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A NEW DRUG FOR HEART FAILURE: LCZ696

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ABSTRACT

Congestive heart failure is a chronic and debilitating disease whose prevalence is 1–2% in the western world and the incidence is 5–10 per 1000 persons per year. Apart from the neurohormonal pathways, the renin-angiotensin-aldosterone system (RAAS) is one of the most potentially beneficial counter-regulatory systems that has now a days become one of the prime focus of therapeutic intervention. A systematic literature search was carried out using databases such as PubMed, Cochrane reviews, Google scholar, etc. And exhaustive information regarding LCZ696 was gathered. The U.S. Food and Drug Administration (US FDA) approved sacubitril/valsartan combination on 7th July, 2015 for the treatment of heart failure and has been given brand name Entresto. US Food and Drug Administration (FDA) granted priority review for LCZ696 on Feb. 13, 2015 and this has reduced the total review time from 12 to 8 months. This sacubitril/valsartan combination comes under the category of "angiotensin receptor-neprilysin inhibitor" (ARNi). Efficacy of LCZ696 in treating heartfailure is based on the PARADIGM-HF trial in which LCZ696 which is a combination of the angiotensin receptor blocker valsartan and the neprilysin inhibitor sacubitril was compared with the angiotensin-converting enzyme inhibitor enalapril in 8,442 patients with

symptomatic chronic systolic heart failure. LCZ696 may offer a promising role in the treatment of heart failure. ARNi may find its place in the classification of drugs used for the treatment of heart failure. It is under trial for essential hypertension and chronic kidney disease like conditions other than heart failure. It has promising role in cardiac and renal protection.

KEYWORDS: Sacubitril, valsartan, neprilysin, LCZ696 ARNi.

INTRODUCTION

Congestive heart failure

Congestive heart failure is a chronic and debilitating disease which is associated with more than 290 000 deaths in the United States each year.[1] Heart failure is basically a syndrome that consists of symptoms and signs caused by cardiac dysfunction, resulting in reduced longevity. The prevalence of heart failure is 1–2% in the western world and the incidence is 5–10 per 1000 persons per year.[2] The prevalence of HF actually shows an exponential pattern, and it rises with age. Heart failure affects 6% to 10% of people over the age of 65 years. Treatment of acute decompensated heart failure incudes hospitalization.[3] Inpatient Monitoring, Diuresis.[4] Vasodilation, Ultrafiltration.[5] and ionotropic therapy.[6][12] Emerging medical therapies for ADHF[12] includes vasopressin receptor antagonists.[7] relaxin.[8] Adenosine Antagonists.[9] Ularitide.[10] and Calcium Sensitizers.[11][12]

Neprilysin

High morbidity and mortality is associated with heart failure with reduced ejection fraction (HfrEF) specially in older people.[13][14] The biologically active natriuretic peptides and several other vasoactive compounds are broken down by neprilysin. Ecadotril, candoxatril, omapatrilat, and LCZ696 act by inhibiting neprilysin. However, ecadotril, candoxatril and omapatrilat have been discontinued due to lesser efficacy and more of side effects.[15] As far as management of heart failure is concerned, apart from the neurohormonal pathways, the renin-angiotensin-aldosterone system (RAAS) is one of the most potentially beneficial counter-regulatory systems that has now a days become one of the prime focus of therapeutic intervention. Natriuretic peptides which are metabolized by the enzyme neprilysin has been studied in detail which promotes vasodilatation and natriuresis, inhibit abnormal growth, suppress the RAAS and sympathetic nervous system, and augment parasympathetic activity.[16]

But, the combination of RAAS blockade with inhibition of neprilysin has recently emerged as a potentially superior treatment strategy.[17]

Neprilysin inhibitor

Neprilysin inhibition (NEPi) is also under trial as a new therapeutic strategy with potential to improve outcomes for patients with CKD.

Omapatrilat showed dual inhibition of NEP/RAS in treating CKD in animal models, and produced greater reductions in proteinuria, glomerulosclerosis and tubulointerstitial fibrosis compared with isolated RAS inhibition.

LCZ696 is now under trial in CKD patients. It acts by both retarding the progression of CKD and reducing the risk of cardiovascular disease and hence delaying the need for renal replacement therapy.[18]

What is LCZ696?

The U.S. Food and Drug Administration (US FDA) approved sacubitril/valsartan combination on 7th July, 2015 for the treatment of heart failure and has been given brand name Entresto. US Food and Drug Administration (FDA) granted priority review for LCZ696 on Feb. 13, 2015 and this has reduced the total review time from 12 to 8 months.[19]

It is indicated to reduce the risk of cardiovascular death and heart failure hospitalization amongst classified NYHA class II-IV heart failure patients. This sacubitril/valsartan combination comes under the category of "angiotensin receptor-neprilysin inhibitor" (ARNi). LCZ696 is the first example of a dual-acting pharmaceutical built as a supramolecular complex delivering two pharmacologic effects-angiotensin receptor1 (AT1) blockade and neprilysin (NEP) inhibition. Its molecular formula is $C_{288}H_{330}N_{36}Na_{18}O_{48}\cdot 15H_2O$ and a molecular mass is 5748.03 g/mol.[22][23]

PARADIGM-HF TRIAL (Funded by Novartis; PARADIGM-HF ClinicalTrials.gov number, NCT01035255.)

Efficacy of LCZ696 in treating heartfailure is based on the PARADIGM-HF (‘Prospective comparison of Angiotensin Receptor neprilysin inhibitors with Angiotensin converting enzyme inhibitors to Determine Impact on Global Mortality and morbidity in Heart Failure’ (PARADIGM-HF, NCT01035255) trial in which LCZ696 which is a combination of the angiotensin receptor blocker valsartan and the neprilysin inhibitor sacubitril was compared

with the angiotensin-converting enzyme inhibitor enalapril in 8,442 patients with symptomatic chronic systolic heart failure. PARADIGM- HF focussed mainly on the endopeptidase pathway and alsothe substitution of one of the cornerstones of modern HF therapy, the ACEi .[13][22]

Total 8399 patients were recruited with symptomatic chronic HFrEF and increased levels of natriuretic peptides. LCZ696 (400 mg daily) was administered and compared with the ACEi enalapril (20 mg daily).[23] However, indirect comparisons of the effects of LCZ696 with putative placebos. [24] It was found that LCZ696 resulted in 20% reduction in the incidence rate of death or HF hospitalization and a 16% reduction in the incidence rate of all-cause death as compared to enalapril which was found o be statistically highly significant. [23]

LCZ696 prevented the clinical deterioration of the patients and caused significant reducton in the required treatment intensification of therapy (520 versus 604; hazard ratio, 0.84; 95% confidence interval, 0.74-0.94; P=0.003), hospital visits and use of advanced management modalities (inotropes, assist devices, transplantation).[23]

Less incidences of hyperkalemia, renal dysfunction and cough were reported with LCZ696 but it led to higher rates of hypotension and nonserious angioedema.[22][23]

Pharmacokinetics of LCZ696

Preclnical studies showed that,oral administration of LCZ696 caused dose-dependent increases in atrial natriuretic peptide immunoreactivity (due to NEP inhibition) in Sprague-Dawley rats and provided sustained, dose-dependent blood pressure reductions in hypertensive double-transgenic rats.[25]

When studied clinically in healthy participants in a randomized, double-blind, placebo-controlled study (n = 80) of single-dose (200-1200 mg) and multiple-dose (50-900 mg once daily for 14 days) oral administration of LCZ696 showed that peak plasma concentrations were reached rapidly for valsartan (1.6-4.9 hours), AHU377 (0.5-1.1 hours), and its active moiety, LBQ657 (1.8-3.5 hours). LCZ696 increased plasma CGMP, concentration and activity of renin, and angiotensin II and provided evidence for NEP inhibition and angiotensin receptor blockade.[25]

Pharmacodynamics of LCZ696

It ihas been documented in an open-label, non-controlled study of 30 patients with stable chronic HF and left ventricular ejection fraction (LVEF) =40%, LCZ696 100 mg titrated to 200 mg twice daily resulted in increase plasma CGMP and urinary ANP after 7 and 21 days of drug administration, which is suggestive of the fact that it has caused inhibition of neprilysin. It also led to significant increase in plasma renin concentration (indicative of AT_1 receptor blockade) and decreased plasma NT-proBNP, while plasma aldosterone and endothelin (ET-1) levels were reduced (confirming clinically relevant RAAS inhibition).[25]

Mechanism of action of LCZ696

RAAS and sympathetic nervous system are activated in the pathogenesis of HF and hence the therapeutic benefit of RAAS blockers in improving HF outcomes is well established. As documented in the previous experimental and clinical studies that the natriuretic peptide (NP) system is also impaired in HF, which mediates beneficial cardiorenal effects. This suggests that newer therapeutic approaches designed to upregulate NPs or enhance their biological activity may be of therapeutic benefit, especially in conjunction with RAAS blockade as shown in figure-1.[25][26]

Ongoing trials

PARAGON HF TRIAL (ClinicalTrials.gov Identifier: NCT01920711 funded by Novartis)

It is a multicentered, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to valsartan, on morbidity and mortality in heart failure patients (NYHA Class II-IV) with preserved ejection fraction. This study was started in July 2014 and is currently recruiting participants. Final data collection date for primary outcome measure is estimated to be May 2019.

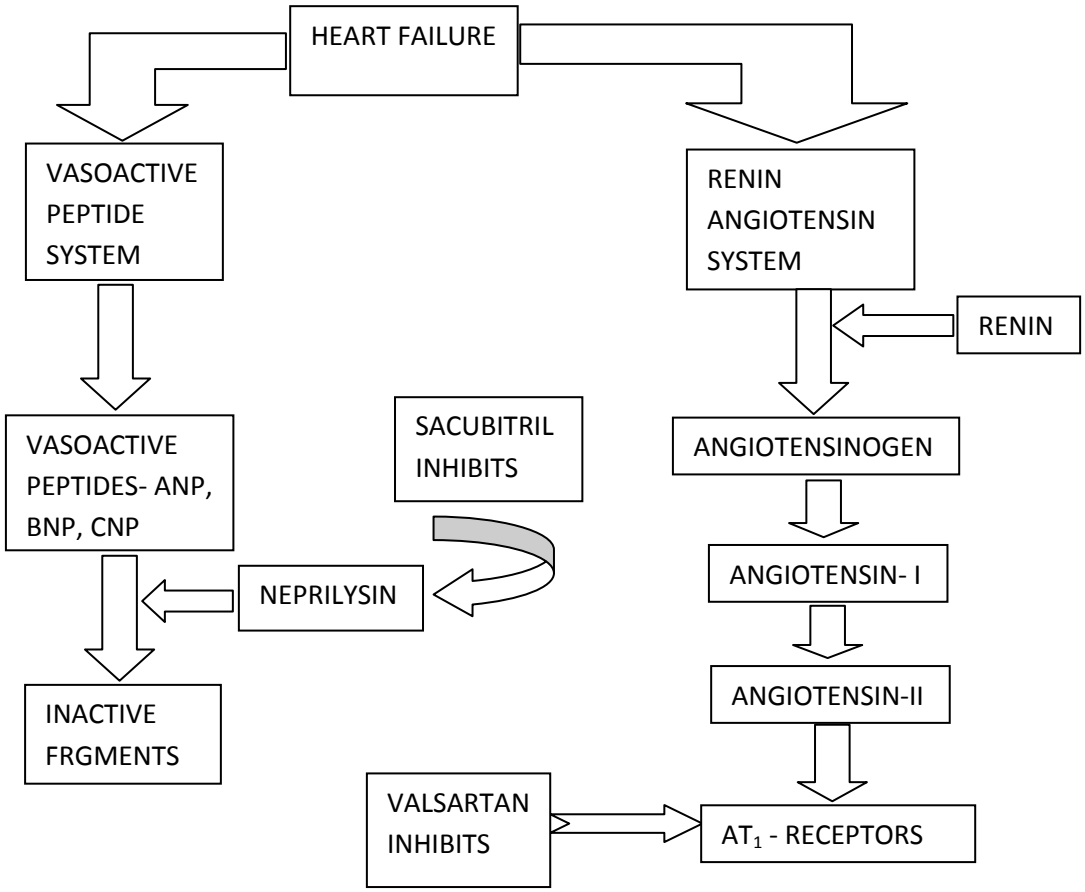

Fig: 1- Mechanism of action of sacubutril and valsartan.

CONCLUSION

LCZ696 may offer a promising role in the treatment of heart failure. ARNi may find its place in the classification of drugs used for the treatment of heart failure. It is under trial for essential hypertension and chronic kidney disease like conditions other than heart failure. It has promising role in cardiac and renal protection.

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