LETTER TO THE EDITOR

MAVACAMTEN: A door that has opened in the treatment of Hypertrophic Cardiomyopathy

Ishaque Hameed[1], Omer Mustafa Siddiqui[2], Syed Abdus Samad[3]

Dear Editor, Hypertrophic cardiomyopathy (HCM) is a complex condition characterized by abnormally elevated cardiac actin-myosin interactions, hypercontractility, abnormalities in diastolic function, and dynamic obstruction of the left ventricular outflow tract (LVOT).[1] Primary left ventricular hypertrophy is the hallmark of hypertrophic cardiomyopathy. People suffering from HCM are frequently symptomatic with heart failure, atrial fibrillation and malignant ventricular arrhythmias.[1] Currently, the treatment options for HCM include calcium channel blockers, disopyramide and β blocker for symptomatic alleviation.[2] These non-specific medicines are frequently ineffective or poorly tolerated,[3] inefficient at targeting the fundamental bio-molecular pathways of HCM and have no impact in altering the disease's course. Invasive therapies focusing on septal reduction, such as septal myectomy and alcohol ablation, may benefit the individuals' refractory to medical treatment.[2] However, it comes with concerns and requires not always available expertise.[4] Recently, myosin inhibitors, a new family of negative inotropic medicines, have been introduced to treat symptomatic obstructive HCM.[5]

The US Food and Drug Administration has recently approved Mavacamten, a new treatment for symptomatic HOCM. This novel allosteric inhibitor selectively targets the myosin ATPase in cardiac myocytes. It targets the underlying molecular pathogenesis involved in HOCM by lowering actin-myosin cross-bridge generation, hence decreasing contractility and enhancing myocardial energetics.[5] Its safety and efficacy were recently investigated in phase III (EXPLORER-HCM) clinical trial in primarily minimally symptomatic HCM patients having LV outflow gradients during rest and with physiologic (exercise) provocation.[5] With improved symptoms and reduced outflow gradients, Mavacamten therapy resulted in NYHA class improvements in around 65 per cent of the participants.

Despite this, the primary endpoint was met by only about a third of patients in the trial. This endpoint was defined by an improvement of 1 NYHA class, associated with a slight gain in functional capacity as measured by exercise stress testing with max VO2. In patients with HOCM, treatment-emergent side effects are common, and in the EXPLORER study, 88% of mavacamten participants reported any adverse event, compared to 79% in the placebo arm. The common side effects were ventricular tachycardia, atrial fibrillation, palpitations, heart failure, and angina.[5]

Introducing new pharmacological regimens, such as mavacamten, to alleviate symptoms associated with outflow blockage is unquestionably a welcome addition to HCM treatment options (Figure). Indeed, despite poor short-term patient experience, mavacamten is the first novel medicine for hypertrophic cardiomyopathy in over decades, and as a result, it has sparked much interest. Consequently, as when dealing with any new therapy, mainly when related to complex heart pathologies like Hypertrophic cardiomyopathy, it is rational to exercise caution, especially at this initial stage, until more substantial data can be tested over a more extended duration to resolve any existing fundamental questions about mavacamten's efficacy and safety. As we witness the

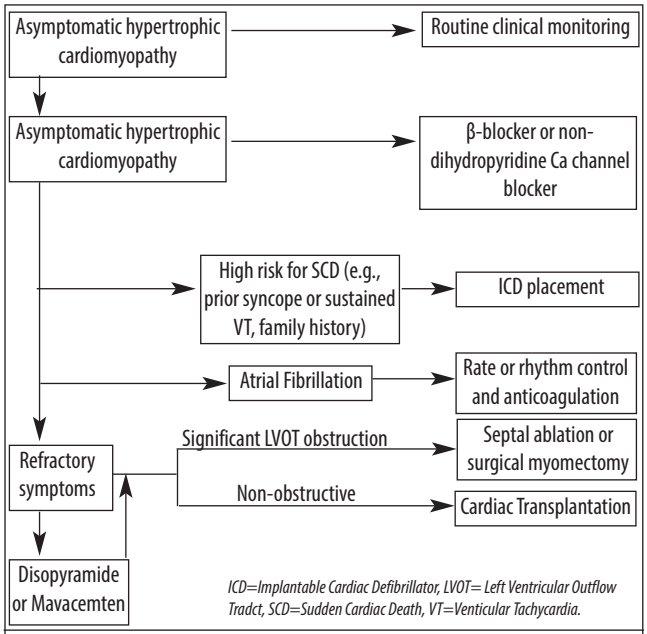

Figure: Management of Hypertrophic Obstructive Cardiomyopathy.

[1,2]epartment of Internal Medicine, Dow University of Health and Sciences, Civil Hospital, Karachi, Pakistan; [3]Department of General Surgery, Dow University of Health and Sciences, Civil Hospital, Karachi, Pakistan.
Correspondence: Ishaque Hameed. e-mail: ishaquehameed@hotmail.com
ORCID ID. 0000-0002-3698-6401

treatment paradigm in HCM evolve, new RCTs should focus on the following concerns/questions:

- Will people with sarcomeric variations have different remodelling than those who do not?
- Will the degree of LVOT blockage influence the extent of remodelling?
- Will the favourable structural remodeling seen so far lead to better outcomes in atrial fibrillation and heart failure development?
- Will the level of remodeling be the same in patients who have recently developed the condition versus those who have had it for a long time?
- Will individuals with non-obstructive HCM benefit from favourable remodelling in the same way that those with HoCM do?
- Will those with apical aneurysms and mid-cavitary blockage have positive or negative cardiac remodelling?
- Could mavacamten, if given to children with HCM, have a comparable beneficial remolding effect and help to limit disease progression and the high rate of bad outcomes?
- Could mavacamten be used as prophylactic therapy in people with a genotype but not a phenotype?

Disclaimer: None.

Conflict of interest: None.

Funding disclosure: None.

DOI: https://doi.org/10.47391/JPMA.7258

Submission completion date: 16-06-2022

Acceptance date: 14-09-2022

References

1. Maron BJ. Clinical Course and Management of Hypertrophic Cardiomyopathy. N Engl J Med 2018;379:655-68. doi: 10.1056/NEJMra1710575.
2. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2761-96. doi: 10.1161/CIR.0b013e318223e230.
3. Ammirati E, Contri R, Coppini R, Cecchi F, Frigerio M, Olivotto I. Pharmacological treatment of hypertrophic cardiomyopathy: current practice and novel perspectives. Eur J Heart Fail 2016;18:1106-18. doi: 10.1002/ejhf.541.
4. Liebregts M, Vriesendorp PA, Mahmoodi BK, Schinkel AF, Michels M, ten Berg JM. A Systematic Review and Meta-Analysis of Long-Term Outcomes After Septal Reduction Therapy in Patients With Hypertrophic Cardiomyopathy. JACC Heart Fail 2015;3:896-905. doi: 10.1016/j.jchf.2015.06.011.
5. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2020;396:759-69. doi: 10.1016/S0140-6736(20)31792-X.