Recent trend in the therapy of hypertrophic cardiomyopathy: Cardiac myosin inhibitors

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Abstract

Cardiac myosin inhibitors are a new class of drugs that have recently been approved in obstructive hypertrophic cardiomyopathy. The main mechanism of action is to reduce the pathologically increased cardiac hypercontractility. Current drug therapies have not been demonstrated to modify the natural progress of the disease. Mavacamten is the first approved oral drug to reduce the generation of actin-myosin cross-bridges, thus inhibiting the probability of systolic and diastolic cross-bridge occurence. In clinical studies, it has been shown that mavacamte increases exercise capacity, reduces the left ventricle outflow tract pressure and improves health status by regressing symptoms. However, mavacamten therapy requires continuous monitoring due to the risk of exacerbation of heart failure symptoms. Altertative cardiac myosin inhibitors, aficamten, MYK-224, MYK-581 and CK-4021586 (CK-586) are currently under investigation. These drugs have provided a novel treatment approach for obstructive hypertrophic cardiomyopathy. Further studies will lead to the development of targeted therapies that have the ability to reduce the natural course of this disease.

Keywords: cardiac myosin ATPase inhibition, hypertrophic cardiomyopathy, mavacamten, aficamten, MYK-224, MYK-581, CK-4021586

1. Introduction

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant cardiac genetic disease caused by a mutation in sarcomere protein genes and is characterized by an elevation in left ventricular wall hypertrophy, which leads to mitral regurgitation, myocardial ischemia, diastolic dysfunction, systolic hyperactivity, and left ventricular outflow tract (LVOT) obstruction (Kogut and Popjes, 2020; Basit et al., 2023). HCM is estimated to affect 1:500 individuals in the general population. Some people with HCM have no symptoms, while others may only feel symptoms with exercise/exertion, or suffer arrhythmias or sudden cardiac death. HCM can be classified as obstructive or nonobstructive. The most common symptoms are heart failure, exertional dyspnea, chest pain, dizziness, fatigue, palpitations (secondary to arrhythmia), and presyncope or syncope (Kogut and Popjes, 2020). Symptoms will frequently be exacerbated by exertion. The classic anatomical appearance of HCM is characterized by asymmetric septal hypertrophy (Kogut and Popjes, 2020). Diagnosis requires a left ventricular wall thickness of ≥15 mm in at least one myocardial segment observed with any imaging technique. An important component of the disease is the development of LVOT obstruction, which is defined as a Doppler LVOT pressure gradient ≥ 30 mm Hg (Raj et al., 2022; Basit et al., 2023).

There has been minimal progress in management options for HCM. Existing therapies for HCM include prescription of negative inotropes and chronotropes (non-vasodilating beta-blockers and non-dihydropyridine calcium channel blockers). In patients with refractory symptoms, the addition of disopyramide, a class IA antiarrhythmic drug, is generally considered as the second-line strategy. In cases refractory to pharmacological treatment, invasive interventions such as septal myectomy or alcohol septal ablation can relieve the structural obstruction (Iavarone et al., 2022). Although septal reduction therapies have been successful, they are not a cure for all patients (Rosenzveig et al., 2023). Importantly, the need for septal reduction therapy has been markedly reduced with mavacamten treatment (Desai et al., 2022 and 2023).

Cardiac muscle is found only in the heart; it is striated like skeletal muscle, but it works involuntarily. As in skeletal muscle, it is composed of sarcomeres containing actin and myosin filaments. Therefore, the basic contractile unit is the sarcomere. The contraction mechanism is based upon the sliding of actin filaments between myosin filaments and shortening

of the sarcomere (Robert-Paganin et al., 2020). Myosin molecules generate force in an ATP-dependent manner. ATP hydrolysis is the rate-limiting step. Myosins are responsible for transforming the chemical energy of ATP hydrolysis into mechanical power required for processes such as muscle contraction (Krendel and Mooseker, 2005; Robert-Paganin et al., 2020). Although the pathophysiology of HCM is complex, it is a chronic disease of the cardiomyocyte, and directly related to dysfunction of the sarcomere.

Cardiac myosin ATPase inhibitors are a novel class of drugs that are presently used for treating adults with symptomatic heart failure secondary to obstructive HCM. This class of drugs acts by decreasing actin-myosin interactions in cardiomyocytes. In HCM, the number of myosin heads bound to actin increases as a result of incomplete relaxation. This leads to excessive force generation, resulting in a pathogenic state of hypercontractility. There is an excess actin-myosin cross-bridges during both diastole and systole. The main mechanism of action of cardiac myosin inhibitors is to reduce the pathologically increased cardiac hypercontractility. Mavacamten, the first approved drug, is an allosteric inhibitor of cardiac myosin ATPase (Figure 1). It has been demonstrated in clinical studies to enhance functional capacity in symptomatic obstructive HCM (Edelberg et al., 2022). Aficamten is another cardiac myosin ATPase inhibitor, the second drug in this class, whose drug safety and pharmacokinetic profile were determined in a phase 1 study (Figure 1) (Grillo et al., 2019; Spudich, 2019; Malik et al., 2022; Maron et al., 2022; Wheeler et al., 2023). MYK-224 (BMS-986435) is the third cardiac myosin ATPase inhibitor whose phase studies have been started (Packard et al., 2022).

2. Mavacamten (MYK-461)

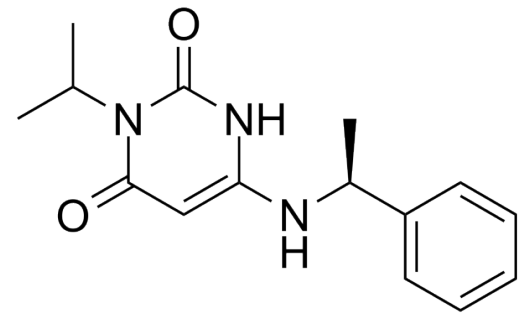
Mutations in β-cardiac myosin can modify power output and lead to some cardiac pathologies. These HCM-associated mutations in the sarcomere augment the number of myosin heads ready to cross-bridge with actin. This causes myocardial hypercontractility. This state of hypercontractility can lead to hypertrophy, fibrosis, and myofilament dysregulation. As a result, both structural and functional disorders occur. Cardiac myofibril contractility is affected by ATPase activity.

2.1. Pharmacodynamics

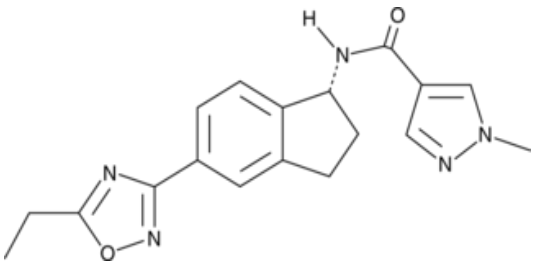
Mavacamten diminishes steady-state ATPase activity by reducing the rate of phosphate release from β-cardiac myosin-S1, which is the rate-limiting step of the myosin chemomechanical cycle (Kawas et al., 2017). This reduces the number of myosin heads that can interact with actin

and decreases the likelihood of diastolic and systolic cross-bridge generation.

In several studies, mavacamten diminished cardiac muscle hypercontractility, ameliorated the active lusitropic function of heart muscle, and acted as a reversible, allosteric, selective inhibitor of cardiac myosin ATPase (Green et al., 2016; Kawas et al., 2017; Anderson et al., 2018; Rohde et al., 2018; Spudich, 2019; Scellini et al., 2021; Awinda et al., 2021; Zampieri et al., 2021; Maron et al., 2022; Lehman et al., 2022).



Mavacamten (MYK-461)



Aficamten (CK-274, CK-3773274)

Figure 1. The chemical structures of mavacamten (MYK-461) and aficamten (CK-274, CK-3773274).

Early administration of mavacamten in a genetic mouse model of HCM depressed myocardial fibrosis, cardiomyocyte dysregulation, and ventricular hypertrophy development and reduced profibrotic and hypertrophic gene expression (Green et al., 2016).

LVOT obstruction is an important constituent of the hypertrophic cardiomyopathy disease phenotype. It plays a crucial role in the progression to heart failure. Mavacamten has been demonstrated to augment exercise capacity, decrease LVOT obstruction, and improve New York Heart Association (NYHA) functional class and health status in patients with obstructive HCM in phase 2 and 3 studies (Heitner et al., 2019; Olivotto et al., 2020; Spertus et al., 2021). The study populations and designs in mavacamten trials are summarized in Table 1.

Mavacamten treatment markedly decreased plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels from baseline to end of treatment in both the obstructive HCM and the nonobstructive HCM studies, including MAVERICK-HCM, PIONEER-OLE, PIONEER-HCM, MAVA-LTE and EXPLORER-HCM. In the EXPLORER-HCM CMR sub-study, mavacamten was associated with a greater decline in maximal LV wall thickness assessed by cardiac magnetic resonance than placebo (Saberi et al., 2021).

Table 1. Summary of the clinical studies with mavacamten

Study[a]	Phase	Age (years)	n	Design	Duration (weeks)	ClinicalTrials.gov ID or Reference
PIONEER-HCM	2	18–70	21	Open-label	12	NCT02842242; Heitner et al., 2019
PIONEER-OLE	2	≥ 18	13	Open-label	120	NCT03496168
EXPLORER-HCM	3	≥ 18	251	Double-blind	30	NCT03470545; Ho et al., 2020b; Olivotto et al., 2020
EXPLORER-HCM CMR sub-study	NA	≥ 18	35	Double-blind	30	NCT03470545; Saberi et al., 2021
MAVA-LTE	2/3	≥ 18	267	Dose-blind[b]	252	NCT03723655; Rader et al. 2021
VALOR-HCM	3	≥ 18	112	Double-blind	16	NCT04349072; Cremer et al., 2022; Desai et al., 2022
MAVERICK-HCM	2	≥ 18	59	Double-blind	16	NCT03442764; Ho et al., 2020a

[a]All studies are obstructive HCM except MAVERICK-HCM which is a nonobstructive HCM study.
[b]All patients enrolled in MAVA-LTE received mavacamten, but patients and investigators were blinded with respect to the mavacamten dose.
CMR, cardiac magnetic resonance; NA, not applicable

VALOR-HCM study revealed that mavacamten improved symptoms and markedly decreased eligibility for requiring septal reduction therapy (Cremer et al., 2022; Desai et al., 2022).

2.2. Pharmacokinetics

There are oral preparations of mavacamten in capsule form of 2.5-5-10-15 mg. The oral bioavailability of mavacamten is estimated as ≥85%, and Tmax is calculated as 1 hour. Mavacamten can be administered with or without food. Mavacamten is extensively protein bound (97-98%) in circulation. It is largely metabolized in the liver mainly via CYP2C9 (8%), CYP3A4 (18%), and CYP2C19 (74%). Mavacamten excretion is inconstant and predominantly dependent upon the status of CYP2C19 polymorphism. The mean elimination half-life is approximately 8 days. A small fraction of individuals of European (approximately 2%) or African (approximately 4%) descent are poor

metabolizers. Poor metabolizers are more prevalent in Asian populations (e.g., approximately 13% in East Asians). After a single 15 mg oral dose, the half-life may be prolonged from 6-9 days in normal metabolizers to 23 days in poor metabolizers. In this case, steady-state concentrations can be reached at 6 weeks. It has been reported that the target plasma concentration for mavacamten can vary from 350 ng/mL to 700 ng/mL (Heitner et al., 2019). Mavacamten is eliminated mainly in the urine. After administration of a single 25 mg dose of radiolabeled mavacamten, 85% of the dose was detected in urine and 7% in feces. No additional dose modification is indicated in patients with mild to moderate renal or hepatic impairment. However, the effect of severe renal impairment or hepatic failure on the pharmacokinetics of mavacamten is currently unidentified (Keam, 2022; Grillo et al., 2019).

2.3. Indications

Mavacamten received US FDA approval on April 28, 2022 for the treatment of adults with symptomatic NYHA class 2-3 obstructive HCM to enhance functional capacity and ameliorate symptoms (Mavacamten FDA label, 2023). In 2021, the European Medicines Agency (EMA) also validated mavacamten's Marketing Authorization Application for the therapy of patients with obstructive HCM (Keam, 2022).

2.4. Contraindications

Concomitant administration of mavacamten with CYP2C19 or CYP3A4 inhibitors and CYP2C19 or CYP3A4 inducers is contraindicated (Keam, 2022). Since animal studies have demonstrated fetal toxicity, the administration of mavacamten is not recommended for pregnant patients (Mavacamten FDA label, 2023).

2.5. Adverse effects

Dizziness (27%) and syncope (6%) were the most common adverse effects in clinical studies of the use of mavacamten (Heitner et al., 2019; Olivotto et al., 2020). However, serious cardiac effects such as atrial fibrillation and stress cardiomyopathy can also occur. Other possible side effects associated with the use of mavacamten include angina pectoris, ventricular tachycardia, syncope, headache, shortness of breath, fatigue, chest pain, palpitations, and leg edema. Reversible decreases in LVEF may occur during treatment; LVEF mostly improves after treatment interruption (Heitner et al., 2019; Olivotto et al., 2020; Keam, 2022; Bello and Pellegrini, 2023). In general, administration of mavacamten is well tolerated and associated with no significant serious adverse events.

2.6. Toxicity

There is limited human overdose experience with mavacamten. During clinical studies, one subject used a single dose of 144 mg and experienced serious adverse reactions, including hypotension, asystole, and vasovagal reaction, but the subject recovered (Mavacamten FDA label, 2023). Doses up to 25 mg were applied for up to 25 days in healthy participants, and 3 out of 8 subjects treated at the 25 mg dose experienced a 20% or greater reduction in LVEF. The most likely consequence of an overdose of mavacamten is systolic dysfunction. In the event of overdose with mavacamten, treatment should be discontinued, and medically supportive measures should be instituted to obtain hemodynamic stability and clinical condition with close monitoring of LVEF and vital signs. Overdose can be serious and life-threatening in humans. Overdose can also cause asystole refractory to medical intervention (Keam, 2022; Mavacamten FDA label, 2023).

2.7. REMS Program

Mavacamten has been reported to be available only through a restricted program called the *Risk Evaluation and Mitigation Strategy* (REMS), where prescribers, patients and pharmacies are registered and certified related to heart failure risk due to systolic dysfunction. All patients should begin treatment with 5 mg of mavacamten. They should undergo transthoracic echocardiography (TTE) every 4 weeks during treatment, and if the peak LVOT gradient is < 20 mm Hg, patients should receive a mandatory dose attenuation to 2.5 mg regardless of LVEF. Another TTE should be performed at week 8, and mavacamten should be stopped if the peak LVOT gradient is < 20 mm Hg. If patients have a ≥ 20 mm Hg peak LVOT gradient at weeks 4 and 8, they should remain at 5 mg up to week 12, which may be increased to 10 mg at week 12, with TTE at 4 weeks after titration and every 3 months thereafter whenever an increase occurs. Despite the strict monitoring program, a major advantage of mavacamten is that it does not require drug level monitoring (Keam, 2022; Altibi et al., 2023).

3. Aficamten (CK-274, CK-3773274)

Aficamten is the second member of the cardiac myosin ATPase inhibitors that remains under investigation for the treatment of symptomatic nonobstructive and obstructive HCM (Chuang et al., 2021; Maron et al., 2023).

3.1. Pharmacodynamics

In the phase 2 REDWOOD-HCM study, aficamten showed reductions in LVOT obstruction and provided symptomatic improvement. Additionally, aficamten was linked with significant

diminutions in NT-proBNP and high-sensitivity cardiac troponin (Maron et al., 2023). The phase 3 trial of aficamten, SEQUOIA-HCM (NCT05186818), is currently enrolling and will investigate the effects of treatment with aficamten on cardiopulmonary exercise capacity and health status in patients with obstructive HCM after 24 weeks of aficamten treatment.

3.2. Pharmacokinetics

Aficamten has a half-life of approximately 3.4 days and requires approximately 2 weeks to reach steady-state concentrations, significantly reducing the time required for the patient to reach the target dose and facilitating once-daily dosing. It was determined that there was no significant CYP inhibition or induction in preclinical studies, providing an advantage for less drug–drug interaction compared with mavacamten. It also has a wide therapeutic window in vivo, and its pharmacokinetic and pharmacodynamic relationship has been clearly explained (Chuang et al., 2021; Malik et al., 2002). In addition, high-dose aficamten (10-30 mg daily) was reported to have a favorable safety profile. In phase studies, it was observed that aficamten can be safely combined with disopyramide and two other negative inotropic drugs, such as calcium channel blockers or beta blockers. There was also no significant effect on the QT interval (Altibi et al., 2023; Maron et al., 2023). Importantly, no serious adverse events related to aficamten and no treatment discontinuations or interruptions due to adverse events were reported. Thus, aficamten has distinctive properties including reversibility of drug effect within 24 h of drug discontinuation, a shorter half-life than mavacamten, a lack of significant drug-drug interactions, and a dose–response ratio that allows for a broad therapeutic window.

4. MYK-224 (BMS-986435), MYK-581, and CK-4021586 (CK-586)

MYK-224 and MYK-581 are two other small molecule cardiac myosin ATPase inhibitors with similar features or analogs to mavacamten and are currently under intense investigation. While MYK-224 is in a phase 1 clinical study, MYK-581 is presently collecting preclinical results (Packard et al., 2022). CK-4021586 (CK-586) is another new cardiac myosin ATPase inhibitor reported recently (Sarkar et al., 2023).

5. Effects on nonobstructive HCM

The thickened heart muscle does not prevent blood outflow from the left ventricle, but does lead to impaired relaxation and diastolic dysfunction, which is believed to play a crucial role in the pathophysiology of nonobstructive HCM. The majority of patients with

nonobstructive HCM remain asymptomatic or mildly symptomatic. Current pharmacological management of symptomatic patients with nonobstructive HCM and preserved ejection fraction includes non-dihydropyridine calcium channel blockers and beta-blockers as first-line therapy, and aldosterone antagonists and loop/thiazide diuretics as the second-line strategy to improve symptoms in case of volume overload and dyspnea (Iavarone et al., 2022). MAVERICK-HCM is a phase 2 study of the administration of mavacamten in symptomatic patients with nonobstructive HCM. In this study, mavacamten was found to be well tolerated in most subjects, and treatment with mavacamten was associated with a dose-dependent reduction in serum NT-proBNP levels. Additionally, in light of the information obtained from the data, it was concluded that patients with more advanced disease expression (e.g., high cTroponin I) may be the most sensitive to treatment. The MAVERICK-HCM study implies that mavacamten can produce beneficial effects for patients with nonobstructive HCM with dosing guided by clinical parameters, such as LVEF (Ho et al., 2020a). The phase 3 ODYSSEY-HCM (NCT05582395) is an ongoning randomized trial of mavacamten versus placebo in symptomatic nonobstructive HCM. Collectively, these data suggest that cardiac myosin inhibitors demonstrate positive results in patients with both nonobstructive and obstructive HCM.

6. Future directions

Long-term efficacy and safety of cardiac myosin inhibitors are important, and this will be evaluated in ongoing trials. DISCOVER-HCM (NCT05489705) is a postmarketing study, which will provide real-world data on the long-term effectiveness and safety of mavacamten and give insight on the patient perspective on symptomatic changes during the course of therapy, while FOREST-HCM (NCT04848506) will present long-term tolerability and safety data of aficamten.

Another area of potential future research is the evaluation of the pharmacokinetic profile, safety, and efficacy of cardiac myosin inhibitors in a pediatric patient population. Further preclinical and clinical data are also required to search the pharmacokinetic profile, safety, and efficacy of cardiac myosin inhibitors in pregnancy and in the postpartum period. EMBARK-HFpEF (NCT04766892) is another ongoing trial to determine the effect of mavacamten in patients with heart failure with preserved ejection fraction.

7. Conclusion

Cardiac myosin inhibitors represent a new class of disease-specific drugs for the

treatment of HCM and provide a novel option for obstructive HCM, especially in those not suitable for septal reduction therapy. Diminishing myocardial contractility by pharmacologic agents appears to be an attractive strategy for the treatment of HCM, but utilization of cardiac myosin inhibitors requires knowledge of dose titration schemes, awareness of drug interactions and monitoring parameters for efficacy and safety.

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