

Mavacamten, a Small Molecule Modulator of β -cardiac Myosin: a Novel Option for Hypertrophic Cardiomyopathy

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Abstract:

Hypertrophic cardiomyopathy (HCM) is a common singlegene cardiovascular disease that often causes symptoms such as dyspnea and exercise intolerance, and is a major determinant of dynamic left ventricular outflow tract (LVOT) obstruction. Mavacamten is a small molecule, selective ATPase allosteric inhibitor for the treatment of hypertrophic cardiomyopathy by reducing actin-myosin bridge formation and thereby reducing contractile force. The pharmacological action, clinical study and safety of Mavacamten were reviewed in this paper.

Keywords:

Mavacamten, Hypertrophic Cardiomyopathy, β -myocardial myosin, Small Molecule Modulator

1. Introduction

Hypertrophic cardiomyopathy is a myocardial disorder characterized by primary left ventricular hypertrophy [1,2]. This complex disorder can be broadly defined by pathologically enhanced cardiac actin-myosin interactions, with core pathophysiology features including hypercontraction, diastolic abnormalities, and dynamic left ventricular outflow tract (LVOT) obstruction [2,3,4]. Hypertrophic cardiomyopathy is characterized by left or right ventricular hypertrophy, ventricular septal hypertrophy, and often asymmetric hypertrophy, which can be divided into obstructive HCM (oHCM) and non-obstructive HCM (nHCM) according to the effect of hypertrophy on the left ventricular outflow tract (LVOT). Typical clinical symptoms of HCM are dyspnea, palpitations, chest pain, and syncope. Available drug options for hypertrophic cardiomyopathy are inadequate or poorly tolerated and are not disease-specific. Mavacamten is a very promising new drug for the treatment of patients with HCM symptoms, improving symptoms and physiological markers in symptomatic HCM patients with minimal adverse events.

Mavacamten, chemically known as ((6-([(1S)-1-phenethyl]amino)-3-(propyl2-yl)-1,2,3,4-tetrahydropyrimidin-2,4-dione), is a small molecule, selective myosin ATPase allosteric inhibitor that reduces contractility by reducing actin-myosin cross-bridging formation, specifically targeting the underlying pathophysiology of hypertrophic cardiomyopathy [5]. In July 2020, the U.S. Food and Drug Administration (FDA) granted Mavacamten (formerly MKY-461 manufacturer: MyoKardia) breakthrough therapy designation for the treatment of symptomatic obstructive hypertrophic cardiomyopathy. Mavacamten represents a promising new class of drugs for the treatment of patients with symptomatic hypertrophic cardiomyopathy, including obstructive and non-obstructive cardiomyopathy [5]. Its molecular weight is 273.33g/mol, and the structural formula is shown in Figure 1.

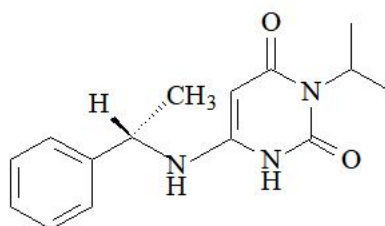


Figure 1. Mavacamten chemical structural formula.

2. Pharmacological Action

Mavacamten targets sarcomeres, in which case it is recommended to simultaneously reduce cardiac contractility and promote diastolic relaxation in patients with HCM. Combined, these features are thought to improve decreased left ventricular compliance and dynamic left ventricular outflow tract obstruction in HCM patients [6]. Mavacamten reduces contractility by reducing strong cross-bridge binding, in part because the 65% faster cross-bridge nucleotide processing rate accelerates myosin isolation [7]. Mavacamten therapy improves exercise capacity, left ventricular obstruction, NYHA functional grade, and health status in patients with obstructive hypertrophic cardiomyopathy [7].

3. Pharmacokinetics

The pharmacokinetic curve of Mavacamten is characterized by rapid absorption and distribution, followed by a long elimination period with an average elimination half-life of approximately 8 days [9]. Existing in vitro and in vivo pharmacokinetic characteristics suggest that mavacamten clearance is low, has a large distribution, long terminal elimination half-life, and excellent oral bioavailability across species [10]. The four simple allometric growth scales predicted plasma clearance, volume of distribution, and half-life of 0.51 ml/min/kg, 9.5 L/kg, and 9 days, respectively. Assuming a single-chamber model, the predicted $t_{1/2}$ ($t_{1/2} = V_{dss} \cdot 0.693 / CL$) in humans is calculated using the predicted pharmacokinetic parameters [10].

A Phase 2 open-label, non-randomized clinical trial called PIONEER-HCM evaluated the pharmacodynamics, pharmacokinetics, safety and tolerability of mavacamten. Twenty-one patients with obstructive HCM and NYHA functional grade II-III symptoms [9] were included, patients were enrolled in two consecutive cohorts, A and B, for 12 weeks of treatment, in group A, patients could not receive background therapy during the study, and if LVEF was not reduced by 15-20%, patients weighing ≤ 60 kg at the beginning of week 4 took 10 mg/day with a body weight of >60 kg take 15 mg / day with an increase in dose. In Cohort B,

patients could continue to use β blockers for the duration of the trial, starting at a dose of 2 mg/day and increasing to 5 mg/day at the end of week 4, with 11 patients participating in the first group of patients with PIONEER-HCM and 10 patients completing the study. During the 12-week treatment period, all 10 study subjects (100%) achieved an average reduction of 125 mmHg from baseline in peak LVOT (left ventricular outflow tract) pressure gradient after exercise. Eight of these patients were reduced below the diagnostic threshold (≤ 30 mmHg) and the other two were measured below 50 mmHg. It is worth mentioning that as early as week 2, a clinically significant improvement in the LVOT pressure gradient at rest (≤ 30 mmHg) was observed in 9 patients. This also provides a basis for low-dose studies in the second group of PIONEER-HCM.

Mavacamten has no inhibitory effect on CYPases, but at high concentrations relative to expected therapeutic concentrations, CYP2B6 and CYP3A4 enzymes *in vitro* can be induced. Mavacamten has high permeability and low jet transport on Caco-2 cell membranes. In human hepatocytes, mavacamten is not a substrate for the drug transporters OATP, OCT and NTCP. Mavacamten was determined to have minimal risk of drug-drug interactions. *In vitro*, mavacamten metabolites include phase I and phase II mediated metabolism, the main pathways are aromatic hydroxylation (M1), aliphatic hydroxylation (M2); N-dealkylation (M6) and m1-metabolite (M4) glucuronidation. The reaction phenotypes were mainly CYPs 2C19 and 3A4/3A5 [6].

4. Clinical Efficacy

Mavacamten has recently entered Phase 3 clinical trials for the treatment of obstructive HCM [11], and more research is needed to test the potential effects of Mavacamten on other forms of HCM [12]. It is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial called EXPLORER-HCM conducted at 68 clinical cardiovascular centers in 13 countries. In an evaluation of a randomized, placebo-controlled, prospective phase 3 clinical trial of mavacamten (a clinical study evaluating mavacamten in adults with symptomatic obstructive hypertrophic cardiomyopathy) [13], 251 patients were randomized to either mavacamten or placebo in a 1:1 ratio, with 123 receiving Mavacamten and 128 receiving placebo for 30 weeks. Follow-up visits are performed every 2-4 weeks to assess the patient's condition. The primary endpoint was an increase in peak oxygen consumption (pVO₂) of 1.5 mL/kg per minute or more, and a reduction in NYHA grade of at least one level; or pVO₂ increases by 3.0 mL/kg per minute and above, and the NYHA grade does not decrease. Dose titrations were performed at weeks 8 and 14 to achieve a decrease in left blood flow gradient < 30 mmHg and mavacamten plasma concentration between 350-700 ng/ml. Patients can continue standard therapy with HCM, including stable doses of β blockers or calcium channel blockers monotherapy. In the mavacamten group, 66 (54%) men aged (58.5 ± 12.2 years) with a maximum left ventricular wall thickness (20 ± 4 mm), and 88 (72%) had NYHA grade II symptoms. In the placebo group, 83 (65%) were male, aged 58.5 ± 11.8 years, with a maximum left ventricular wall thickness of 20 ± 3 mm, and 95 (74%) had NYHA class II symptoms. Gene sequencing was performed in 190 (76%) patients, of whom 50 (26%) had pathogenic or probably pathogenic mutations in one of the identified sarcoma protein genes. In the entire study population, 35 (14%) patients had atrial fibrillation, 19 (8%) had atrial septal reduction therapy, 110 (44%) patients had hypertension, 18 (7%) had coronary artery disease, 28 (11%) patients had asthma, and

5 (2%) patients had chronic obstructive pulmonary disease. Treatment with mavacamten was associated with improvement in primary outcomes and all secondary outcomes compared to placebo. Forty-five (37%) patients treated with mavacamten had no deterioration in NYHA grade compared with 22 (17%) patients treated with placebo ($p=0.0005$); In terms of secondary outcomes, LVOT gradients after exercise were reduced by 47 ± 40 mmHg ($p<0.0001$) in the mavacamten group compared to 10 ± 30 mmHg in the placebo group. Compared with the placebo group - 0.1 ± 3.0 ml/kg/min, the mavacamten group increased by 1.4 ± 3.1 ml/kg/min ($p=0.0006$). In the mavacamten group, a larger proportion of patients improved by at least one NYHA level (65% vs. 31%, $p<0.0001$). Patients taking mavacamten had more significant improvements in KCCQ-CSS and HCMSQ-SoB scores (13.6 ± 14.4 vs 4.2 ± 13.7 , $p<0.0001$, -2.8 ± 2.7 vs -0.9 ± 2.4 , $p<0.0001$) [12].

Patient-reported outcome assessments using KCCQ-CSS and the new HCMSQ-SoB score, specifically designed to assess symptom burden in patients with hypertrophic cardiomyopathy, showed that mavacamten had a favorable effect on subjective well-being. Notably, the improvement in KCCQ-CSS scores is several times higher than that observed in heart failure drug trials over the past few years and is almost half the effect achieved by placing a left ventricular assist device in the treatment of end-stage heart failure [14,15]. Clinical benefit persists, in addition to treatment with β blockers or calcium antagonists, accompanied by decreased serum NT-proBNP and hs-cTnI concentrations, two predictors of long-term prognosis for hypertrophic cardiomyopathy [16,17,18]. In the MAVERICK-HCM study [5], there was a similar decrease in cardiac biomarkers in patients with non obstructive diseases, suggesting that the decrease in gradient may only be a partial reason for the observed benefits of EXPLORER-HCM. These impacts require further research.

5. Safety and Tolerability

Data from preliminary studies suggest that mavacamten is generally well tolerated and has a high safety profile. In this study, mavacamten reduced LVEF in a concentration-dependent manner, with significant reduction in LVOT occlusion occurring when plasma concentrations were between 350 and 695 ng/mL [9]. In this range, left ventricular ejection fraction is maintained at 50% or higher in all patients. Higher plasma concentrations were associated with a significant decrease in LVEF (34-49% at 695 to 1500 ng/mL), and LVEF returned to baseline within 4 weeks of discontinuation of treatment in four patients (17%) [9].

Data on adverse events can be obtained from the first 12 weeks of PIONEER and its open label extension studies PIONEER ole [9], MAVERICK [12], and EXPLORER [13]. In the pioneer study, 99% of adverse events were classified as mild or moderate, including decreased LVEF, atrial fibrillation, ventricular tachycardia, angina, headache, dizziness, nausea, fatigue, site rash, dyspnea on exertion, upper respiratory tract infection, urinary tract infection, and rash. The development of atrial fibrillation led to serious adverse events of hospitalization and reversion, leading to discontinuation of the study drug [9]. Similarly, in the MAVERICK experiment, 96% of adverse events were classified as mild or moderate, including atrial fibrillation, nausea, fatigue, dyspnea, upper respiratory tract infections, dizziness, palpitations, nasopharyngitis, constipation, bloating, dental abscess, and sinusitis. Six serious events occurred in four patients, including atrial fibrillation, systolic dysfunction, arthritis, altered mental status, and renal failure [19]. In the explorer group, 10 (8%) of patients using mavacamten experienced serious adverse reactions, compared with 11

(9%) in the placebo group. These events include atrial fibrillation, syncope, stress cardiomyopathy, diverticulitis, infection, contusion, and forearm fracture in the Mavacamten group [13].

The results of its Phase 3 clinical trial show that the first targeted drug therapy specifically designed to target the basic pathophysiology of obstructive hypertrophic cardiomyopathy has a significant efficacy. Treatment with Mavacamten significantly improves hemodynamic status, functional volume, and subjective well-being. An ongoing, long-term, extended study will provide further evidence for the clinical benefit and safety of mavacamten over 5 years [8]. Mavacamten is well tolerated, either when used with β blockers or calcium channel blockers, in patients with unsuccessful previous septal reduction therapy, or alone in a small number of patients. Only a mild decrease in the overall mean systolic function of the left ventricle was observed, and LVEF was less than 50% in 7 patients (4 patients at the end of treatment), which returned to normal after a temporary interruption of treatment in all patients, without affecting the completion of the study. In addition to this, the safety profile of mavacamten is similar to that of placebo. Studies evaluating the long-term efficacy and safety of mavacamten over 5 years are ongoing (MA VA-LTE; NCT03723655)[8]. Limitations of the study included the exclusion of patients taking dipyrimidine and those with severe symptoms (NYHA class IV). Both populations will be examined in the VALOR-HCM study. In addition, younger patients (< 50 years of age) and non-white patients were less represented in this study. In summary, in this first randomized, positive Phase 3 trial of patients with obstructive hypertrophic cardiomyopathy, mavacamten treatment improved key aspects of functional capacity, left ventricular volume gradient, symptoms, and well-being. The results of this pivotal trial highlight the benefits of disease-specific treatments for hypertrophic cardiomyopathy.

In addition, as mentioned earlier, patients with symptomatic non-obstructive HCM disease are a particularly challenging patient population, as there is no specific medical therapy demonstrating its benefit [8]. UNFORTUNATELY, THE RESULTS FOR MAVERICK-HCM WERE LESS FAVORABLE. The use of mavacamten in patients with non-obstructive HCM disease did not show benefit in terms of comprehensive functional improvement endpoints ≥ 1 NYHA functional class and $1.5 \geq$: in the NYHA functional scale, pVO2 increased by ml/kg/min overall, or pVO2 increased by ≥ 3.0 ml/kg/min without deterioration. NTproBNP was significantly reduced, suggesting a physiological mechanism underlying potential symptom improvement in future studies [19], although the benefit of mavacamten in patients with non-obstructive HCM disease is unclear at this time.

6. Conclusions

For patients with symptomatic obstructive HCM, mavacamten appears to be a useful new drug that improves function and symptoms in patients with low clearance, large distribution, long terminal elimination half-life, excellent cross-species oral bioavailability, good tolerability and safety, and dose-dependent action. According to the current research results, Mavacamten has shown sufficient benefits in the treatment of hypertrophic cardiomyopathy and has a good application prospect.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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