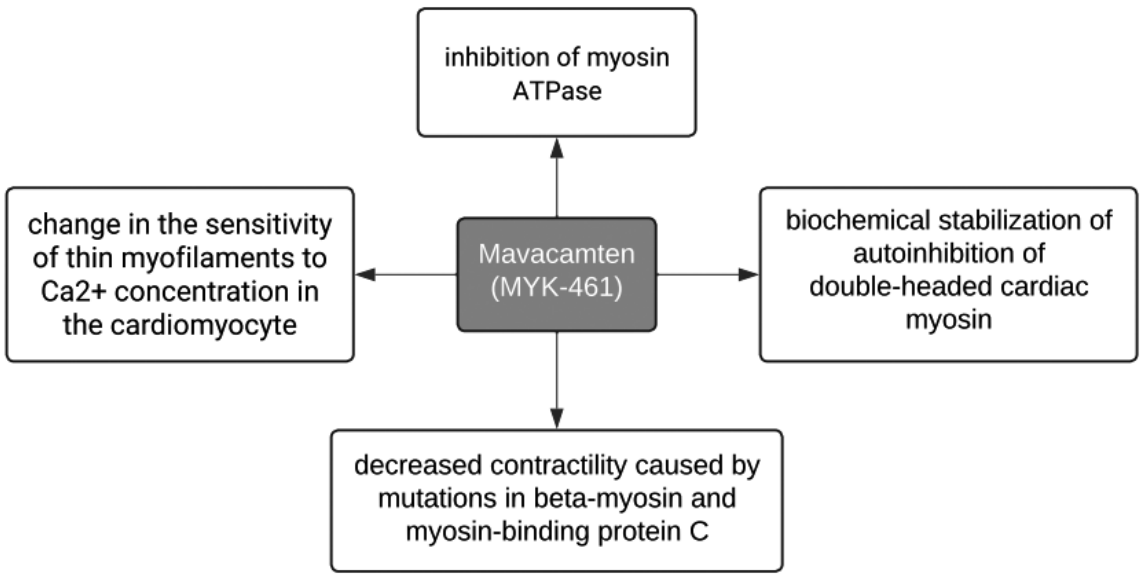

Figure 2. Mechanism of action of the drug

about 80% of cases of inherited HCM [39]. The drug also affects the sensitivity of thin myofilaments to the concentration of Ca2+ in the cardiomyocyte [40,41]. Mavacamten reduces work and maximal power output, showing clear potential to alleviate the energy deficit thought to occur in hypertrophic myocardium [42].

Mavacamten has been registered as 2.5 mg, 5 mg, 10 mg, and 15 mg capsules for treating symptomatic hypertrophic cardiomyopathy with left ventricular outflow tract stenosis in adults (NYHA class II-III required) [43].

Mavacamten has been shown to regulate the Ca2+ sensitivity of thin myofilaments: cardiac troponin T (cTnT) and cardiac troponin I (cTnI). However, this effect is not fully understood. It is possible that mavacamten may also have adverse effects on Ca2+ handling mechanisms in cardiomyocytes and modulate myofilament Ca2+ sensitivity. Therefore, caution should be exercised when using mavacamten to treat thin filament mutations, and the precise molecular mechanisms of disease pathogenesis should be considered [40].

Mavacamten increases peak oxygen uptake (pVO2) in HCM patients with a narrowed LV outflow tract. The drug has beneficial effects on several parameters measured by cardiopulmonary exercise testing (CPET): peak VE/VCO2 ratio, peak MET, peak circulatory power, and peak PETCO2. Mavacamten also prolonged peak exercise time compared to placebo [44].

Mavacamten improves echocardiographic indicators of LV filling pressures (LAVI and E/e'), LVOT gradients, and SAM [45]. In addition, a reduction in serum NTproBNP is observed [45,46].

Emphasis should be placed on conducting more studies in the future to restore, confirm, and evaluate the long-term durability of previous results and provide additional therapeutic value [47,48]. Surgical myectomy should continue to be considered the gold standard in treating HCM patients with severely symptomatic obstructive HCM, enabling permanent abolition of outflow gradients, resulting in long-term restoration of normal (or significantly improved) quality of life and the chance of prolonging life [48].

Pharmacokinetics

Mavacamten is administered orally, and its bioavailability after such administration is 85%. Maximum serum concentration (T_{max}) is reached 1 hour after administration. The substance binds 97-98% to plasma proteins. Mavacamten is metabolized by CYP2C19 (74%), CYP3A4 (18%), and CYP2C9 (8%), and its half-life ($t_{½}$) is 6-9 days. The drug is excreted 85% in the urine [49].

Table I. The comparison of individual data from available clinical trials on mavacamten

Study	Data collected							
	LVOT gradient	NYHA classification	LVEF	E/e	LAVI	CPET (peak VO2)	NT-pro BNP levels	Cardiac troponin I
PIONEER-HCM	↓	↔	↓	↔	↔	↑	↓	Ø
PIONEER-OLE	↓	↓	↔	↓	↓	Ø	↓	Ø
EXPLORER-HCM	↓	↓	↓	↓	↓	↑	↓	↓
VALOR-HCM	↓	↓	↓	↓	↓	Ø	↓	↓
MAVA-LTE								
EXPLORER-LTE cohort	↓	↓	↓	↓	↓	Ø	↓	Ø

↑ – increase, ↓ – decrease, Ø – not reported, ↔ – no significant change

CPET – cardiopulmonary exercise testing; E/e' – ratio between early mitral inflow velocity and early diastolic mitral annular velocity; HCM – hypertrophic cardiomyopathy, IVS – interventricular septum; LAVI – left atrial volume index; LTE – long-term extension; LVEF – left ventricular ejection fraction; LVOT – left ventricular outflow tract; NT-pro BNP – N-terminal pro B-type brain natriuretic peptide; NYHA – New York Heart Association; OLE – open-label extension; SRT – septal reduction therapy.

Mavacamten and pregnancy, fetus and lactation

Animal studies have shown that mavacamten may have toxic effects on the fetus while the mother is taking the drug. Therefore, pregnancy should be excluded in women of childbearing age before starting therapy, and contraception should be recommended during therapy and for four months afterward. Hormonal contraceptives should not be used, as mavacamten may impair their effectiveness [49].

The possibility of mavacamten getting into breast milk, the effect on lactation, or the effect of the drug on a breastfed infant is not known [49].

Summary

In summary, HCM is a complex condition with various genetic and non-genetic causes that lead to the thickening of the left ventricular wall. While treatment options traditionally included medications and invasive procedures, the approval of mavacamten by the European Medicine Agency (EMA) in June 2023 marked a significant advancement. Mavacamten, an allosteric reversible cardiac myosin inhibitor, offers a novel approach to treating HCM by targeting its primary pathophysiology. Alongside existing treatments, such as surgical myectomy and implantable cardioverter--defibrillators (ICDs), mavacamten provides hope for improved outcomes in patients with HCM. However, further research is needed to fully understand its effectiveness and long-term implications. Overall, mavacamten represents a promising development in managing HCM, offering new possibilities for patients and clinicians alike.

Conflict of interest
None

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