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NOVEL AGENTS FOR THE TREATMENT OF HEART FAILURE

Parchami Ghazaee Sepideh

PhD in biological sciences, assistant of the Department of Pharmacology,
Clinical Pharmacology, Pathological Physiology
Kiev Medical University, Ukraine

Hameed Murtaza

3rd year student of Medicine
Kiev Medical University, Ukraine

Heart failure (HF), in its various pathological forms, can be described as a global pandemic affecting more than 26 million people worldwide and is increasingly prevalent (Savarese & Lund, 2017 p. 1). Although advances in treatment and evidence-based drug therapies have led to an improvement in prognosis during the last two decades particularly, the growing global healthcare burden of HF is driving the need for new therapeutic approaches. All forms of HF are characterized by a decreased stroke volume and cardiac output (Berliner & Bauersachs 2019, p. 4), however three types are distinguished according to the left ventricular ejection fraction (LVEF): HF with reduced LVEF <40% (HFrEF), HF with midrange LVEF 40-49%, and HF with preserved LVEF ≥50%. Standard evidence-based therapies for the treatment of HF include inotropic agents, vasodilators and loop diuretics along with angiotensin-converting-enzyme inhibitors and beta-blockers (Machaj et al, 2019 p. 147). Levosimendan, a calcium sensitizer, has been used extensively for the treatment of a variety of cardiac pathologies in many countries for two decades, although it currently in active clinical evaluation in the United States (Papp et al., 2020). A 2019 meta-analysis by Heng Li and co-authors assessing clinical outcomes of pharmacological interventions included 32 studies and found levosimendan was more effective in reducing ventricular wall tension and improving systolic function in patients with HFrEF as compared with other drugs including tolvaptan and ivabradine. (Li et al, 2019 p. 7). Novel therapies being developed include natriuretic peptide receptor (NPR) downregulators (such as ularitide), synthetic recombinants of relaxins (such as serelaxin) and myosin activators (such as omecamtiv mecarbil). Ularitide has undergone preliminary trials and was found to produce beneficial hemodynamic effects and reduce cardiac wall stress, although there is no evidence the therapy however, reduces myocardial injury or disease progression (Machaj et al, 2019, p149). A recent multicenter, double-blind, placebo-controlled, event-driven trial investigating the effects of serelaxin in the treatment of HF found significantly reduced hypotension in the trial group, although no evidence of a lower cardiovascular mortality rate (Metra et al, 2019, p. 726). A randomized, double-blind,

placebo-controlled phase 3 trial investigating the safety and efficacy of serelaxin therapy in Asian patients (RELAX-AHF-ASIA) found that while it was safe, it was not effective (Machaj et al, 2019 p. 151). Omecamtiv mecarbil is a promising novel treatment with an atypical positive inotropic effect; as a myosin activator it results in a more powerful stroke by increasing the number of myosin heads binding with actin filaments, without increasing the calcium level or oxygen use in the cardiomyocytes unlike standard inotropic agents (Machaj et al., 148). A recent review of trials found a significant increase in stroke volume and a decrease in left ventricular end-systolic diameter, left ventricular end-diastolic diameter and N-terminal pro B-type natriuretic peptide concentration in plasma (Berliner and Bauersachs 2019, p. 9). Machaj et al. note the promising results of preliminary trials and suggest that while further studies must be conducted, there are very high expectations for impending phase III trials such as the upcoming Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects With Chronic Heart Failure With Reduced Ejection Fraction (GALACTIC-HF) (Machaj et al, 2019, p149).

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