2025 Volume: 01 Issue: 04 www.ijrpa.com Case-Study

International Journal Research Publication Analysis

Page: 219-226

THE INTEREST OF MAVACAMTEN IN OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

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Article Received: 30 June 2025
Article Revised: 20 July 2025
Published on: 10 August 2025

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a disease of the heart muscle, primarily characterized by hypertrophy of the left ventricle, but it can also affect both ventricles. It manifests without any other cardiac, systemic, or metabolic cause. The diagnosis relies on the identification of this hypertrophy in the absence of abnormal loading conditions or infiltrative diseases, often accompanied by fibrosis, mitral valve abnormalities, and other alterations. The obstructive form of HCM is the most common among genetically originated heart diseases, leading to thickening of the heart muscle that hinders blood expulsion. To establish a diagnosis, multimodal imaging and genetic testing are essential, and a multidisciplinary approach is recommended for the management of patients. It is also crucial to differentiate sarcomeric conditions from phenocopies, such as overload diseases and Fabry disease.

KEYWORDS: Hypertrophic cardiomyopathy – Obstruction – Mavacamten.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common heart disease, with an estimated prevalence between 1 in 200 and 1 in 500. Its clinical expression is highly variable, ranging from the absence of symptoms to severe manifestations such as heart failure, syncope, chest pain, and arrhythmias, which represent the main cause of morbidity. In some cases, sudden death may be the first manifestation of the disease.

A frequent complication of HCM is obstruction, which defines obstructive hypertrophic cardiomyopathy (OHC). This obstruction is identified by a pressure gradient greater than 30 mmHg on echocardiography and is considered significant when it exceeds 50 mmHg. This latter threshold can be reached either at rest or following provocative maneuvers, such as the

Valsalva maneuver or during a stress echocardiogram, especially in symptomatic patients. Approximately 50 to 60% of patients with HCM present with obstruction, with figures reaching up to 75% in some American studies. Obstruction may be present at the time of diagnosis (in about 30% of cases) or revealed by provocative testing.

The obstruction is often localized at the left ventricle outflow tract and can be intraventricular, generally related to the severity of hypertrophy and sometimes to abnormalities in the implantation of the mitral valve chordae. The presence of obstruction is a negative prognostic factor, associated with worsening signs of heart failure, an increased risk of syncope, ischemia, arrhythmias, and sudden death.

In practice, it is recommended to systematically assess the presence of obstruction in any symptomatic patient with HCM, using both resting and stress echocardiography, especially if no obstruction is detected at rest. The significance threshold for the gradient is set at 50 mmHg.

Standard management typically begins with lifestyle and dietary measures, while avoiding intense exercise. Pharmacological treatments include vasodilators, beta-blockers, or the introduction of the new selective allosteric inhibitor of myosin, mavacamten. As for surgery, septal myectomy and ventricular pacing are options.

CLINICAL CASE

This is a young patient, 39 years old, of Tunisian origin, working in construction as a mason, with no cardiovascular risk factors and no particular medical history, who presents to the emergency department with the onset of acute effort dyspnea, NYHA stage III-IV, without associated signs of prolonged lower thoracic pain without irradiation, prompting the patient to seek emergency care at our facility.

Upon admission, the clinical examination reveals a tachycardic and polypneic patient with persistent pain, with normal blood pressure in both arms. The cardiovascular examination shows a soft 3/6 systolic murmur at the mitral area, radiating towards the axillae, associated with signs of right heart failure in the form of localized edema in the lower limbs at the ankles.

The electrocardiogram shows sinus rhythm with a heart rate of 110 bpm, with left ventricular hypertrophy (Sokolow index at 41 mm), complemented by a transthoracic echocardiogram

showing hypertrophy of the left ventricular walls with an interventricular septum measuring 23 mm and a posterior wall measuring 13 mm. An obstruction is identified with a maximum pressure gradient exceeding 120 mmHg, associated with moderate mitral regurgitation and global left ventricular hypokinesis with impaired left ventricular function estimated at 30% at SBP with elevated filling pressures.

Immediate management included the administration of furosemide IV and a beta-blocker to stabilize the patient. After multidisciplinary consultation, the patient was deemed a good candidate for the administration of mavacamtem at an initial dose of 2.5 mg per day while awaiting the results of the cytochrome test, and possibly for the placement of an implantable cardioverter-defibrillator (ICD). The patient refused the defibrillator, so we continued with medical treatment alone.

A follow-up after one month of treatment showed slight improvement in the patient, clinically with decreased dyspnea and absence of signs of heart failure, and echocardiographically, a small improvement was noted, with the maximum gradient decreasing from 120 mmHg to 100 mmHg. With the results of the cytochrome test indicating an intermediate metabolizer, we doubled the dose of mavacamtem to 5 mg per day. After a control two months later, the gradient decreased to 60 mmHg.

To date, the patient has been placed on mavacamtem at a dose of 15 mg per day, and after several clinical and echocardiographic checks, the patient is doing well with a stable maximum gradient around 30 mmHg.

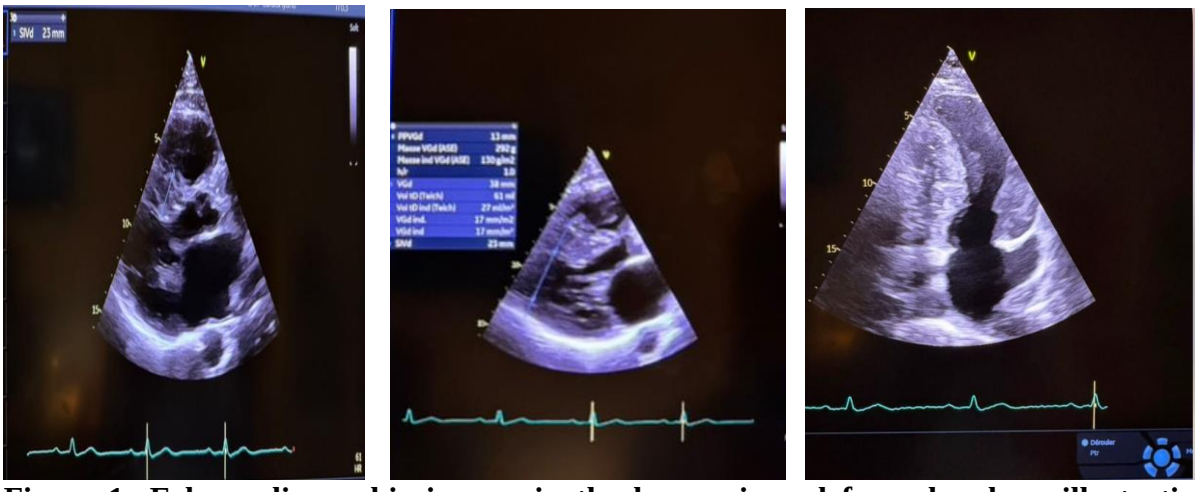

Figure 1: Echocardiographic images in the long axis and four chambers illustrating hypertrophic cardiomyopathy.

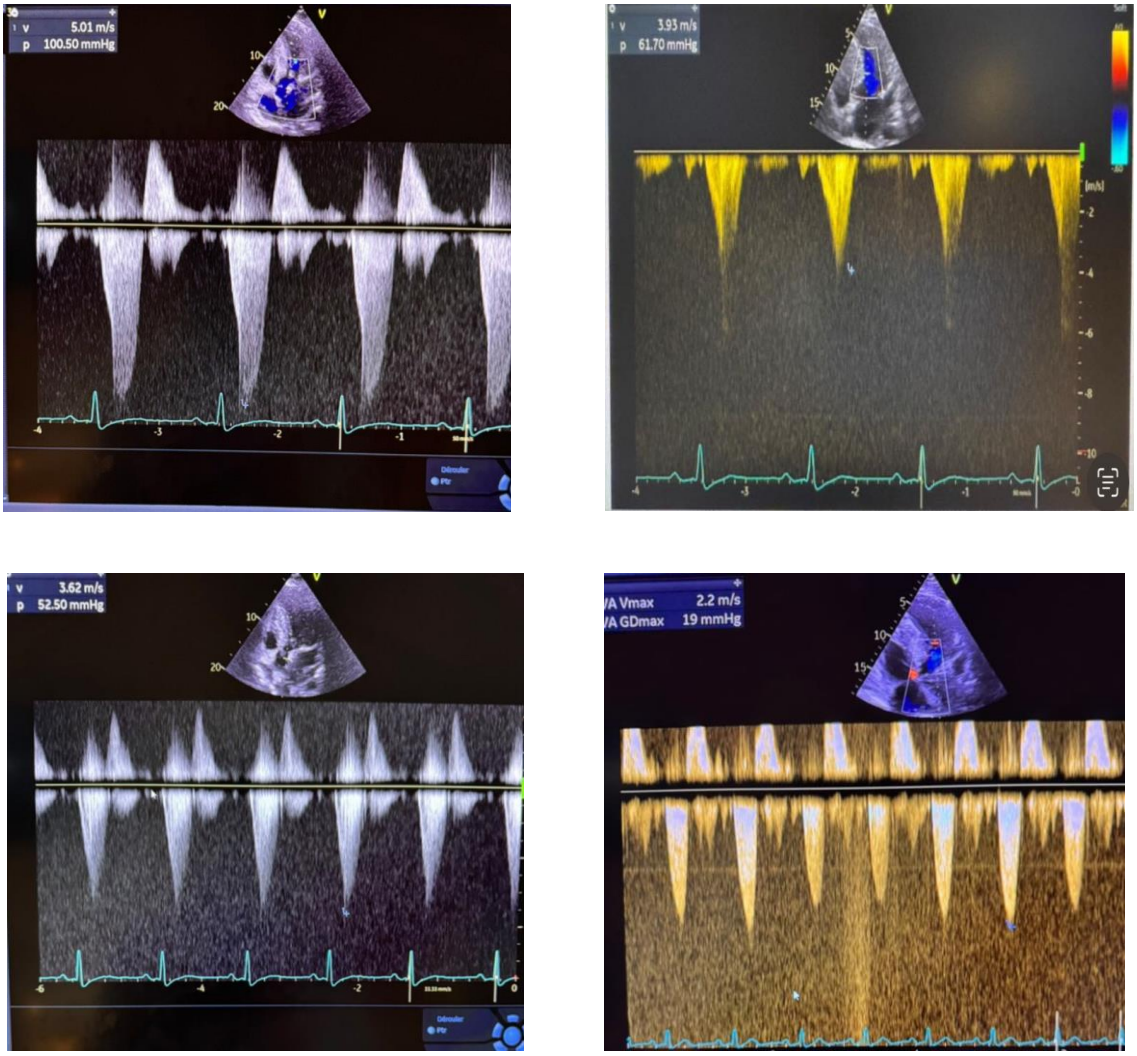

Figure 2: Echocardiographic images illustrating the evolution of the gradient since the administration of mavacamtem after 3 months of treatment.

DISCUSSION

One of the main objectives of treating symptomatic patients with obstructive hypertrophic cardiomyopathy is to relieve their symptoms in order to improve their quality of life. The 2020 professional treatment recommendations from the American Heart Association and the American College of Cardiology for patients with hypertrophic cardiomyopathy identified a clear and unmet need for new trial protocols and patient-reported outcome measurement tools to assess the effect of new therapies on meaningful endpoints, such as quality of life. The evidence supporting the benefits of alternative therapeutic approaches on health status was limited, and the benefits of direct myosin modulation were not available.

Mechanism of action of mavacamten

Despite the diversity of genotypes in patients with HCM, a common feature is hyperdynamic contraction, which appears to be a final trait of the disease's pathophysiology. To treat this condition, mavacamten was developed. This drug works by selectively reducing myocardial contractility, decreasing the affinity between actin and myosin, and restoring a normal ratio of myosin heads in a super-relaxed conformation. Preclinical studies have shown that early administration of mavacamten in mouse models of HCM could prevent and even reverse pathological changes such as ventricular hypertrophy, disorganization of cardiomyocytes, and myocardial fibrosis. These promising results have paved the way for clinical trials in patients with HCM, offering hope for a new therapeutic approach to this complex disease.

The dosing range is between 2.5 mg and 15 mg, and the initiation of treatment depends on the phenotyping of the cytochrome P450 2C19 of the patients, which should be determined by genotype to identify the appropriate dose of mavacamten.

Slow metabolizer phenotype of CYP2C19

The recommended initial dosage is 2.5 mg orally once daily. The maximum dose is 5 mg once daily. Early clinical response in the patient should be assessed by the left ventricular outflow tract gradient (LVOTG), with Valsalva maneuver, at 4 and 8 weeks after treatment initiation.

Intermediate, normal, rapid, and ultrarapid metabolizer phenotypes of CYP2C19

The recommended initial dosage is 5 mg orally once daily. The maximum dose is 15 mg once daily. Early clinical response in the patient should be assessed by the LVOTG with Valsalva maneuver, at 4 and 8 weeks after treatment initiation. Once the individualized maintenance dose is reached, patients should be evaluated every 12 weeks. If, during a visit, the patient has an ejection fraction (EF) < 50%, treatment should be interrupted for 4 weeks and until the EF returns to a value ≥ 50%. In patients with an intercurrent condition such as a severe infection or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia) that may impair systolic function, it is recommended to assess the EF; moreover, dose increases are not recommended until the intercurrent condition is resolved. Consideration should be given to stopping treatment in patients who have shown no response (e.g., no improvement in symptoms, quality of life, exercise capacity, or LVOTG) after 4-6 months at the maximum tolerated dose.

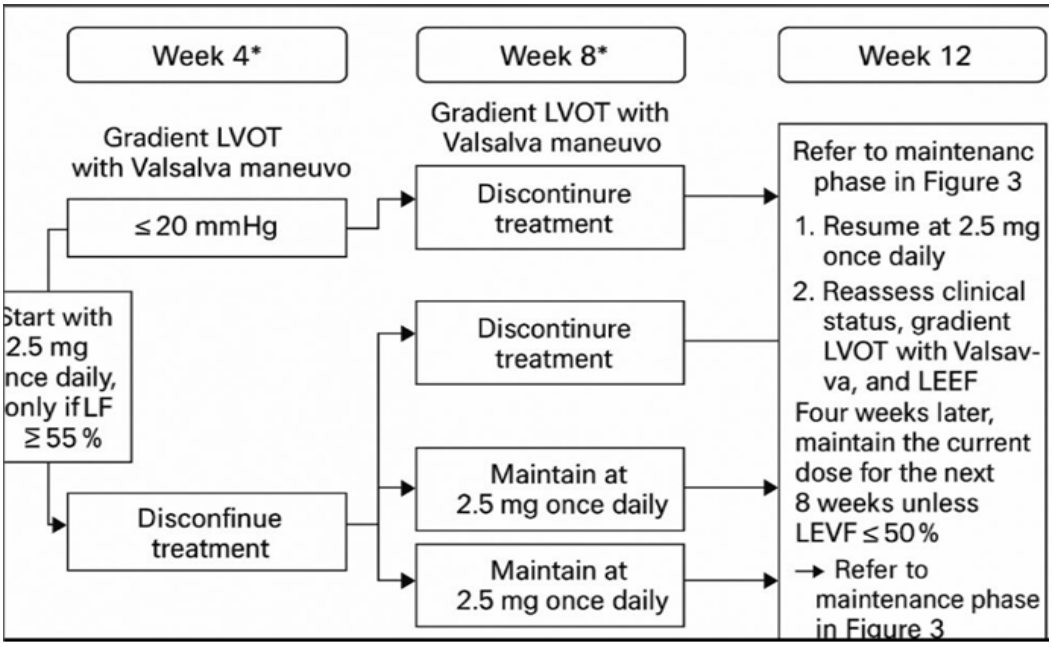

Figure 3: Establishment of mavacamten for the slow metabolizer phenotype of CYP2C19.[6]

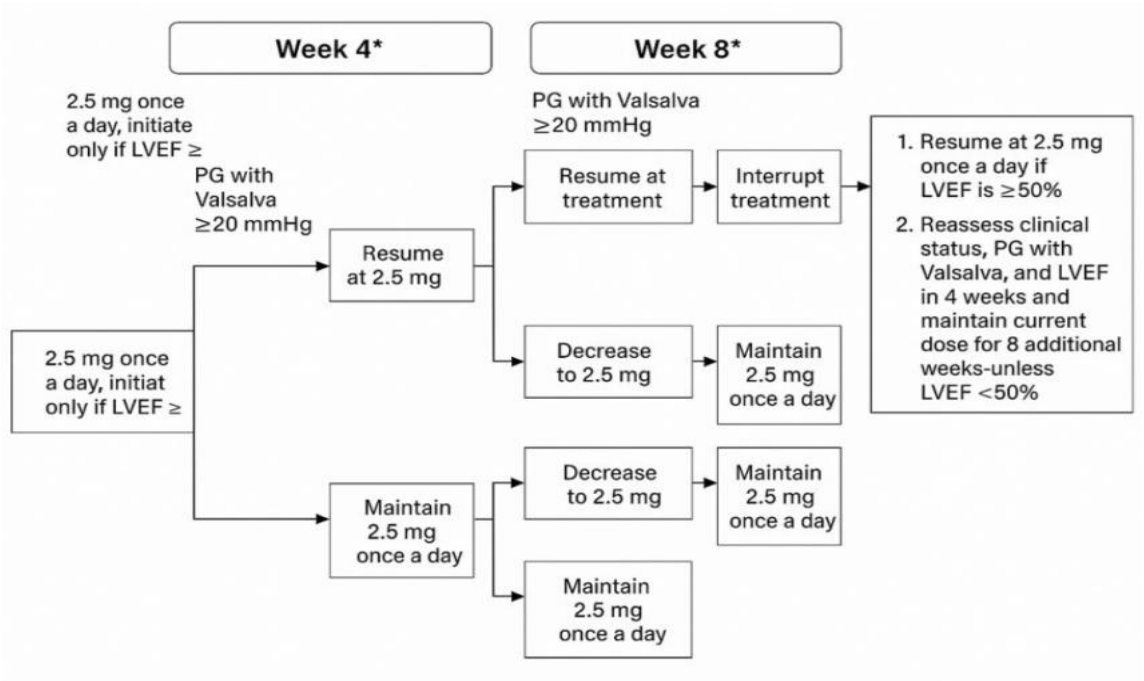

Figure 4: Establishment of mavacamten for the intermediate, normal, rapid, and ultrarapid metabolizer phenotype of CYP2C19.[6]

CONCLUSION

Hypertrophic cardiomyopathy is a common but complex condition. Its symptomatic management is entering a new era with the emergence of innovative treatments. Among them, mavacamten represents a new class of therapy that directly targets the actin-myosin

interaction, which is responsible for cardiac hypertrophy. This drug not only improves obstruction and patients' functional status, but also shows promising potential in cardiac remodeling, fibrosis reduction, and control of hypertrophy. These deeper effects are currently being investigated in several clinical trials. Mavacamten thus paves the way for a targeted therapeutic approach, marking a major breakthrough in the management of HCM.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Author contribution

- MB: Study concept, Data collection, Data analysis, writing the paper.
- RL: Study concept, Data collection, Data analysis.
- RF: Study concept, Data analysis, writing the paper.
- NM: Supervision and data validation
- IA: Supervision and data validation
- AB: Supervision and data validation
- All authors reviewed the final manuscript.

Funding Sources

There are no funding sources to declare.

Statement of informed consent

The authors confirm that written consent for the submission and publication of this case, including images, has been obtained from the patients in line with the Committee on Publication Ethics (COPE) guidance.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Consent for publication

Written informed consent was obtained from the patients for publication of this cases report.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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