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Review Article

A Short Review of New Drugs for Heart Failure: Omecamtiv Mecarbil and Vericiguat

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Abstract

Heart failure is associated with increased morbidity and mortality. Although developments of therapeutic agents have shown benefit and have improved the patients' condition, there is only a slight decreased of mortality rate throughout the years. This condition becomes a reason to develop efficient drugs which can further improve the condition and reducing the mortality significantly. New therapeutic agents have been proposed and studied. Among them is cardiac myosin activator, such as omecamtiv mecarbil. This drug will increase the binding of myosin head to the actin and therefore form a stronger contraction. Omecamtiv mecarbil is beneficial due to its mechanism which not related to higher oxygen consumption and less adverse events. Another promising drug is vericiguat, a soluble guanylate cyclase (sGC) stimulator. This drug enhances the binding of nitric oxide to sGC and therefore increasing cyclic guanosine monophosphate (cGMP) production. cGMP important in regulating physiological processed in the cardiovascular system. In this review, we will discuss about the current evidence about these novel agents.

Keywords: *heart failure, novel agent, omecamtiv mecarbil, vericiguat, management*

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INTRODUCTION

Heart failure (HF) is still a global health burden and causes high morbidity and mortality rates. The incidence increases each year [1]. Efforts on improving quality of life of the patients with HF had been done throughout the years, including studies on drugs for HF. There have been several drugs that are used as standard therapy such as angiotensin-converting-enzyme inhibitors (ACEI), angiotensin-II receptor blockers (ARB), beta blockers, and mineralocorticoid receptor antagonist (MRA). These drugs have shown beneficial effect for HF patients [2]. However, despite these efforts, the mortality rates only decreased slightly and even the 5-year mortality rate did not show any decreased for the last 10 years [3]. Novel agents such as angiotensin receptor-neprilysin inhibitor (ARNI) and sodium glucose co-transporter 2 inhibitors (SGLT2i) have been suggested as the treatment for HF, but the utilisation remains low [4]. Despite this current development of HF treatment, it is necessary to study another novel agent that could be beneficial in HF treatment. Novel agents should not just able to improve clinical status and quality of life, but also reducing adverse events incidence that might happen. This review aims to present new evidence of novel HF agent, omecamtiv mecarbil and vericiguat.

CARDIAC MYOSIN ACTIVATOR: OMECAMTIV MECARBIL

Contractility is an important factor related to HF progression. There have been several drugs used to improve cardiac contractility. Inotropes such as adrenergic receptor agonist (i.e., dobutamine) and phosphodiesterase inhibitors (i.e., levosimendan) are able to improve the contractility via cyclic adenosine monophosphate and intracellular calcium-handling mechanisms [5]. Despite the benefit, these drugs are associated with several limitations. Higher oxygen demand, increased heart rate, arrhythmia, hypotension, and risk of myocardial ischemia are related to the use of inotropic agents [6].

Further research has shown a newer agent called cardiac myosin activators. This drug works by augmenting cardiac sarcomere function. Sarcomere is the core unit of cardiac contractility. It is a structure consists of thin and thick filaments. Myosin is a part of sarcomere, being the core of thick filament. Myosin uses energy that is generated from hydrolysis of adenosine triphosphate (ATP) to generate a contraction. Myosin also acts on thin filaments, consist of actin and troponin-tropomyosin [7]. Omecamtiv mecarbil is the first cardiac myosin activator. Omecamtiv mecarbil is known firstly as CK-1827452, a selective cardiac myosin activator that binds

the catalytic S1 domain of cardiac myosin without effect to the other types of myosin. This drug works by augmenting the process of ATP hydrolysis to adenosine diphosphate (ADP) and inorganic phosphate (Pi). Due to this augmentation, there will be acceleration in Pi being released from the myosin. This will promote a transition from weak bound to a stronger bound force-generating state. Furthermore, this will result in increased myosin heads bound to the actin and form a more active cardiomyocyte cross-bridge, therefore enhance a stronger contraction [8,9]. In a normal state, only 10-30% of cardiac myosin heads interact with actin filaments [10]. Unlike other currently available inotropes, omecamtiv mecarbil is not related to increased intracellular cAMP and calcium, so it would not increase oxygen consumption and reducing the risk of cardiac arrhythmia (7). An in vitro study shows that omecamtiv mecarbil inhibit non-actin-dependent cardiac myosin ATPase. This will result in decreasing oxygen consumption [8].

STUDIES ON OMECAMTIV MECARBIL

Omecamtiv mecarbil has been investigated in several studies. The first study in human was conducted by Teerlink et al. in 2011 in 34 men [11]. This study focused on finding the tolerated dose, pharmacokinetic, pharmacodynamics, safety, and tolerability of the drug. This study found the maximum tolerated dose of omecamtiv mecarbil was 0.5 mg/kg/hour. This study also showed highly dose-dependent augmentation of left ventricular systolic function in response to omecamtiv mecarbil. Greenberg et al. studies the safety and tolerability of omecamtiv mecarbil during exercise [12]. The population of this study was HF patients with ischaemic cardiomyopathy and angina. In this study, patients would do exercise treadmill test (ETT). Patients were randomized to placebo group and omecamtiv mecarbil group. Patients who received omecamtiv mecarbil were also divided to group 1 receiving 24 mg/h for 2 hours plus 6 mg/h for 18 hours and group 2 receiving 48 mg/h for 2 hours plus 11 mg/h for 18 hours. The treadmill tests were done three times (ETT1 & ETT2 at baseline and ETT3 before the end of 20-hour omecamtiv mecarbil infusion). The endpoint was the proportion of patients needed to stop ETT3 due to angina at earlier stage than baseline. There were no patients who needed to stop ETT3 in omecamtiv mecarbil group, unlike in the placebo group.

The role of omecamtiv mecarbil was studies in patients with acute heart failure in ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) trial. Patients were observed to evaluate the pharmacokinetic, pharmacodynamic, tolerability, safety, and efficacy of omecamtiv mecarbil in acute HF patients. Patients were randomized to receive omecamtiv mecarbil infusion (in 3 sequential, escalating-dose cohorts) or placebo. The primary endpoint was dyspnea improvement. The result of this study showed that omecamtiv mecarbil administration did not improve the primary endpoint (placebo: 41%, cohort 1: 42%, cohort 2: 47%, cohort 3: 51%; p= 0.33). However, high dose omecamtiv mecarbil may improve dyspnea compared to placebo at 48h and 5 days. It was also well tolerated, the adverse events and tolerability were similar to placebo group [13].

Another large trial, the Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF) trial, was conducted to assess the pharmacokinetics and effects of omecamtiv mecarbil on cardiac function. COSMIC-HF trial was a randomized, double-blind, phase II study. Patients aged 18-85 years with chronic HF (New York Heart Association class II or III) who were stable and treated with optimum pharmacological therapy for at least 4 weeks were included. Patients were randomized to receive fixed-dose omecamtiv mecarbil (25 mg, twice daily), pharmacokinetic – titration group (25 mg omecamtiv mecarbil twice daily titrated up to 50 mg twice daily), or placebo for 20 weeks. This study showed that omecamtiv mecarbil improves systolic ejection time (SET) and stroke volume compared to placebo. Left ventricular end systolic & end diastolic diameters and heart rate were reduced in pharmacokinetic-titration group, unlike in the fixed-dose group [14]. Adverse events were comparable between groups.

The latest trial on omecamtiv mecarbil has been published. GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) trial. 8000 patients with HF reduced ejection fraction (HFrEF) were recruited in this study, the most among other two trials. The purpose of this trial was to determine the effect of omecamtiv mecarbil on cardiovascular outcomes. The primary endpoint was a composite of first heart failure event or death from cardiovascular causes. The secondary endpoints were cardiovascular death, alteration of total symptoms score (Kansas City Cardiomyopathy Questionnaire; KSSQ), first HF hospitalization, and death from any cause. Patients were randomized to receive oral omecamtiv mecarbil or placebo. Patients received omecamtiv mecarbil with the dosage of 25 mg, 37.5 mg, or 50 mg twice daily on the basis of the drug plasma level. The median follow-up duration was 21.8 months. Primary outcome occurred in 1523 of 4120 (37%) patients who received omecamtiv mecarbil, whereas 1602 of 4112 (39.1%) in the placebo group (hazard ratio, 0.92; 95% confidence interval, 0.86 – 0.99; p=0.03). There was no significant difference in cardiovascular death events, 808 patients (19.6%) and 798 (19.4%) respectively. There was also no significant difference in the change of KCCQ total symptom score between groups. For the safety outcomes, the incidence of ischemia and arrhythmia was similar in the two groups [15].

These findings from several trials showed the benefit of omecamtiv mecarbil on improving cardiac function by targeting the cardiac sarcomere. These findings became a new light in HF treatment because of increased incidence of myocardial ischemia, arrhythmia, or death from the drugs that has been developed before. In several trials, there were found an increase level of troponin in plasma [13-15]. However, treatment with omecamtiv mecarbil does not increase the risk of adverse events.

SOLUBLE GUANYLATE CYCLASE: VERICIGUAT

One of several mechanism associated with progression of heart failure is the cyclic guanosine monophosphate (cGMP) pathway. cGMP is an intracellular messenger generated by the binding of guanylyl cyclase to either nitric oxide (NO) or natriuretic peptide (NP) [16,17]. The signal is generated by binding and activating protein kinase G. Furthermore, interactions with other phosphodiesterase will regulate the companion second messenger cyclic adenosine monophosphate. This will contribute in antifibrotic and antihypertrophic signalling, reducing vascular tone and increases quality control of the protein [18,19]. Disruptions in this pathway have been studied in several heart diseases. In heart failure, there will be an increased inflammation and vascular dysfunction, lowering NO bioavailability [20]. NO has a role in activating soluble guanylate cyclase (sGC). sGC in physiological condition will trigger the production of cGMP [21]. Lower NO bioavailability will decrease cGMP synthesis. Disruption in this pathway has been linked to worse outcomes in patients with HFrEF and HF with preserved ejection fraction (HFpEF) [22,23].

Derangements in cGMP signalling led to development of new agent that can augment this pathway in patients with HF. There are expressions of phosphodiesterase (PDE) which

transform cGMP to GMP in heart [24]. PDE-3 inhibitor (e.g., enoximone and milrinone) and PDE-5 inhibitors (e.g., sildenafil) are several drugs that benefit the cGMP signalling by decreasing the degradation of cGMP to GMP and promote good haemodynamic effects. However, these drugs haven't been proven to improve the clinical outcome [25,26].

A novel agent has been studied with mechanism to improve cGMP pathway. Vericiguat is a novel drug that works by stimulating sGC through a binding site that is independent of NO (figure 1). Vericiguat will augment the sensitivity of the enzyme and therefore increasing the formation of cGMP. This effect of vericiguat is also a result of stabilizing NO binding to the binding site [27]. This ability of vericiguat to augment cGMP pathway will benefit cardiovascular system including systemic and pulmonary vasodilation, promote decongestion, and elevate the coronary blood flow. Vericiguat also has the ability to reduce hypertrophy, remodelling, fibrosis, and platelet activation [28].

STUDIES ON VERICIGUAT

The Soluble Guanylate Cyclase Stimulators in Heart Failure with Reduced Ejection Fraction Study (SOCRATES-REDUCED) was a phase II, dose-finding, placebo-controlled randomised clinical trial with objective to determine the role of vericiguat on natriuretic peptide and tolerability of the treatment. This clinical trial included patients with worsening HFrEF with ejection fraction less than 45%. Worsening condition was defined as worsening HF symptoms which caused hospitalization or outpatient administration of intravenous diuretics, congestion symptoms, and increased NP levels. Patients who were included in this study were randomized to five groups (four groups of vericiguat and one group of placebo). Four groups of vericiguat were divided to receive a targeted maximal dose of 1.25 mg, 2.5 mg, 5 mg, and 10 mg. Vericiguat was administered for 12 weeks and followed by follow-up for 16 weeks. Primary outcome was alteration of log-transformed N-terminal pro-B natriuretic peptide (NT-proBNP) levels from baseline to week 12. The result of this trial showed there was no significant difference ($p = 0.15$) of NT-proBNP levels from baseline to week 12 between the pooled vericiguat group (log-transformed → difference = −0.402) and placebo (log-transformed → difference = −0.280). However, higher dose of vericiguat was associated with reduction of NT-proBNP levels. Patients who received 10 mg of vericiguat showed greater reductions in NT-proBNP levels compared to the placebo group and improvement in LVEF. Further secondary analyses of the primary outcome using linear regression model showed a dose-response relationship. For the safety measures, incidence of adverse events was comparable between groups [29]. This study had shown that vericiguat is a potential agent to improve clinical condition of patients with HFrEF without causing alteration in vital signs.

The recent VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial, furthermore, evaluated the efficacy and safety of vericiguat. In this randomized, double-blind, placebo-controlled trial, patients with chronic HF and LVEF < 45% with worsening symptoms and requiring hospitalization for the last 6 months were included. Patients were randomized to receive 2.5 mg vericiguat or placebo. The doses of vericiguat were then increased to 5 mg and 10 mg. The primary endpoint was a composite of death from cardiovascular etiologies or first hospitalization due to HF. Patients in the vericiguat group received a median dose of 9.2 mg and the median follow-up in this study was 10.8 months. In this trial, patients who received vericiguat had a lower incidence of primary endpoint compared to placebo (35.5% vs 38.5%, respectively; hazard ratio, 0.90; 95% confidence interval [CI], 0.82 to 0.98; P=0.02). The secondary outcomes of death from any cause or first hospitalization for HF; and total hospitalization for HF were also significantly lower in the vericiguat group. Adverse events of symptomatic hypotension and syncope did not differ significantly between groups [30]. In this trial, vericiguat showed a favourable outcome which occurred around 3 months post treatment. These results have showed than vericiguat as a sGC stimulator become a game-changer in augmenting cGMP pathway, due its ability of selectively stimulating the binding of sGC and NO which is not found in other agent such as PDE inhibitors.

CONCLUSION

Heart failure is still a challenge even after massive development of treatment modalities in this field. Current HF treatment agents still face challenges in improving clinical condition and also quality of life of the patient. Novel agents such as omecamtiv mecarbil and vericiguat shed a new light in HF treatment. Both these agents can work selectively in their own pathway and could reduce the incidence of adverse events.

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