New saviour for an old problem: Omecamtiv mecarbil for systolic heart failure

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Title: Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure

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Summary

In the GALACTIC-HF trial, Teerlink and coauthors compared the selective cardiac myosin activator omecamtiv mecarbil (OM) in heart failure patients with reduced ejection fraction (HFrEF).[1] Omecamtiv activates the sarcomere proteins directly, resulting in an increased cardiac contractility and a prolonged systolic ejection time.[2] Presently, drugs such as ACE inhibitors, angiotensin receptor blockers (ARBs), beta blockers (BBs), angiotensin receptor neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonist (MRA), and sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors are approved for HFrEF. For symptomatic relief, diuretics and digoxin are used. Cardiac resynchronisation treatment and cardiac transplantation are nonpharmacological approaches approved for patients resistant to drug therapy. Omecamtiv is a new drug approved as a fast track by the United States Food and Drug Administration (USFDA) in May 2020.[3] Being an orally active drug and acting directly on the cardiac myocytes, OM shows promising results for HFrEF patients.

The GALACTIC-HF is a randomised placebo controlled double blind two-arm trial conducted in Europe, Russia, Western Europe, South Africa, Australia, Latin America, USA, Canada, and Asia. Patients were recruited in a 1:1 ratio of OM versus placebo using stratification of inpatient versus outpatient setting and geographic region. The test group received either 25mg, 37.5mg or 50mg of OM as decided based on plasma drug levels which were blinded for patients and investigators. Both drugs (OM or placebo) were suspended temporarily if patients presented any symptoms of acute myocardial infarction (MI) or ischemia. Both groups were assessed at intervals of 2, 4, 6, 8, 12, 24, 36 and 48 weeks and further follow-up once every 16 weeks for a total duration of 208 weeks.

The primary endpoints were either a composite onset of new heart failure or cardiovascular (CV) related death. The secondary outcomes were CV death, decrease in Kansas City Cardiomyopathy Questionnaire (KCCQ) score, first heart failure hospitalisation, and death due to any cause. A total of 8,256 patients were randomised into two groups among whom 24 were excluded due to good clinical practice guidelines violations and the remaining 8,232 (4,120 in OM group versus 4,112 in placebo group) were included in the analyses. The study subjects enrolled were between 18-85 years old, with NHYA functional class II, III or IV symptoms with an ejection fraction of less than 35%. The enrolled subjects were followed up for a median (IQR) duration of 21.8 (15.4–28.6) months.

The primary end point of a first heart failure or CV death occurred in 37% patients (1,523 out of 4,120) in the OM arm and 39.1% (1,607 out of 4,112) patients in the placebo arm (hazard ratio 0.92; 95%CI, 0.86 to 0.99; p=0.03). Secondary outcome of CV death occurred in 19.6% (n=808) in the OM arm and 19.4% (n=798) in the placebo arm (hazard ratio 1.01; 95%CI, 0.92 to 1.11; p=0.86). First hospitalisation was noted in 27% (n=1,142) in the OM arm versus 28.7% (n=1,179) in the placebo arm. The N-terminal pro b-type natriuretic peptide (NT-proBNP) levels at 24 weeks was 10% less (95% CI, 6 to 14) in the OM group compared with the placebo group.

In the OM arm, the drug was discontinued in 20.6% (n= 847) patients, and 21.9% (n= 897) patients in the placebo arm. There was no difference in the potassium, creatinine levels or ventricular arrhythmic events. Major cardiac events occurred in 4.9% (n=200) of patients in the OM arm versus 4.6% (n=188) in the placebo arm.

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The GALACTIC-HF trial showed HFrEF patients who received OM had a lower composite heart failure events and CV death in comparison with the placebo arm. The major limitation of the trial was the exclusion of patients aged over 85 years, and clinically unstable patients. In addition, racial and gender differences were not well executed.

Opinion

Globally, HFrEF is a major health concern, with an estimated 23 million people affected worldwide.[4] Nearly half of the heart failure (HF) patients die in five years and hence there is an urgent need for therapies to evolve with more focus on the addition of new drugs with better outcomes. Studies on inotropes in HF reported worsening of HF progression, arrythmias and survival. The search is on for an agent without these effects and OM is expected to offer these benefits. The major pathophysiology in HFrEF lies in reduced cardiac contractility and hence activating cardiac myosin can be a potential treatment approach for those affected patients. Crystalline studies revealed OM to bind to the catalytic domain of myosin and increase cardiac contractility without affecting cardiac myocyte intracellular calcium concentrations (not a calcitropic drug) or myocardial oxygen consumption.[5] Inotrope use is currently restricted to decompensated HF and there is no place in the guideline directed medical therapy (GDMT) for use in HF. Inotropes in current usage act by: increasing the calcium influx during phase 2 of action potential (e.g. digoxin); increasing calcium release by sarcoplasmic reticulum (e.g. dobutamine); and increasing the sensitivity of troponin C to calcium (e.g. levosimendan). Omecamtiv on the contrary activates actin-myosin cross bridging without affecting intracellular calcium concentration or myocardial oxygen consumption while maintaining potassium homeostasis.

Digoxin, the only currently available oral inotrope, does not reduce the mortality associated with HF, it only minimises the hospitalisation rate (both overall and for worsening heart failure).[6] Nevertheless, it is still used for symptomatic relief even considering the risks associated with its narrow therapeutic index, multiple drug interactions (DIs) and adverse drug reactions (ADRs).

The potential advantages of OM are: a cardiac remodelling effect seen in ventricular volume; and the lack of significant hemodynamic effects, benefiting the patients with low blood pressure (BP) and tachycardia. This is of tremendous clinical importance as it might be the only drug tolerated, other than diuretics and spironolactone, in the subgroup with low BP with low ejection fracture (EF) of less than 28%. In the GALACTIC-HF trial, only two thirds of participants were on Renin-Angiotensin-Aldosterone System (RAAS) inhibition, BB and ARNI as a triple therapy, which has: a wide therapeutic range; no effect on potassium homeostasis, and hence less proarrhythmic effect, unlike other inotropes; and the lack of potential to worsen ischemia in ischemic cardiomyopathy. There is no increase in oxygen consumption, and ischemia can occur only with high doses;[7] it has beneficial effect on right ventricular (RV) contractility, as shown in the Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF) trial,[8] demonstrating reduction in RV systolic volumes and improvement in the RV outflow tract (RVOT) ventricular tachycardia and decrease in pulmonary artery systolic pressure; the GALACTIC-HF trial gives data for use in both inpatient and outpatient settings; OM can be given by IV in decompensated HF patients and smoothly transitioned to oral use;[9] the target dose can be easily achieved as there is no effect on BP, heart rate, renal functions and potassium levels; and it is safe up to an estimated glomerular filtration rate (eGFR) of up to 20 ml/min, unlike RAAS inhibition or MRA.

In the GALACTIC-HF trial, OM was studied in oral administration and in both hospital and ambulatory settings, offering an edge over the existing drugs for HFrEF. Omecamtiv in Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure (ATOMIC-AHF) study in acute heart failure showed efficacy in terms of dyspnea improvement in higher IV doses.[9] Omecamtiv, as shown in the GALACTIC-HF trial, can be considered for patients with HF who are generally on multiple medications and vulnerable to DI leading to dyskalemia. It also provides an option for combining with other medications for HFrEF such as ACEIs, ARBs, BBs, ARNI and SGLT 2 inhibitors.

Since OM decreases NT-proBNP (a marker for heart failure) levels in chronic HF patients,[10] it can be a useful alternative to digoxin and other available options for symptomatic treatment. In addition, digoxin, due to its narrow TI, high volume of distribution, unpredictable kinetics with huge interindividual variation,[10] offers pharmacokinetic challenges. Digoxin is primarily excreted in urine which is closely correlated with glomerular filtration rate,[11] a physiological phenomenon largely compromised in patients with HFrEF, giving rise to further worsening of its already unpredictable plasma levels. All these findings suggest OM to be a valuable drug for symptom control and better CV outcome in HFrEF.

The GALACTIC-HF trial was limited by an under-representation of non-white racial groups (7% blacks) and women (21%). Also, this study predated use of SGLT2 inhibitors in heart failure.[12] Since the mechanism of action of SGLT2 inhibitors is entirely different from OM, a complimentary beneficial effect of both drugs is possible. In patients with very low EF (28% or less) the drug is found to be beneficial since they present with hypotension. Overall, this drug can be a potential choice for patients with HF in addition to currently available standard treatment options. Presently it is the first and only major study published with an exciting finding, and more long-term safety studies are needed to validate the findings. In future, the ongoing METEORIC-HF trial[13] will provide data on the effect of OM on exercise capacity in HFrEF using cardiopulmonary exercise testing which is the most acceptable objective measure of exercise tolerance.

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