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EDITORIAL

New heart failure pharmacotherapy in clinical trials: *a hope in progress*

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1. Introduction

Heart failure (HF) is one of the leading causes of mortality and health-care expenditure, with 5.7 million patients currently carrying this diagnosis, and 900,000 new cases diagnosed every year. It is projected that the number of HF patients in the United States will exceed 8 million by the year 2030 [1]. The search for pharmacotherapeutic agents to treat systolic HF in the late twentieth century and the early years of the twenty-first century has been remarkably successful; it has led to the development of many agents that changed our way of managing HF and offers significant survival and quality-of-life benefits to this patient population. Nevertheless, the majority of the agents that were introduced to clinical trials in the last 15 years have failed to show any added benefits to the available treatment regimens [2]. Some authors suggest that the current standard-of-care therapies, including the adrenergic beta-receptor blockers and the renin–angiotensin–aldosterone system inhibitors, are capable of achieving the maximum possible peripheral benefit and that any further neurohormonal modulation could potentially cause more harm than good in these patients [3].

In this short review, we will discuss a number of agents that are currently in the final stages of clinical trials, including omecamtiv mecarbil, empagliflozin, serelaxin, and SERCA2 gene therapy. These agents use novel pathways, some of which aim at modifying the underlying disease process and some are meant to improve outcomes in certain subgroups of HF patients that have poor prognosis. All of the phamacotherapeutic agents included in this review had successful early phases of clinical trials.

2. Omecamtiv mecarbil

Medications that increase myocardial contractility, including dopamine, dobutamine, milrinone, and digoxin, have been in clinical use for a long time. Because of their unfavorable effect on survival, the use of such inotropic agents (except for digoxin which has a neutral effect on mortality) has been limited to patients with cardiogenic and those receiving palliative therapy for end-stage HF [2]. Unlike most of the currently available inotropes that work by increasing intracellular calcium, omecamtiv mecarbil works by accelerating the conversion of the actin–myosin complex into the strongly bound state and leads to an increase in the duration of systole and stroke volume and an improvement in the systolic function without increasing the myocardial oxygen consumption [4,5]. The effect of omecamtiv mecarbil, used in two phase II trials, COSMIC-HF and ATOMIC-AHF ($n > 1000$ total), showed improvement in myocardial function and symptoms. It should be noted that an elevation in troponin was reported in both studies, which raises a question about a potential O_2 supply–demand mismatch when used in humans with HF. In both trials, the elevation in troponin was not associated with other clinical evidence of myocardial ischemia [6,7].

There is an ongoing phase III trial, GALACTIC-HF, that investigates the effect of omecamtiv mecarbil on mortality and morbidity in patients with chronic HF, both in the outpatient and in the inpatient populations [8]. The study will enroll patients with chronic systolic HF, ejection fraction ≤35%, and New York heart association (NYHA) class II–IV.

If GALACTIC-HF turns out to be positive, omecamtiv mecarbil will be the first oral agent that can improve myocardial contractility in a reasonably short time while enhancing survival. This study is designed to show the effect of omecamtiv mecarbil in patients with all classes of symptomatic heart failure with reduced ejection fraction (HFrEF), however we see that it can have a special value in treating end-stage HF patients who are not candidates for advanced cardiac therapies (such as left ventricular assist devices [LVADs] and cardiac transplantation). These patients are usually offered the difficult choice of using long-term inotropic agents for symptomatic relief in exchange for their expected survival.

3. Empagliflozin

Empagliflozin is a sodium–glucose cotransporter 2 inhibitor that is used to treat patients with diabetes. It causes a decrease in blood sugar by allowing more glucose to be secreted in the urine. Via the same mechanism, empagliflozin also functions as an osmotic diuretic that causes a reduction in blood pressure and body weight. In a *post hoc* analysis of the EMPA-REG OUTCOME trial that included 706 diabetic patients with HF, there was a significant reduction in the rate of cardiovascular death, HF hospitalization, and all-cause

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hospitalization in patients treated with empagliflozin (compared to placebo) [9]. Given that diabetes has high prevalence in patients with HF (40% of admitted HF patients are diabetic), and given the higher mortality and hospital admission rates that are reported in this group [10], empagliflozin could be of a special value in treating patients with both conditions. Although the available data on empagliflozin in HF is promising, it should be noted that HF was not well characterized in the EMPA-REG OUTCOME trial, and so caution should be used when interpreting these results. A multicenter, randomized clinical trial is currently underway investigating the impact of empagliflozin on outcomes in the diabetic as well as nondiabetic HF patients [11,12].

4. Serelaxin

Since HF is a condition with a reported 30-day mortality and readmission rate up to 12% and 23%, respectively, there is an imminent need for agents that can improve outcomes. The mainstay medications currently used to treat volume overload and pulmonary congestion in the acute setting (namely vasodilators and non-potassium-sparing diuretics) have no proven survival benefits to support their use, while other acute agents (i.e. inotropes) were shown to be associated with increased mortality. On the other hand, the results of the recent studies investigating new agents for acute HF like synthetic natriuretic peptides and adenosine receptor antagonists were disappointing [13]. Serelaxin is a recombinant form of a human peptide hormone called relaxin, which is secreted from the corpus luteum during pregnancy. In addition to its function as a pelvic relaxant, relaxin is also a potent vasodilator that leads to an increase in the renal blood flow and glomerular filtration rate. In patients with HF, serelaxin was shown to increase cardiac index, improve renal functions, and decrease pulmonary wedge pressure and NT-proBNP. In a phase III, double-blind randomized trial (RELAX-AHF) that included acute heart failure (AHF) patients who received 48 h of intravenous serelaxin, there was an improvement of patients' symptoms, decreased length of hospital stay, and increased 180-day survival. Even with these results, the trial failed to show any difference in hospital readmission rates [14]. Another phase III clinical trial (RELAX-AHF-2) failed to show improvement of AHF symptoms at 5 days or improvement in survival at 180 days. [15] The data is currently under further analysis by the sponsor to determine the next step for this investigational drug.

5. SERCA 2A activator and gene therapy

The sarcoplasmic reticulum Ca^{++} ATPase (SERCA2a) activator is delivered inside the cell by a viral vector (adenovirus). SERCA 2a pump activator aims at regulating the cytosolic calcium concentration, which was found to be impaired in patients with HF. SERCA 2a activators showed a significant reduction in pulmonary capillary wedge pressure in phase II clinical trials, but failed to decrease HF-related hospital admissions [16]. The SERCA-LVAD trial is currently underway to evaluate the effect of SERCA2a activators in advanced HF patients postimplantation of LVADs. [17] If shown to be beneficial, and in addition to its novel approach in treating HF, SERCA 2a activators will be the first-in-class gene-based therapy used to treat cardiac patients. This long-awaited paradigm shift can lead to major advancements in treating certain types of HF (i.e. those secondary to gene mutation).

Gene therapy can also contribute to the development of new therapeutic approaches like angiogenesis in patients with coronary artery diseases and the modification of action potential to treat ventricular arrhythmias [18]. A successful experience with gene therapy in HF should also encourage the development of new vectors that are safe and efficient at the same time. Of note that viral vectors can perform a more efficient transduction compared to nonviral vectors; however, they are known to cause multiple immunologic, inflammatory, and degenerative complications.

6. Conclusion and perspectives

The pharmacotherapeutic agents discussed in this article aim at maximizing survival and quality of life of HF patients using a set of new cellular targets. These agents focus on improving outcomes in patients with advanced disease and high comorbidity burden, and some aim at treating the underlying pathology rather than only modulating the neurohormonal responses triggered by the body.

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Declaration of interest

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