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Mavacamten in Hypertrophic Cardiomyopathy: Unraveling Therapeutic Potential and Clinical Implications in Advancing Cardiovascular Medicine

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ABSTRACT:
Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by myocardial hypertrophy, often leading to various cardiovascular symptoms and complications. While traditional management approaches focus on symptom control, the emergence of mavacamten, a novel cardiac myosin inhibitor, has revolutionized treatment strategies. Mavacamten selectively targets hypercontractility in sarcomeres, addressing the underlying pathophysiology of HCM. This manuscript provides a comprehensive overview of the pathophysiology of HCM, the pharmacological and pharmacokinetic profile of mavacamten, preclinical and clinical trial data, adverse events associated with its use, company agreements, and limitations in its clinical application. Clinical trials demonstrate mavacamten's efficacy in reducing left ventricular outflow tract obstruction, improving symptoms, and mitigating adverse cardiac remodeling in patients with HCM. Despite its promising therapeutic potential, mavacamten presents challenges such as contraindications and potential adverse effects, necessitating careful patient selection and monitoring. Overall, mavacamten represents a significant advancement in the treatment landscape for symptomatic HCM, offering a promising avenue for improved patient outcomes.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) represents a genetic anomaly affecting the myocardium, manifesting as significant myocardial hypertrophy exceeding 15 millimeters, without attributable causation from pressure overload or the presence of myocyte disarray[1]. The occurrence rate of HCM is estimated at 0.2%; however, with advanced imaging techniques and the inclusion of asymptomatic carriers of the associated genes, this figure could potentially rise to approximately 0.6%[2]. HCM arises from mutations predominantly affecting genes responsible for sarcomere proteins, following an autosomal dominant inheritance pattern.

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This condition primarily affects the myofilaments, wherein alterations in structure and function precipitate characteristic pathological and pathophysiological manifestations of varying severity. Dyspnea, angina pectoris, and stress-induced (pre)syncope constitute the cardinal symptoms of HCM, with notable variability in their presentation. Many patients remain oligosymptomatic or even asymptomatic for extended periods[3]. Nevertheless, individuals with HCM face a heightened risk of sudden cardiac death, especially those in younger age groups. HCM stands out as the most commonly reported cause of cardiac fatalities among athletes[4]. The typical pathophysiological alterations in HCM encompass diastolic dysfunction, variable intracavitary obstruction (known as hypertrophic obstructive cardiomyopathy, HOCM), and ischemia. A significant outcome of HOCM involves the blockage of the left ventricular outflow tract, which is a dynamic condition greatly affected by alterations in left ventricular loading and contractility. The blockage results in elevated left ventricular systolic pressure, initiating a chain of intricate processes including heightened wall stress, prolonged ventricular relaxation, compromised left ventricular filling, increased filling pressure, secondary mitral insufficiency, myocardial ischemia, and diminished cardiac output[1]. While HCM typically progresses without major complications in many individuals affected, it is associated with the development of chronic and worsening heart failure symptoms over time. Moreover, it carries an elevated risk of atrial fibrillation and stroke, alongside the potential for sudden cardiac death, particularly notable among adolescents and younger adults.[5] Contemporary management strategies for obstructive HCM predominantly revolve around pharmacological interventions aimed at symptom control. Treatment approaches may involve the use of β-blockers, non-dihydropyridine calcium channel blockers, and disopyramide. Furthermore, non-pharmacological interventions such as implantable cardiac defibrillators and septal reduction therapy (SRT) are also considered as therapeutic options[6]. Mavacamten (marketed as Camzyos™) represents a small-molecule allosteric and reversible inhibitor of cardiac myosin ATPase. It selectively targets the hypercontractility observed in the sarcomeres, a characteristic feature of HCM, by inhibiting the formation of excessive myosin actin cross-bridges. This action leads to a shift in the overall myosin population towards a state that conserves energy while remaining recruitable, termed the super relaxed state. Mavacamten was initially approved on April 28, 2022, in the United States for the treatment of symptomatic New York Heart Association (NYHA) class II-III obstructive HCM in adults, intending to improve functional capacity and alleviate symptoms. The recommended starting dose of mavacamten is 5 mg once daily, irrespective of food intake. Subsequent doses can be titrated as needed, with options ranging from 2.5 to 15 mg once daily[7].

PATHOPHYSIOLOGY OF HYPERTROPHIC CARDIOMYOPATHY (HCM)

The pathophysiology of HCM remains incompletely understood, owing to its complex and multifaceted nature. Nonetheless, the prevailing consensus suggests that HCM arises from sarcomeric dysfunction attributed to missense mutations affecting one or multiple genes encoding contractile proteins, notably beta-myosin heavy chain, myosin-binding protein C, or troponin. These genetic anomalies induce alterations in sarcomere physiology, such as heightened sensitivity of myofilaments to calcium and an elevation in myosin adenosine triphosphatase (ATPase) activity. Consequently, these changes promote the transition of more myosin heads from the physiologically relaxed state to the active state. In a normal cardiomyocyte, approximately 40–50% of myosin heads remain in the relaxed state, resulting in minimal energy consumption[8-13]. In contrast to normal cardiomyocytes, those affected by HCM exhibit a reduced proportion of myosin heads in the relaxed state, typically ranging from 15–20%. This imbalance results in excessive activation and unnecessary energy expenditure. The heightened activation of myosin heads not only consumes ATP inappropriately via myosin ATPase activation but also facilitates a greater propensity for myosin heads to bind actin, leading to an increase in actin–myosin cross-bridging throughout the cardiac cycle. Ultimately, this results in detrimental cardiac remodelling brought about by fibrotic change, myofibre hypertrophy with disarray secondary to increased activation of pathways involving hypertrophy, inflammation and fibrosis (Figure 1).

Sarcomere hyperactivity, driving myocardial hypercontractility, plays a pivotal role in HCM

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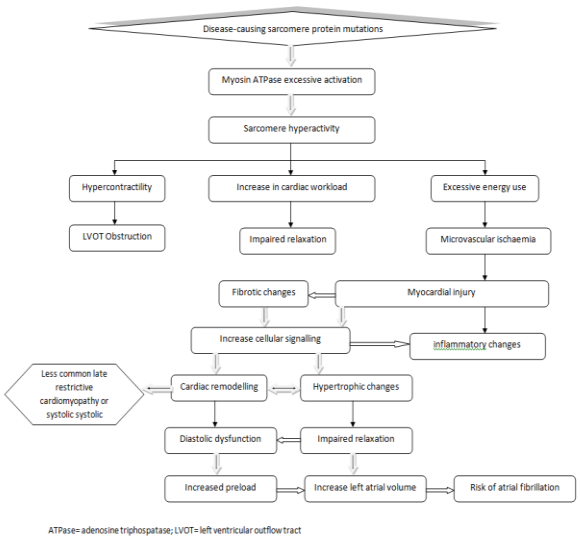
pathophysiology by triggering increased cellular signaling pathways associated with hypertrophic changes. Consequently, this cascade culminates in adverse cardiac remodeling characterized by fibrotic alterations, myofiber hypertrophy accompanied by disarray, and activation of pathways involving hypertrophy, inflammation, and fibrosis. These pathological changes contribute to outflow tract obstruction and diastolic dysfunction, ultimately augmenting cardiac workload. As a consequence, the heart's efficacy as a pump is compromised, leading to the onset of heart failure symptoms, notably the inability to maintain normal left atrial pressure[14].

Figure 1: Pathomechanisms of hypertrophic obstructive cardiomyopathy



ATPase= adenosine triphospatase; LVOT= left ventricular outflow tract

OVERVIEW OF MAVACAMTEN

Company Agreements

In November 2020, Bristol Myers Squibb finalized the acquisition of MyoKardia, Inc., making MyoKardia a wholly owned subsidiary of Bristol Myers Squibb. This acquisition followed a definitive merger agreement announced by Bristol Myers Squibb in October 2020 to acquire MyoKardia. In August 2020, MyoKardia partnered with LianBio to license mavacamten for development and commercialization in several Asian territories, including China, Hong Kong, Macau, Taiwan, Thailand, and Singapore. Initially, the collaboration aimed to pursue regulatory approval for mavacamten in China for obstructive hypertrophic cardiomyopathy (HCM), including conducting a phase 3 registrational trial. Subsequent indications were also planned in alignment with MyoKardia's development strategy. In July 2019, MyoKardia re-obtained the US royalty rights to mavacamten from Sanofi. Prior to that, in January 2019, MyoKardia regained worldwide rights to all programs, including mavacamten, covered under its license and collaboration agreement with Sanofi. The collaboration, initiated in August 2014 and concluded in December 2018, was not extended beyond its initial research term and was fully terminated on April 1, 2019[15].

Pharmacodynamic profile

Mavacamten functions by targeting the myosin-S1 motor protein, thereby modulating multiple facets of the myosin chemo-mechanical cycle. Notably, it reduces ATPase activity, a crucial determinant of cardiac myofibril contractility. In laboratory settings, mavacamten inhibits the rate of phosphate release from β-cardiac myosin-S1, a pivotal step in the myosin chemomechanical cycle, resulting in a decrease in steady-state ATPase activity. Furthermore, mavacamten diminishes the quantity of myosin heads capable of entering "on actin" states, crucial for power generation, while concurrently reducing the likelihood of force-producing (systolic) and residual (diastolic) cross-bridge formation. In vitro investigations encompassing isolated cells, muscle fiber preparations, and engineered human heart tissue models demonstrate mavacamten's ability to stabilize cardiac myosin, mitigate cardiac muscle hypercontractility, and enhance the active lusitropic function of cardiac muscles[16].

pharmacokinetic profile

The pharmacokinetics of oral mavacamten administered once daily typically exhibit dose proportionality within a range of 1–15 mg. In individuals with HCM, mavacamten exposures are approximately 170% higher compared to those observed in healthy individuals receiving equivalent doses. Mavacamten boasts an estimated oral bioavailability of ≥85%, with a time to maximum plasma concentration (Tmax) of approximately 1 hour. Notably, co-administration with food, including a high-fat meal, does not exert clinically significant effects on mavacamten pharmacokinetics.

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Furthermore, mavacamten demonstrates high plasma protein binding, with a binding rate ranging between 97% to 98%. At steady state following once-daily dosing, the peak-to-trough plasma concentration ratio of mavacamten is approximately 1.5. Mavacamten undergoes extensive hepatic metabolism, primarily mediated by cytochrome P450 enzymes, with approximately 74% of metabolism attributed to CYP2C19, 18% to CYP3A4, and 8% to CYP2C9. The elimination of mavacamten is subject to variability and is largely influenced by the polymorphic status of CYP2C19. Individuals classified as normal metabolizers possess two normal function alleles, while poor metabolizers carry two nonfunctional alleles. A small subset of individuals of European descent (approximately 2%) or African descent (approximately 4%) are categorized as poor metabolizers, whereas this proportion is higher in Asian populations (e.g., approximately 13% in East Asians). Following a single 15 mg dose, mavacamten exposure is notably increased in CYP2C19 poor metabolizers compared to normal metabolizers, with the area under the curve (AUC∞) elevated by 241% and the maximum plasma concentration (Cmax) raised by 47%. Moreover, the elimination half-life (t1/2) is prolonged in poor metabolizers, extending to 23 days compared to the typical range of 6–9 days in normal metabolizers. Mavacamten is primarily eliminated via urine. Upon administration of a single 25 mg dose of radiolabeled mavacamten, approximately 85% of the dose was recovered in urine (with 3% as unchanged drug) and 7% in feces (with 1% as unchanged drug)[7].

Alternative names	Camzyos, HCM 1, MAVA-Bristol Myers Squibb/MyoKardia, MYK-461, and SAR-439152 are all terms or entities associated with hypertrophic cardiomyopathy (HCM) treatment
Class	Cardiovascular therapies; Ethylamines; Heart failure therapies; Pyrimidinones; Small molecules
Mechanism of action	Cardiac myosin inhibitors
Route of administration	Oral
Pharmacodynamics	This compound stabilizes cardiac myosin, thereby reducing the availability of myosin heads for "on actin" states, leading to decreased likelihood of systolic and diastolic cross-bridge formation. As a result, it diminishes left ventricular outflow tract (LVOT) obstruction, reduces left ventricular (LV) mass, lowers left atrial (LA) volume, and decreases levels of NT-proBNP.
Pharmacokinetics	The drug reaches peak plasma levels within 1 hour and is highly bound to plasma proteins. It undergoes extensive liver metabolism, mainly by CYP enzymes. Elimination is affected by genetic variations in CYP2C19, resulting in increased drug exposure in poor metabolizers. It is primarily excreted in urine.
Adverse events	Dizziness, syncope , Reversible ↓ in LVEF to <50%
Chemical name	3-(1-methylethyl)-6-[[(1S)-1-phenylethyl]amino]-2,4(1H,3H)-pyrimidinedione

Table 1: Features and properties of mavacamten

PRECLINICAL STUDIES OF MAVACAMTEN IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

In a preclinical study, mavacamten administration exhibited promising effects in mice with HCM, both in preventing the development of hypertrophy in those yet to exhibit myocardial thickening and in reversing hypertrophy in mice already displaying established cardiac changes. These effects were attributed to a decrease in the expression of genes associated with fibrosis and hypertrophy. Histopathological analysis confirmed mavacamten's prevention of myocardial fibrosis and cardiomyocyte disarray, though some irreversible changes persisted. Untreated hearts of mice with HCM exhibited patchy fibrosis similar to human HCM hearts, whereas mavacamten-treated mice displayed minimal fibrosis. Mavacamten also showed a dose-dependent reduction in tension and fractional shortening in isolated cardiac muscle fibers. Moreover, it facilitated the regression of left ventricular wall thickness in mice with HCM[17].

CLINICAL TRIALS OF MAVACAMTEN IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

In the phase 2 MAVERICK-HCM trial, a placebo-controlled study involving 59 participants, mavacamten demonstrated favorable effects on biomarkers of cardiac function and wall stress in adults with symptomatic NYHA class II/III nonobstructive HCM. Specifically, mavacamten led to a greater reduction in geometric mean levels of NT-proBNP, indicative of cardiac wall stress, compared to placebo (-435 vs -6 pg/mL; p = 0.0005). Additionally, mavacamten resulted in reductions in geometric mean levels of cardiac troponin I, a biomarker of cardiac injury, whereas placebo did not produce significant changes (+0.001 ng/mL with placebo vs -0.008 ng/mL with mavacamten; p = 0.009). These findings underscore the potential of mavacamten in improving cardiac dysfunction and wall stress in individuals with symptomatic nonobstructive HCM[18]. Patients who completed the MAVERICK-HCM trial could enroll in the long-term extension (LTE) cohort of the 5-year MAVA-LTE trial (NCT03723655). In this follow-up study, reductions in median NT-proBNP levels with mavacamten treatment at weeks 24 and 48

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mirrored those seen in the initial trial, suggesting sustained beneficial effects on cardiac wall stress over an extended treatment period[19]. In the 30-week phase 3 randomized, placebo-controlled EXPLORER-HCM trial involving 251 participants (NCT05174416), mavacamten therapy showed significant benefits in patients with symptomatic obstructive HCM. It led to reductions in left ventricular outflow tract (LVOT) obstruction, left ventricular (LV) mass, and left atrial (LA) volume. Additionally, mavacamten treatment resulted in decreased levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker indicating cardiac wall stress. These results highlight mavacamten's efficacy in addressing key pathophysiological features of obstructive HCM and improving clinical outcomes in affected individuals[20]. In the 30-week EXPLORER-HCM trial, mavacamten demonstrated superior efficacy compared to placebo in reducing mean resting and Valsalva left ventricular outflow tract (LVOT) gradients. Specifically, at 30 weeks, the mean resting LVOT gradient was 14.1 mmHg in mavacamten recipients versus 45.9 mmHg in placebo recipients (baseline values: 51.7 mmHg and 51.1 mmHg, respectively). Similarly, the mean Valsalva LVOT gradients were 24.8 mmHg in the mavacamten group and 62.7 mmHg in the placebo group (baseline values: 72.4 mmHg and 73.9 mmHg, respectively). Mavacamten also demonstrated notable effects in relieving LVOT obstruction, with 57% of patients experiencing post-exercise gradients below 30 mmHg (compared to 7% in the placebo group). Furthermore, mavacamten reduced the gradient to below the standard threshold for invasive septal reduction therapy (<50 mmHg) in 74% of patients, in contrast to 21% in the placebo group. Although decreases in left ventricular ejection fraction (LVEF) accompanied reductions in Valsalva LVOT gradient in the mavacamten arm, these changes were generally within the normal range, with a mean absolute change from baseline over the 30-week period of -3.9%. Conversely, the mean LVEF reduction in the placebo group was minimal (-0.01%). Following an 8-week treatment interruption at week 38, mean LVEF in both treatment arms returned to levels similar to baseline. Reductions in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in the mavacamten group were observed as early as week 4 and were sustained throughout treatment. At week 30, the reduction in NT-proBNP from baseline in the mavacamten group was 80% greater than in the placebo group. Additionally, mavacamten treatment led to a 41% greater reduction in high-sensitivity cardiac troponin 1 levels compared to placebo[21]. In a cardiac magnetic resonance substudy of EXPLORER-HCM involving 35 randomized patients (17 mavacamten, 18 placebo), mavacamten demonstrated significantly greater reductions in mean left ventricular (LV) mass index compared to placebo (−17.4 vs −1.6 g/m^2; $p < 0.0001$), with a between-group difference of −30.0 g ($p < 0.0001$). Additionally, mavacamten led to greater reductions in LV mass and maximum left atrial volume index (LAVI) compared to placebo, with mean between-group differences of −10.3 mL/m^2 ($p = 0.0004$) for maximum LAVI[22].

ADVERSE EVENTS ASSOCIATED WITH HYPERTROPHIC CARDIOMYOPATHY

In clinical trials involving patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM), mavacamten demonstrated favorable tolerability profiles. In the phase 3 randomized, double-blind, placebo-controlled EXPLORER-HCM trial (NCT03470545), treatment-emergent adverse events (TEAEs) were reported in 88% of patients receiving mavacamten at doses ranging from 2.5 to 15 mg once daily (n = 123), compared to 79% of placebo recipients (n = 128)[21]. In the EXPLORER-HCM trial, dizziness (27% vs 18%) and syncope (6% vs 2%) were the most commonly reported adverse reactions, each occurring in more than 5% of patients. Importantly, these adverse events had a higher incidence in the mavacamten treatment arm compared to the placebo group[7]. In the EXPLORER-HCM trial, serious adverse events occurred in 8% of mavacamten recipients and 9% of placebo recipients. The most frequent serious adverse events included atrial fibrillation (2% vs 3%), syncope (2% vs 1%), and stress cardiomyopathy (2% vs 0%)[2]. In the EXPLORER-HCM trial, syncope was the sole adverse drug reaction leading to discontinuation of mavacamten treatment, occurring in 0.8% of recipients. Reversible reductions in left ventricular ejection fraction (LVEF) to <50% (median 48%) were observed in 7 (6%) mavacamten recipients and 2 (2%) placebo recipients during treatment. Of these, reductions were asymptomatic in 3 mavacamten recipients and 1 placebo recipient. LVEF recovered after treatment

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interruption in all 7 mavacamten recipients, with 3 of them undergoing a temporary interruption and 2 resuming treatment at the same dose, while 1 had the dose reduced from 10 mg to 5 mg. The median duration of mavacamten exposure in the EXPLORER-HCM trial was 30 weeks, ranging from 2 to 40 weeks[7]. In the phase 2 MAVERICK-HCM trial with 58 participants, treatment-emergent adverse events were observed in 90% of mavacamten recipients and 68% of those receiving placebo. Notably, dizziness was the most common adverse event reported in the mavacamten group, occurring in 17.9% of mavacamten recipients compared to 5.3% of placebo recipients[18]. In the phase 3 VALOR-HCM trial (NCT04349072), a randomized, double-blind, placebo-controlled study involving severely symptomatic drug-refractory obstructive hypertrophic cardiomyopathy (HCM) patients receiving mavacamten, preliminary safety findings revealed encouraging outcomes. None of the patients permanently discontinued therapy due to left ventricular ejection fraction (LVEF) ≤30%. Furthermore, there were no instances of serious adverse events related to congestive heart failure, syncope, or sudden cardiac death reported in the mavacamten group. These preliminary results suggest a favorable safety profile for mavacamten in this patient population[23].

LIMITATIONS OF USING MAVACAMTEN

While mavacamten represents a highly effective treatment for symptomatic hypertrophic obstructive cardiomyopathy (HOCM), its clinical utility is hindered by certain challenges. One limitation is its contraindication in patients with reduced left ventricular ejection fraction (LVEF), thereby excluding a considerable portion of individuals with longstanding cardiomyopathy. Furthermore, mavacamten is contraindicated in pregnant patients and those receiving medications known to interact with CYP2C19 and CYP3A4 enzymes, either as inhibitors or inducers. Regular echocardiographic assessments are essential for monitoring LVEF, adding to healthcare costs and potentially burdening patients. Additionally, frequent medication reconciliations are vital to optimizing mavacamten's efficacy and safety. These factors collectively underscore the importance of careful patient selection and comprehensive management protocols in the clinical use of mavacamten for HOCM[14].

CONCLUSION

Until recently, treatment options for hypertrophic obstructive cardiomyopathy (HOCM) have been limited to a few medications, leaving a significant number of patients with refractory symptoms requiring invasive septal reduction therapies. While these therapies are effective, they carry procedural risks. The emergence of mavacamten, a novel myosin inhibitor addressing the underlying cause of HCM-related symptoms, has improved medical treatment for HOCM. However, due to its complexities, including potential side effects and drug interactions, mavacamten's role in treatment algorithms is still evolving. Nonetheless, early data suggests that mavacamten may alter the disease course and could become the preferred first-line treatment for HOCM in the future.

Declarations

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