Pharmaceutica Analytica Acta

Diaconu et al., Pharm Anal Acta 2015, 6:10
http://dx.doi.org/10.4172/2153-2435.1000e181

Editorial Open Access

LCZ 696, a New Treatment for Patients with Heart Failure

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Heart failure represents the final stage of evolution of a large majority of cardiovascular diseases. Nowadays, due to prolonged survival of patients with chronic cardiovascular diseases, heart failure has become a major problem of healthcare systems, with increasing prevalence, especially among persons over 70 years of age. The cornerstone of heart failure treatment is the blockade of the renin-angiotensin-aldosterone system. Neprilysin is an enzyme that breaks down the natriuretic peptides, a family of hormones involved in the balance of sodium and water. By maintaining the fluid homeostasis, natriuretic peptides protect the cardiovascular system from the negative effects of fluid overload. In patients with heart failure, the increases of natriuretic peptides are ineffective in clearing the fluid overload. Neprilysin inhibition is an alternative therapeutic strategy in these patients. The first drug acting as a dual neprilysin and renin-angiotensin system inhibitor was omapatrilat. Despite initial promising results of omapatrilat in patients with heart failure and arterial hypertension, further trials failed to demonstrate a substantial benefit of omapatrilat versus an angiotensin-converting enzyme inhibitor, enalapril [1]. Moreover, the great incidence and severity of angioedema in hypertensive patients treated with omapatrilat led to the withdrawal of this drug by the Food and Drug Administration. LCZ696 appeared as a first-in-class angiotensin receptor neprilysin inhibitor. LCZ696 is a complex composed of sacubitril (a neprilysin inhibitor) and valsartan (an angiotensin receptor blocker).

In July 2015 the Food and Drug Administration has approved LCZ 696 (sacubitril/valsartan), for the treatment of heart failure with reduced ejection fraction. This decision is based on the results of PARADIGM-HF trial, a double blind trial that included 8442 patients with heart failure with reduced ejection fraction [2]. The patients with chronic heart failure class II, III or IV and an ejection fraction <40% were randomized to receive either an angiotensin converting enzyme inhibitor, enalapril (10 mg twice daily) or LCZ 696, an angiotensin receptor–neprilysin inhibitor (200 mg twice daily), added to the standard treatment of heart failure. The main objective of the trial was to compare the rates of death from cardiovascular causes between the two groups of patients (that received LCZ696 or enalapril). Patients that received LCZ696 had a reduced risk of death from cardiovascular causes (by 20%) and a lower rate of hospitalizations for heart failure (by 21%) as compared to patients that received enalapril. Also, heart failure patients treated with LCZ696 had a reduced risk of death from any cause, reduced symptoms and a better tolerance to physical effort [2]. These advantages of LCZ696 were significant, taking into consideration the fact that LCZ696 was compared to a dose of enalapril that has been shown to decrease mortality, as compared to placebo [3,4]. These advantages were apparent early in the trial and were observed in patients who were already treated with other classes of drugs demonstrated to prolong survival in patients with heart failure, such as beta blockers and mineralocorticoid-receptor antagonists [1]. These better outcomes of patients with heart failure treated with LCZ696 were not accompanied by significant safety concerns. Patients treated with LCZ696 presented more frequently symptomatic hypotension compared to patients treated with enalapril (14% vs. 9.2%, $p<0.001$); however, this led to discontinuation of treatment only in few cases. One major concern related to the treatment with LCZ696, the risk of angioedema, was not confirmed in the PARADIGM trial. This concern was raised by the results of previous OVERTURE trial with the related drug, omapatrilat [1]. Omapatrilat was associated with life-threatening angioedema due to its inhibition of angiotensin-converting enzyme, neprilysin and aminopeptidase P. LCZ696 avoids inhibition of angiotensin-converting enzyme and aminopeptidase P and has a much lower risk of angioedema.

One half of the patients with heart failure have preserved ejection fraction (heart failure with preserved ejection fraction, HFpEF). Currently, there are no specific therapies proven to be beneficial in patients with HFpEF. The PARAMOUNT trial investigated the effects of LCZ696 in patients with HFpEF [5]. Patients were randomized to receive either LCZ696 or valsartan. The primary endpoint of the study was the change of NT-proBNP after 12 weeks of treatment. NT-proBNP was significantly reduced, by 26%, at 12 weeks, in the arm treated with LCZ696, without significant adverse effects. After 36 weeks, patients treated with LCZ696 presented greater improvements in left atrial size and New York Heart Association class. These findings set the stage for further studies regarding the potential benefit of LCZ696 in patients with HFpEF.

In conclusion, LCZ696 is a promising treatment for patients with heart failure, recently approved by Food and Drug Administration. This drug might become the first-line therapy in patients with heart failure and reduced ejection fraction, after the international heart failure treatment guidelines will be updated. Further studies will determine if LCZ696 is beneficial also for patients with HFpEF.

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Received October 15, 2015; **Accepted** October 16, 2015; **Published** October 19, 2015

Citation: Diaconu CC (2015) LCZ 696, a New Treatment for Patients with Heart Failure. Pharm Anal Acta 6: e181. doi:10.4172/21532435.1000e181