

Myosin Modulators: The New Era of Medical Therapy for Systolic Heart Failure and Hypertrophic Cardiomyopathy

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Abstract

A new uprising pharmacological treatment for systolic heart failure and hypertrophic cardiomyopathy demonstrates very promising results the last years. Myosin modulators have already been tested in numerous studies. Myosin inhibitor (mavacamten) and myosin stimulator, (omecamtiv mecarbil) exhibit their effect by improving clinical outcomes, as well as reducing morbidity and mortality. More studies are however required for further evaluation and particularly effect on sarcomeric level. Side effects of both pharmacological agents have been described and should always be close monitored. Cardiopulmonary exercise test has a pivotal role by means of assessing treatment efficacy.

Keywords: Myosin inhibitor; Myosin stimulator; Heart failure; Hypertrophic cardiomyopathy

Introduction

Sarcomeres are the principal contractile units. Genetic mutations give rise to different forms of cardiomyopathy. Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease. It is the most common cause of sudden cardiac death in young patients. This type of cardiomyopathy is characterized primarily by hypertrophy together with myofibrillar disarray and diastolic dysfunction in the absence of pressure or volume overload.

In the contrary, systolic heart failure is characterized by impaired systolic function. Compared with HCM, systolic heart failure is characterized by great heterogeneity. From genetic perspective, dilative cardiomyopathy (DCM) is the most common representative of sarcomere mutation that can lead to

systolic heart failure. Such mutations give rise to diminished sarcomere force generation, impaired force transmission, alterations in energy production or defects in calcium handling [1].

Current Medical and Interventional Treatment

In case of HCM, treatment is standard-wise initiated with beta-blocker, verapamil and additional disopyramide in case of pressure gradient, persistent symptoms, and absence of contraindication to disopyramide.

In case of persistent symptoms and an existing pacemaker, DDD pacemaker upgrade with short atrioventricular delay is an option. Furthermore, myectomy, alcohol septal ablation (ASA) and ultimately heart transplantation must be considered in patients who may need a more invasive management [2].

In case of systolic heart failure, essential is the correct diagnosis of the causes of reduced systolic function (ischemic or non-ischemic). Primarily, an angiotensin-converting enzyme (ACE)-blocker and beta-blocker should be initiated in every patient and uptitrated until the maximal tolerated doses. Patients with persistent symptoms and ejection fraction of 35% or less, a further escalation of medical therapy with mineralocorticoid receptor antagonist (MRA) is required. Furthermore, in case of sinus rhythm and heart frequency more than 70 beat/min, medical therapy with ivabradin improves clinical outcomes. Moreover, studies have shown that angiotensin receptor-neprilysin inhibitors can dramatically improve mortality and morbidity in patients with systolic heart failure. Additionally, cardiac resynchronization therapy (CRT) is strongly recommended in patients with left ventricular ejection fraction (LVEF) 35% and a wide QRS (more or equal to 130 ms). In case of terminal heart failure, not all patients can benefit from heart transplantation, in the frame of insufficient donations compared to demand. Over the last years, implantation of left ventricular assist devices (LVAD) has been an important and effective alternative in long term [3].

Hypertrophic Obstructive Cardiomyopathy

Mutations leading to HCM have been detected in genes encoding for sarcomeres. Even if a numerous gene mutations in sarcomeres have been identified, it has not been specified clearly yet, how mutations in a single protein lead to a positive

Manuscript submitted March 19, 2021, accepted April 13, 2021
Published online May 14, 2021

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doi: <https://doi.org/10.14740/cr1243>

phenotype.

Recent development of mavacamten, a myosin inhibitor, has given an answer to this question. Increased contractility was shown to be the primary defect in HCM, in a scene of excess sarcomere power [4].

This inhibitor of cardiac myosin adenosine triphosphatase (ATPase) increases the length of the total time of the ATPase cycle, as well as decreases the rate of phosphate release without slowing adenosine diphosphate (ADP) release [4, 5]. This leads to a reduction of force of contraction. Moreover, recent studies have demonstrated that mavacamten exerts its effects by stabilizing the state of relaxation of β -cardiac myosin [5, 6]. Throughout, there is a reduction of myosin heads that are functionally accessible for interaction with actin filaments. This is predominantly the mechanism of the effect of mavacamten.

In chronic setting, mavacamten infusion leads to suppression of the phenotype, including hypertrophy, myocardial disarray and myocardial fibrosis in mice models [4].

Interestingly, mavacamten may decrease the left ventricular outflow tract (LVOT) pressure gradient by reducing contractility and eliminating systolic anterior motion of the mitral [7].

Furthermore, the PIONEER-HCM trial tested the effects of mavacamten in patients with HCM [8]. In this first patient cohort, 11 patients enrolled and 10 completed the study. LVOT gradient and maximal oxygen consumption (peak VO_2) were tested at 12 weeks. As a primary endpoint, mavacamten led to significant decrease of pressure gradient as well as increased peak VO_2 ($P = 0.002$).

Lately, in EXPLORER-HCM trial, mavacamten was effective in terms of reducing LVOT gradients and improving symptoms, exercise performance, and health status [9]. A total of 251 patients received once daily mavacamten or placebo for 30 weeks. As primary endpoint, an increase of 1.5 mL/kg per minute or greater of peak VO_2 and at least one New York Heart Association (NYHA) class reduction or a 3.0 mL/kg per minute or greater pVO_2 increase without NYHA class worsening at week 30 has been considered.

Results showed 36.6% of patients met the primary endpoint compared with 17.2% patients on placebo ($P = 0.0005$). All secondary endpoints (including post-exercise LVOT gradient and outcomes) demonstrated statistically significant improvements ($P < 0.0006$) [9].

Systolic Heart Failure

The direct sarcomere activator omecamtiv mecarbil (OM) exerts inotropic effects by directly increasing sarcomere contractility without affecting intracellular calcium concentration, which is responsible for adverse effects of inotropic agents [10].

In ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) trial, intravenous use of OM did not lead to improvement of dyspnea ($P = 0.034$). However, decrease of left ventricular end systolic diameter has been demonstrated. The results were sufficient to warrant further investigation of OM [11].

The COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) trial was a multicenter, randomized, double-blind, placebo-controlled trial, which evaluated the tolerability of OM and its effects on left ventricle (LV) systolic function and ventricular remodeling in patients with heart failure with reduced ejection fraction (HFrEF). The study showed that OM led to an improvement in cardiac function as well as a reduction of ventricular diameters compared to placebo [12].

Finally, the GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) trial is the first trial of examining whether selectively increasing cardiac contractility will result in improved clinical outcomes [13].

Side Effects of Myosin Modulators

In case of systolic heart failure, adverse effects of OM, for example ischemia, were observed at very high doses, in particular due to overlengthening of ejection time. However, adverse effects that typically lead to limited use of current medical treatment, such decreased blood pressure, orthostatic dysregulation, electrolyte disturbances or acute renal failure, were not observed [14].

On the other hand, in case of HCM, myosin inhibitors were discontinued due to adverse events, such as atrial fibrillation and syncope. Additionally, some patients have been found to have stress cardiomyopathy. Furthermore, some patients had a drop in LVEF, and a small part of those required protocol-driven temporary discontinuation of the drug. Importantly, there were no incident heart failure events [8].

Conclusions

Myosin modulators represent promising agents for the therapy of systolic heart failure and HCM.

Mavacamten and OM, recently developed direct sarcomere modulators, have demonstrated significant therapeutic effects in HCM and systolic heart failure. The optimal treatment depends however on each mutation. Development of mutation-specific therapies is essential to prevent the progression of cardiomyopathies. Further development of more specific sarcomere modulators, which can influence in a positive manner the sarcomere function, is expected in the following years.

The ongoing range of research on OM will further highlight its full range of effects and its usefulness in patients with systolic heart failure. In the broad spectrum of studies concerning systolic heart failure, cardiopulmonary exercise test (CPET) plays a pivotal role in the evaluation of treatment efficacy [3, 15].

Ongoing studies are about to evaluate the efficacy of mavacamten to reduce the need for septal reduction therapies. In case of HCM, careful evaluation of mitral valve apparatus should take place, due to the fact that abnormalities of mitral valve apparatus may be the only phenotypic expression of the disease, even in the absence of hypertrophy [16].

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Author Contributions

Both authors have equally contributed to the article.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

ACE: angiotensin-converting enzyme; ADP: adenosine diphosphate; ASA: alcohol septal ablation; ATPase: adenosine triphosphatase; CPET: cardiopulmonary exercise test; CRT: cardiac resynchronisation therapy; DCM: dilative cardiomyopathy; HCM: hypertrophic cardiomyopathy; HF: heart failure; H(O)CM: hypertrophic (obstructive) cardiomyopathy; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; OM: omecamtiv mecarbil

References

1. Tsukamoto O. Direct sarcomere modulators are promising new treatments for cardiomyopathies. *Int J Mol Sci.* 2019;21(1):226.
2. Fifer MA, Vlahakes GJ. Management of symptoms in hypertrophic cardiomyopathy. *Circulation.* 2008;117(3):429-439.
3. Sakellaropoulos S, Svab S, Mohammed M, Dimitra L, Mitsis A. The role of mitral valve in hypertrophic obstructive cardiomyopathy: an updated review. *Curr Probl Cardiol.* 2021;46(3):100641.
4. Green EM, Wakimoto H, Anderson RL, Evanchik MJ, Gorham JM, Harrison BC, Henze M, et al. A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice. *Science.* 2016;351(6273):617-621.
5. Kawas RF, Anderson RL, Ingle SRB, Song Y, Sran AS, Rodriguez HM. A small-molecule modulator of cardiac myosin acts on multiple stages of the myosin chemomechanical cycle. *J Biol Chem.* 2017;292(40):16571-16577.
6. Anderson RL, Trivedi DV, Sarkar SS, Henze M, Ma W, Gong H, Rogers CS, et al. Deciphering the super relaxed state of human beta-cardiac myosin and the mode of action of mavacamten from myosin molecules to muscle fibers. *Proc Natl Acad Sci U S A.* 2018;115(35):E8143-E8152.
7. Stern JA, Markova S, Ueda Y, Kim JB, Pascoe PJ, Evanchik MJ, Green EM, et al. A small molecule inhibitor of sarcomere contractility acutely relieves left ventricular outflow tract obstruction in feline hypertrophic cardiomyopathy. *PLoS One.* 2016;11(12):e0168407.
8. Heitner SB, Jacoby D, Lester SJ, Owens A, Wang A, Zhang D, Lambing J, et al. Mavacamten treatment for obstructive hypertrophic cardiomyopathy: a clinical trial. *Ann Intern Med.* 2019;170(11):741-748.
9. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, Saberi S, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2020;396(10253):759-769.
10. Malik FI, Hartman JJ, Elias KA, Morgan BP, Rodriguez H, Brejc K, Anderson RL, et al. Cardiac myosin activation: a potential therapeutic approach for systolic heart failure. *Science.* 2011;331(6023):1439-1443.
11. Teerlink JR, Felker GM, McMurray JJV, Ponikowski P, Metra M, Filippatos GS, Ezekowitz JA, et al. Acute treatment with Omecamtiv Mecarbil to increase contractility in acute heart failure: the ATOMIC-AHF study. *J Am Coll Cardiol.* 2016;67(12):1444-1455.
12. Teerlink JR, Felker GM, McMurray JJ, Solomon SD, Adams KF, Jr., Cleland JG, Ezekowitz JA, et al. Chronic oral study of myosin activation to increase contractility in heart failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial. *Lancet.* 2016;388(10062):2895-2903.
13. Registrational study with Omecamtiv Mecarbil/AMG 423 to treat chronic heart failure with reduced ejection fraction (GALACTIC-HF). *ClinicalTrials.gov.* Identifier: NCT02678923. [Accessed: March 26, 2018].
14. Teerlink JR. A novel approach to improve cardiac performance: cardiac myosin activators. *Heart Fail Rev.* 2009;14(4):289-298.
15. Sakellaropoulos S, Lekaditi D, Svab S. Cardiopulmonary Exercise Test in heart failure: A Sine qua non. *International Journal of Physical Education, Fitness and Sports.* 2020;9(2):1-8.
16. Sakellaropoulos S, Mitsis A. Cardiopulmonary exercise test-the revolving door of left ventricular assist devices in heart failure. *Curr Probl Cardiol.* 2021;46(3):100651.