Myosin Activators

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Abstract

Inotropes historically all increased intra-cellular calcium levels and they commonly caused intracellular Ca2+ overload and triggered malignant arrhythmias. The myosin activators, such as Omecamtiv Mecarbil (OM), increase myosin activity and function, and modify acto-myosin interaction through calcium-independent mechanisms. OM is a selective cardiac myosin activator that binds specifically the catalytic domain of cardiac myosin without any significant effect over other types of non-cardiac myosin. It increases the speed of ATP hydrolysis and, therefore, accelerates the transition rate to a strongly bound force-producing state, increases the number of myosin heads that interact with actin filaments and increases the proportion of time they are in a force producing state. OM decreases the inefficient use of non-contractile energy. OM has been studied in 4 phase II clinical trials with more than 1,300 patients with heart failure. The GALACTIC-HF trial is a nearly 8,000 patient HFrEF mortality/morbidity trial which started recruiting in January 2017 and should be completed soon.

Keywords: heart failure; myosin activators; omecamtiv mecarbil

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Introduction

The term inotropes is used to describe all pharmacological agents that directly improve the contractile function of the heart.[1-3] Therefore, agents that alter cardiac performance by modifying the cardiac calcium ion (Ca^{2+}) balance and its flux into the cardiac myocyte are included under this definition.[4] These agents increase left ventricular systolic pressure generation per unit time (dP/dt) and thereby improve cardiac output and stroke volume. Some of these agents may also affect vascular tone and this effect may further improve their cardiac effects.

When used chronically these drugs have a detrimental effect on myocardial energetics and decrease the adenosine triphosphate (ATP) to adenosine diphosphate (ADP) ratio. This, in turn, reduces the re-uptake of Ca^{2+} from the sarcoplasmic reticulum, causes intracellular Ca^{2+} overload and triggers malignant arrhythmias. [4} However, newer agents that improve myocardial performance and contraction by novel means have been developed. These agents may improve myocardial energetics and function through mechanisms of action that are distinct from conventional Ca^{2+}-acting medications.

Inotropic agents improve ventricular systolic performance by affecting the myocardial contractile apparatus. The three main components of this apparatus are the Ca^{2+} cycling elements responsible for the flow and uptake of myocardial Ca^{2+} and the contractile components. Myosin is the active enzyme of the myocardial sarcomere and converts the energy stored as high energy phosphates into contractile force. Myosin is constituted of head, neck and tail domains. The head domain binds the actin and moves along it, the neck binds the light chains while the tail regulates motor activity by interacting with cargo molecules and other myosin sub-units. Molecules of myosin aggregate to form thick filaments that are the core of the muscle contractile unit. They are inter-digitated with the thin filaments of actin on which they pull to mediate contraction.[5,6] Troponin and tropomyosin enable the intracellular Ca^{2+} status and other factors to regulate the myosin-actin interaction.

Myosin activators

Myosin has more recently become an attractive therapeutic target as it elicits myocardial contraction and is involved in the ATP hydrolysis outside of the myosin mechanochemical cycle. Newer therapeutic agents have been developed aimed at increasing myosin activity and function. Myosin activators are compounds that modify acto-myosin interaction through calcium-independent mechanisms. The first in class myosin activator omecamtiv mecarbil, that is currently completing its clinical development, is a small molecule that binds directly to the enzymatic domain of cardiac myosin and directly activates it in a calcium-independent manner by modulating its activity. [7] Omecamtiv mecarbil is a selective cardiac myosin activator that binds specifically the catalytic domain of cardiac myosin without any significant effect over other types of non-cardiac

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myosin. The omecamtiv mecarbil binding site is the amino acid serine 148, which is about 6.5 ηm from the actin-binding interface. The conformational changes induced by omecamtiv mercabil increase the speed of ATP hydrolysis and, therefore, accelerate the transition rate to a strongly bound force-producing state. Omecamtiv mecarbil increases the number of myosin heads that interact, in the force producing activity, with actin filaments during depolarization (see figure 1). This compound increases the proportion of time the myosin head is tightly bound to actin in a force producing state. Binding to myosin it decreases the inefficient use of non-contractile energy.[7] Omecamtiv mecarbil does not increase the rate of force generation (dP/dt) but increases the total amount of time spent in a contraction state.

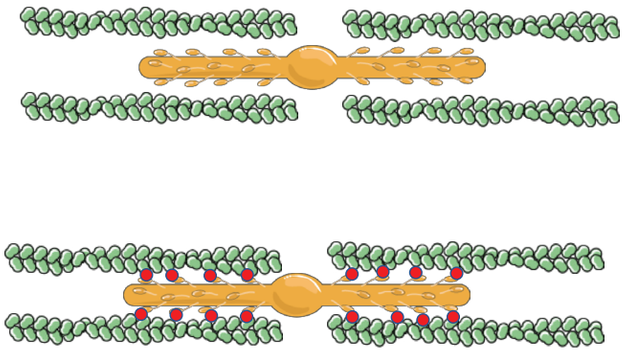

Figure 1. Omecamtiv mecarbil activates cardiac myosin and increases the ATP hydrolysis and accelerates the formation of a strong actin-myosin complex, linked to increased contractile force

Omecamtiv mecarbil

Omecamtiv mecarbil lengthens the total duration of systole by increasing the entry rate of myosin into a force-generating state. This effect entails more active cross-bridge formation and a consequently stronger cardiac contraction. Omecamtiv mecarbil infusion (bolus and 24-hour) induced a reduction of heart rate, vascular peripheral resistance and mean left atrial pressure, and left ventricular end diastolic pressure in two canine models of heart failure. These effects were associated with systolic wall thickening, and improvements in stroke volume (SV) and cardiac output (CO). Omecamtiv mecarbil increased systolic ejection time (SET) and cardiac myocyte fractional shortening without increasing left ventricular dP/dtmax, myocardial oxygen consumption nor myocyte intracellular calcium.

Omecamtiv mecarbil has been studied in nine phase I clinical trials including over 200 healthy volunteers and four phase II clinical trials with more than 1,300 patients with heart failure. The first-in-man phase I study in 34 healthy men aimed to establish the maximum tolerated dose and plasma concentrations after i.v. infusions of omecamtiv mecarbil (0.005–1 mg/kg/h).[8] This study reported a dose-dependent improvement of cardiac systolic function parameters including left ventricular fractional shortening (LVFS 8±1%), left ventricular ejection fraction (LVEF, 7±1%), systolic ejection time (SET, 85±5 ms), stroke volume (SV, 15±2 mL). These effects were not associated with any increase in heart rate. The study also found that the maximum tolerated dose was 0.5 mg/kg/h and that doses of 0.75 mg/kg/h or higher were associated with troponin elevation.

Cleland et al. assessed the effects of omecamtiv mecarbil on cardiac function in a double-blind, placebo-controlled, dose-ranging phase II study including 45 patients with heart failure with reduced ejection fraction (HFrEF).[9] Patients were divided into 5 cohorts of 8 to 10 patients and allocated to receive omecamtiv mecarbil infusion in escalating doses. Omecamtiv mecarbil plasma concentrations showed a significant direct relation with the change in SET and SV. Reductions in LV end-systolic volume and LV end-diastolic volume (LVEDV) were observed with higher plasma concentrations (>500 ηg/mL). Myocardial ischaemia was induced at very high concentrations (1750 and 1350 ηg/mL) in two patients.

Given the suggestion of a possible precipitation of myocardial ischaemia at very high doses, the safety and tolerability of omecamtiv mecarbil during exercise was studied in 94 heart failure patients with ischaemic cardiomyopathy. All patients had angina and entered a double-blind, randomised, placebo-controlled trial.[10] Patients were randomised to receive omecamtiv mecarbil or placebo at escalating doses previously shown to improve systolic function. The study included 2 exercise treadmill tests at baseline and one before the end of the 20-hour omecamtiv mecarbil infusion. Omecamtiv mecarbil was dosed to target different plasma levels in the two cohort studied (~295 ηg/mL and ~550 ηg/mL). Patients who tolerated IV infusion continued with oral omecamtiv mecarbil or placebo for 7 days. No patients receiving omecamtiv mercabil and one patient in the placebo arm developed limiting angina during the exercise test. The results of this study showed that in heart failure patients with ischaemic cardiomyopathy and angina omecamtiv mecarbil is well tolerated and there is no evidence that it may induce myocardial ischaemia.

ATOMIC-AHF trial.

The ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure)[12] was a phase IIb double-blind, randomised, placebo-controlled sequential cohort study aimed at investigating the pharmacokinetics/pharmacodynamics, safety, and efficacy of omecamtiv mecarbil infusion in hospitalised patients with acute heart failure. The primary end-point of the study was improvement in dyspnoea assessed using the Likert scale. The study included 606 patients who were treated in three sequential cohorts with a 48-hour omecamtiv mecarbil infusion in escalating dose regimens targeting a mean plasma concentration of 115, 230 and 310 ηg/mL.

The response rates of dyspnoea relief throughout the 48 hours did not differ between placebo groups and the three treatment cohorts (p=0.316). A greater relief of dyspnoea was noted in the high-dose omecamtiv mecarbil cohort compared with placebo. Although more patients receiving omecamtiv mecarbil had elevated troponins compared to placebo, no clear relationship to omecamtiv mecarbil concentrations was found. The echocardiographic sub-study patients receiving omecamtiv mecarbil were found to have a significantly greater reduction in LVESD ($p<0.05$) and a significantly greater plasma concentration-dependent increase in SET ($p<0.0001$).

A similar occurrence of serious adverse events was observed in the placebo and omecamtiv mecarbil groups at 30 days [placebo n=70 (23%), omecamtiv mecarbil n=66 (22%)]. All-cause and heart failure rehospitalisation as well as occurrence of cardiovascular deaths were similar between placebo and omecamtiv mecarbil groups. This study, therefore showed that i.v. omecamtiv mecarbil did not improve dyspnoea, although an improvement in the high-dose group was observed. However, omecamtiv mercabil increased SET, decreased LVESD and was well tolerated, thereby supporting its further investigation in a phase III mortality/morbidity study.

COSMIC-HF trial

The Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF trial) was a phase II, randomised, parallel-group, double-blind, placebo-controlled study conducted in 448 patients with chronic HFrEF with LVEF less than or equal to 40%.[12] The primary end-point was based on pharmacokinetics and was to dose titrate omecamtiv mecarbil to a targeted plasma concentration range for the duration of the study.

The study included patients with NYHA class II or III chronic heart failure who had received an optimal heart failure treatment for at least 4 weeks. The 448 patients were randomised 1:1:1 to receive oral placebo or omecamtiv mecarbil in either a fixed-dose (25 mg twice daily) or with pharmacokinetic [PK]-titration (25 mg with up-titration to 50 mg b.d., according to omecamtiv mecarbil plasma concentration).

A significant improvement compared to placebo was observed with omecamtiv mecarbil in SET (fixed-dose group: +11 ms, p=0.007; PK-titration group: +25 ms, p<0.001) and SV (fixed-dose group: +5 mL, p=0.0036; PK-titration group: + 4 mL, p=0.0217). The PK-titration group showed significantly reduced LVESD (–1.8 mm, p=0.0027) and LVEDD (–1.3 mm, p=0.0128) and heart rate (–3 beats per minute, p=0.0070). Similarly, a reduction in LVESV, LVEDV and an improvement in LVFS were found in the omecamtiv mercabil groups. LVEF was significantly improved in the fixed-dose group (p=0.025) but only reached a positive trend towards improvement in the PK-titration group (p=0.063). Plasma concentrations of NT-proBNP were reduced in both omecamtiv mecarbil groups at 20 weeks and this effect persisted after discontinuation of omecamtiv mecarbil. Adverse events and rates of deaths were comparable between omecamtiv mecarbil and placebo. Cardiac and noncardiac adverse events were also similar between the placebo and the two treatment groups. Cardiac troponin levels at week 20 increased in the omecamtiv mercabil groups compared with placebo (0.001 ηg/mL in the fixed-dose and by 0.006 ηg/mL in the PK-titration group). Therefore, the results of COSMIC-HF confirmed the improvement in cardiac function and the reduction of ventricular dimensions with omecamtiv mercabil compared to placebo.

GALACTIC-HF

The Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure is a phase III, double-blind, randomised, placebo-controlled multicentre clinical trial conceived to compare omecamtiv mecarbil with placebo added to guideline-recommended heart failure treatment in nearly 8000 patients with chronic HFrEF. The primary endpoint of the study is the composite end-point of time-to-cardiovascular death or first heart-failure event, whichever occurs first. Secondary endpoints include time to first heart-failure hospitalization, time to all-cause death and measurement of patient-reported quality of life measured with the Kansas City Cardiomyopathy Questionnaire, KCCQ.

The study started its recruitment in January 2017 and should be completed by early 2021.[13] Included in the study will be those with LVEF ≤35%, NYHA II–IV, and elevated BNP or NT-proBNP levels. Patients will be randomised to placebo or oral omecamtiv mecarbil at a starting dose of 25 mg twice daily followed by a PK-guided dose optimisation up to one of three target doses (25, 37.5 or 50 mg twice daily). It is an event-driven study.

Conclusions

Omecamtiv mecarbil is a cardiac myosin activator that increases the speed of ATP hydrolysis, and accelerates the production of a strong actin-myosin complex leading to increased contractile force production. Animal and human studies have shown that it causes dose-dependent increases in SET, SV, ejection fraction and fractional shortening. The GALACTIC-HF is currently investigating the prognostic effect of omecamtiv mecarbil compared to placebo when added to guideline-recommended heart failure treatment in patients with chronic heart failure and reduced ejection fraction and it is expected to be completed in by early 2021.

Declarations of interest

The authors declare no conflict of interest.

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The authors state that they abide by the authors' responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal.[14]

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