State of the art paper

Omecamtiv mecarbil, a cardiac myosin activator with potential efficacy in heart failure

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Abstract

Heart failure (HF) is a growing global epidemic resulting in significant morbidity and mortality. The pathophysiology of HF with reduced ejection fraction (HFrEF) is characterized by impaired systolic function resulting in diminished cardiac output. A new class of inotropes, cardiac myosin activators were developed to directly augment cardiac sarcomere function and improve myocardial activity in HFrEF. The first drug in this class, omecamtiv mecarbil selectively activates cardiac myosin and improves cardiac contractility by increasing the efficiency of the actin-myosin cross-bridge cycle, increasing the duration of systolic ejection without raising myocardial oxygen demand. The first major trial investigating omecamtiv mecarbil use in HFrEF demonstrated a statistically significant decrease in the composite endpoint of the first HF event or death from cardiovascular causes. A post hoc analysis demonstrated that omecamtiv mecarbil produced a statistically significant reduction in the composite endpoint of time to the first HF event or cardiovascular death among patients with severe HFrEF.

Key words: omecamtiv mecarbil, heart failure, guideline-directed medical therapy.

Introduction

Heart failure (HF) is a growing global epidemic resulting in significant morbidity and mortality. Over the years, substantial progress has been made in the development of pharmacotherapies that improve survival in HF. Current approved guideline-directed medical therapy (GDMT) for HF with reduced ejection fraction (HFrEF) includes angiotensin-converting enzyme inhibitors (ACE inhibitors)/angiotensin receptor blockers (ARBs)/angiotensin receptor-neprilysin inhibitors (ARNI), β-blockers, mineralocorticoid-receptor antagonists (MRAs), and sodium-glucose cotransporter-2 (SGLT-2) inhibitors [1].

Understanding the pathophysiology of HFrEF has been critical in helping researchers identify new therapeutic avenues. HFrEF is characterized by decreased systolic function resulting in diminished cardiac output. However, there is currently no therapy approved by the Food and Drug Administration (FDA) to directly stimulate systolic cardiac function, as studies investigating positive inotropes have failed to show any mortality benefits [2].

A new class of inotropes, cardiac myosin activators have been developed to directly augment cardiac sarcomere function and improve myo-

cardial activity [3]. Omecamtiv mecarbil, the first drug in this class, activates cardiac myosin and improves cardiac contractility by increasing the efficiency of the actin-myosin cross-bridge cycle, increasing the duration of systolic ejection, without raising myocardial oxygen demand or intracellular calcium levels [4, 5].

Initial studies investigating the efficacy of omecamtiv mecarbil in HFrEF demonstrated potential benefits, leading to the development of a large clinical trial studying its efficacy and safety in HFrEF. The GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure) trial assessed whether treatment with omecamtiv mecarbil in patients with HFrEF lowered the risk of HF events and cardiovascular death.

This review will discuss all the clinical trials investigating omecamtiv mecarbil use in HFrEF, including GALACTIC-HF, while also detailing the mechanism of action of this drug and how it represents a new target of therapy in HFrEF.

Mechanism of action

To understand the mechanism of action of omecamtiv mecarbil, it is critical to review the cardiac sarcomere physiology. The sarcomere consists of thin and thick interdigitating filaments. Myosin is the core of the thick filament and uses chemical energy from adenosine triphosphate (ATP) hydrolysis to perform the power stroke for muscle contraction. Actin, which forms the backbone of the thin filament in cardiac muscle, has its myosin-binding sites covered by tropomyosin, a regulatory protein. When calcium is released from the sarcoplasmic reticulum into the cytoplasm, it binds to troponin C, causing a conformational change that displaces the tropomyosin and exposes the myosin-binding sites on actin. The myosin heads then bind to the actin thin filaments, pulling them toward the center of the sarcomere during the power stroke, shortening the sarcomere and causing contraction. When calcium is removed from the cytoplasm, the muscle relaxes. At rest, there are low levels of free calcium, preventing the myosin-actin interaction and contraction [6].

Omecamtiv mecarbil is the first cardiac myosin activator that increases cardiac contractility by binding directly to cardiac myosin. In its usual state, when ATP is bound to myosin, the actin-myosin interaction is weak. Once ATP is hydrolyzed to adenosine diphosphate (ADP) and inorganic phosphate, it results in the release of the inorganic phosphate from the myosin. The resulting myosin-ADP complex remains firmly attached to actin in a stable force-generating complex. When ATP binds myosin at the end of the cycle, it causes a conformational change that results in the dissociation of myosin from actin, ending the cycle. This transition is the rate limiting step during the actin-myosin cycle [7].

Omecamtiv mecarbil works by binding to the catalytic S1 domain of cardiac myosin, inducing a conformational change that augments the speed of ATP hydrolysis, which causes the release of the inorganic phosphate and accelerates the transition from a weakly bound to a firmly bound myosin-actin interaction [8]. Omecamtiv mecarbil essentially stabilizes the pre-power stroke conformation of the myosin head, promoting a stronger myosin-actin interaction. It also effectively increases the proportion of myosin heads that are tightly bound to actin and creates a force-producing state that is independent of an increase in intracellular calcium [9]. Omecamtiv mecarbil prolongs total systole duration by augmenting the entry rate of myosin into this force-generating state, increasing the formation of active cross bridges and promoting a stronger cardiac contraction, without increasing the rate of contraction [10].

The distinction between omecamtiv mecarbil and other positive inotropes is that omecamtiv mecarbil does not act on β-adrenergic receptors or alter intracellular calcium levels as many traditional inotropes do. Rather, it improves cardiac contractility by increasing the efficiency of the actin-myosin cross-bridge cycle, without increasing myocardial consumption/demand or heart rate [11].

Omecamtiv mecarbil in clinical trials

The first trial investigating omecamtiv mecarbil use in HFrEF was the ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) trial in 2016. This phase 2, randomized, double-blind, placebo-controlled, dose-escalation trial included 606 patients admitted for acute HF with left ventricular ejection fraction (LVEF) ≤ 40%, dyspnea, and elevated plasma concentrations of natriuretic peptides. Patients were randomized to receive omecamtiv mecarbil in 3 sequential, escalating-dose cohorts or placebo. The primary endpoint was change in dyspnea from baseline to 48 h, measured using a 7-point Likert scale. The results showed no significant improvement in the primary endpoint of dyspnea relief across all cohorts. In supplemental analyses, omecamtiv mecarbil did result in greater dyspnea relief at 48 h and through 5 days in the high-dose cohort (310 ng/ml) compared to placebo. It also resulted in significant plasma-concentration-related increases in the LV systolic ejection time ($p < 0.0001$) and decreases in the end-systolic dimension ($p < 0.05$) [12].

The COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Fail-

ure) trial in 2016 was a phase 2, randomized, placebo-controlled, double-blind trial of 299 patients with stable, symptomatic chronic heart failure and LVEF ≤ 40%. Patients were randomly assigned to receive 25 mg oral omecamtiv mecarbil twice daily, 25 mg twice daily titrated to 50 mg twice daily guided by pharmacokinetics, or placebo. The primary endpoint was the maximum concentration of omecamtiv mecarbil in the plasma, and the secondary endpoints were changes in cardiac function and ventricular diameters. The results showed that the administration of omecamtiv mecarbil for 20 weeks increased the LV systolic ejection time ($p < 0.0001$) and stroke volume ($p = 0.0217$), decreased the LV end-systolic diameter ($p = 0.0027$), and reduced the plasma natriuretic peptide levels ($p = 0.0069$) and heart rate ($p = 0.0070$). This trial led researchers to design a subsequent large clinical trial to further investigate omecamtiv mecarbil's potential efficacy and safety in HFrEF [13].

The GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) trial in 2020 was a phase 3, double-blind, placebo-controlled, multicenter trial designed to assess whether treatment with omecamtiv mecarbil in patients with HFrEF would lower the risk of HF events and cardiovascular events. The study included 8,256 patients (inpatients and outpatients) with symptomatic chronic HF with LVEF ≤ 35%. Patients were currently hospitalized for HF (inpatients) or had either made an urgent visit to the emergency department or been hospitalized for HF within 1 year (outpatients). Patients were randomized to receive omecamtiv mecarbil, using pharmacokinetic-guided doses of 25 mg, 37.5 mg, or 50 mg twice daily, or placebo in addition to standard HF GDMT. The primary outcome was a composite of a first HF event (hospitalization or urgent visit for HF) or death from cardiovascular causes. The results showed a significant difference in the primary outcome event in the omecamtiv mecarbil group (37%) compared to the placebo group (39.1%) (hazard ratio (HR) = 0.92; 95% confidence interval (CI): 0.86 to 0.99, $p = 0.03$). Regarding secondary outcomes, there was no significant difference in death from cardiovascular causes or change from baseline on the Kansas City Cardiomyopathy Questionnaire total symptom score between the groups. There was also no significant difference in the rate of the first hospitalization for HF or death from any cause in the omecamtiv mecarbil group compared to the placebo group. Regarding adverse outcomes, there was no significant difference in the change in systolic blood pressure between baseline and 24 or 48 weeks between the omecamtiv mecarbil group and the placebo group [14]. While the results of this study showed statistical significance for the primary endpoint, there remains a debate among clinicians regarding the clinical significance of these findings.

In a post hoc analysis of the GALACTIC-HF trial, researchers evaluated the efficacy and safety of omecamtiv mecarbil among patients classified as having severe HF compared to patients without severe HF. Severe HF was defined as the presence of all of the following criteria: New York Heart Association (NYHA) class III to IV, LVEF ≤ 30%, and hospitalization for HF within the previous 6 months. A total of 2,258 patients who met the criteria for severe HF were randomized to either the omecamtiv mecarbil or placebo group. Patients with severe HF who received omecamtiv mecarbil experienced a significant treatment benefit for the primary endpoint (HR = 0.80; 95% CI: 0.71–0.90) compared to patients without severe HF, who had no significant treatment benefit (HR = 0.99; 95% CI: 0.91–1.08). The authors concluded from this post hoc analysis that omecamtiv mecarbil may have provided a clinically meaningful reduction in the composite endpoint of time to the first HF event or cardiovascular death among patients with severe HF, potentially supporting a role for omecamtiv mecarbil therapy among patients with severe HF for whom current treatment options are limited [15].

The METEORIC-HF (Multicenter Exercise Tolerance Evaluation of Omecamtiv mecarbil Related to Increased Contractility in Heart Failure) trial in 2022 was a phase 3, randomized, placebo-controlled, double-blind, multicenter study designed to assess whether omecamtiv mecarbil can improve peak exercise capacity in patients with chronic HFrEF. The study included 276 patients with HFrEF (LVEF ≤ 35%), NYHA class II-III symptoms, NT-pro-BNP ≥ 200 pg/ml. Patients were randomized to receive either omecamtiv mecarbil orally twice daily at 25 mg, 37.5 mg, or 50 mg based on target plasma levels versus placebo for 20 weeks. The primary endpoint was a change in exercise capacity from baseline to week 20. The results showed that the use of omecamtiv mecarbil did not significantly improve exercise capacity over 20 weeks compared to placebo. The authors concluded that the study's findings do not support the use of omecamtiv mecarbil for treatment of HFrEF for improvement of exercise capacity [16].

Given the post hoc analysis of the GALACTIC-HF trial, there is a need for a clinical trial to identify whether omecamtiv mecarbil is more efficacious in patients with severe HFrEF compared to those without severe HFrEF. The COMET-HF (Confirmation of Omecamtiv Mecarbil Efficacy Trial in Heart Failure) trial is a multicenter, double-blind, randomized, placebo-controlled study designed as a confirmatory study to further assess the efficacy

and safety of omecamtiv mecarbil in patients with symptomatic HF with severely reduced EF (LVEF < 30%). The primary endpoint is the time to the first event in the composite endpoint of cardiovascular death, first HF events, left ventricular assist device (LVAD) implantation or cardiac transplantation, or stroke. Secondary endpoints will evaluate the risk of individual components, including HF hospitalization, cardiovascular death, and stroke. The study is expected to include approximately 1,800 patients to receive either omecamtiv mecarbil or placebo. The eligibility criteria include symptomatic HFrEF with LVEF < 30%, NT-proBNP ≥ 1,000 pg/ml, and a HF event within the preceding 6 months. The study is expected to conclude in April 2028 [17].

Guidelines for omecamtiv mecarbil use

Omecamtiv mecarbil did not receive the FDA approval for use in HFrEF patients. The FDA concluded that the data from the GALACTIC-HF trial was not sufficient to demonstrate the effectiveness for reducing the risk of HF events and cardiovascular death in adults with HFrEF. The FDA is requiring an additional study of omecamtiv mecarbil in HFrEF patients to determine whether the FDA approval is appropriate. The COMET-HF trial will likely serve this role, as it seeks to identify the potential efficacy of omecamtiv mecarbil in severe HFrEF [18].

Brief discussion regarding cardiac myosin inhibitors

Cardiac myosin has been targeted in recent research investigating treatment options for various cardiovascular diseases. While omecamtiv mecarbil was developed as a cardiac myosin activator, another avenue of therapy targets the inhibition of cardiac myosin. Mavacamten, a selective cardiac myosin inhibitor, was approved by the FDA in 2022 for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (HCM). This medication inhibits excessive myosin-actin cross-bridge formation, reducing hypercontractility of the cardiac muscle [19]. Another similar cardiac myosin inhibitor, aficamten, is currently being investigated in clinical trials for the treatment of obstructive HCM, as it has faster onset/offset kinetics compared to mavacamten, allowing for more flexible dosing and titration [20].

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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