IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 12 Ver. VIII (Dec. 2017), PP 83-86
www.iosrjournals.org

The Utility of Sacubitril/Valsartan in Heart Failure

*Melvin George[1], Damal Kandadai Sriram[2]
1. Dept of Clinical Research, Hindu Mission Hospital, West Tambaram, Chennai-600045
2. Dept of Diabetology & Endocrinology, Hindu Mission Hospital, West Tambaram, Chennai-600045
**Corresponding author: *Melvin George1*

Abstract: *Despite the significant advances in the diagnosis and treatment of heart failure (HF), the disease predisposes individuals to a higher risk of re-hospitalization, mortality and morbidity worldwide. Inspite of the presence of several drugs such as angiotensin-converting enzyme inhibitors (ACEI), beta-adrenergic blockers, angiotensin receptor blockers (ARB), and aldosterone antagonists for HF, patients with the illness continue to have a downward spiral due to the disease progression. After more than a decade, a new fixed dose combination has been approved for HF, namely Sacubitril-valsartan. While valsartan is a well-known molecule that blocks angiotensin type 2 receptor, sacubitril is a neprilysin inhibitor. Sacubitril/valsartan an ARNI (angiotensin receptor antagonist/neprilysin inhibitor) has been approved for the treatment of HF with reduced ejection fraction in USA, Europe and Canada. The drug has demonstrated an excellent safety profile, and the drug is purported to become a block-buster for the treatment of HF based on its commendable results in the PARADIGM-HF trial.*

Date of Submission: 30-11-2017 Date of acceptance: 23-12-2017

I. Introduction

Despite the significant advances in the diagnosis and treatment of heart failure (HF), the disease continues to remain at a higher risk of re-hospitalization, mortality and morbidity worldwide. "Heart failure is defined as the pathophysiologic state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues" [1]. The overall estimated prevalence of HF in India was found to be about 1% of the total population or about 8–10 million individuals. The re-hospitalization rate among HF patients has increased over the years, causing a major financial burden on HF patients [2]. The advances in pharmacology lead to the development of drug molecules such as angiotensin-converting enzyme inhibitors (ACEI), beta-adrenergic blockers, angiotensin receptor blockers (ARB), and aldosterone antagonists for the treatment of chronic HF with reduced ejection fraction (HFrEF) [3]. However, there is still a need for a novel molecule in HF, due to the relentless progression of the disease resulting in increased mortality and morbidity. This lead to the development of an innovative drug named Sacubitril/valsartan (LCZ696), which is an angiotensin receptor neprilysin inhibitor (ARNI). The working of the drug was based on the simultaneous mechanism: neprilysin inhibition and angiotensin-II receptor blockade. The innovative drug was formerly named as LCZ696 [4]. The safety, efficacy and tolerability profile of this drug were studied separately under various trials, and the drug has been approved in USA, Europe and Japan for the treatment of HF. This review is an attempt to describe the history of Sacubitril/valsartan, their mechanism of action, efficacy, safety and its current status.

Mechanism of action:

Valsartan/Sacubitril is a novel combination of sacubitril and valsartan with a 1:1 molar ratio. The fixed dose combination (FDC) of the novel molecule is sacubitril/valsartan (24 & 26 mg), (49 & 51 mg) and (97 & 103 mg). The novel drug molecule consists of two active components namely valsartan, an angiotensin-II receptor blocker and sacubitril, a neprilysin inhibitor. Valsartan inhibits the activation of angiotensin II receptor type 1 (AT_1), which in turn causes vasodilation, reduction in the production and secretion of aldosterone, an increase in the excretion of sodium and water through the kidneys that causes a reduction in the blood volume. Sacubitril is a neprilysin inhibitor which is responsible for the inhibition of neprilysin enzyme via LBQ657, an active metabolite of sacubitril. Neprilysin is an endopeptidase that causes the degradation of various vasoactive peptides such as natriuretic peptides, bradykinin, and adrenomedullin. The blocking of neprilysin enzyme will enhance the production of the natriuretic peptides, which in turn reduces the vasoconstriction, sodium retention and maladaptive remodelling [5, 6]. Therefore, the combination of sacubitril and valsartan has been found to be a novel approach for the treatment of chronic heart failure (CHF) patients with reduced ejection fraction.

Pharmacokinetics:

Valsartan/Sacubitril is available in the form of an oral tablet. After the oral administration of Valsartan/Sacubitril, the drug is dissociated into two forms: sacubitril and valsartan. The drug molecule

sacubitril is further metabolized into LBQ657. The drug molecules sacubitril, LBQ657 and valsartan reach their peak plasma concentration at 0.5 hours, 2 hours and 1.5 hours respectively. After the oral administration of valsartan/sacubitril, about 52% to 68% of sacubitril and 13% of valsartan and its other metabolites are eliminated in the urine. About 42% of sacubitril and LBQ657 and 86% of valsartan are excreted in the faeces. The terminal half life ($T_{1/2}$) of the drug components sacubitril, LBQ657, and valsartan are approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively. The administration of the drug did not show significant food-drug interactions. The administration of sacubitril/valsartan is restricted to patients who are already on Angiotensin-converting enzyme (ACE) inhibitors. The starting dosage of sacubitril/valsartan should be reduced to (24/26) mg twice daily for patients suffering with severe renal impairment and moderate hepatic impairment. According to the patient's tolerability, the dosage can be doubled every two to four weeks to attain a target maintenance dose of 97/103 mg (sacubitril/valsartan) twice-daily according to the patient's tolerability [7].

Efficacy of sacubitril/valsartan in HF:

The PARAMOUNT trial was a phase 2, randomised, parallel-group, double-blind multicentre trial, where 301 HF patients with (NYHA class II-IV with a LVEF<40%) were randomized to receive LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily, and were treated for 36 weeks. The primary end point of the study was the change in the N-terminal pro–B-type NP (NT-proBNP) levels from baseline to 12 months. At the end of 12 months the NT-proBNP levels were significantly lower in the LCZ696 group (ratio of change LCZ696/valsartan 0.77, 95% CI 0.64-0.92, p=0.005) than the valsartan group. Therefore, the LCZ696 significantly lowered the NT-proBNP level, a marker of left ventricular wall stress [8].

The Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ACEI [ACE inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) was a randomized, double-blind, phase III trial, which was conducted to evaluate the long-term effects of sacubitril/valsartan among 8442 chronic symptomatic HF patients with reduced ejection fraction (NYHA class II-IV with a left ventricular ejection fraction (LVEF<40%). The primary end point of the study was composite of mortality due to cardiovascular diseases and first hospitalization for HF. The secondary outcome measures included time to death from any cause, quality of life (QOL) Kansas City Cardiomyopathy Questionnaire (KCCQ), time to the new onset of atrial fibrillation and decline in renal function. The study subjects were randomly assigned in a 1:1 ratio to receive either 10 mg of enalapril twice daily or 200 mg of LCZ696. After the median duration of 27 months of follow-up, the primary outcome measures were compared using the using Kaplan-Meir estimates. The total number of deaths due to cardiovascular diseases was 558 (13.3%) in the LCZ696 group and 693 (16.5%) in the enalapril group (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). The total number of patients hospitalized for HF was 537 (12.8%) in the LCZ696 group and 658 patients (15.6%) in the enalapril (hazard ratio, 0.79; 95% CI, 0.71 to 0.89; P<0.001) group. The secondary outcome measure of death due to any cause was significantly lower in the LCZ696 group (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001) when compared to the enalapril group. Furthermore, the LCZ696 group showed an improvement in the QOL than the (between-group difference, 1.64 points; 95% CI, 0.63 to 2.65; P = 0.001) enalapril group. Therefore, the drug molecule LCZ696 was found to be superior to the gold standard drug enalapril for the treatment of HF [9]. The PARADIGM-HF study has lead to several other analyses that has provided understanding about the potential benefits of sacubitril/valsartan. Another study sought to determine if LCZ696 reduced the rates of hospital readmission at 30 days following the HF hospitalization. In this study, the investigators of the PARADIGM-HF study reported the hospitalizations for HF in both the LCZ696 and enalapril treatment groups. A total of 2,383 investigators reported HF hospitalizations, among which 1,307 (54.8%) occurred in the enalapril group and 1,076 (45.2%) occurred in the LCZ696 group. The rates of readmission for any cause at 30 days were significantly lower in the (17.8%) LCZ696 group (odds ratio: 0.74; 95% confidence interval: 0.56 to 0.97; p=0.031) when compared to the (21%) enalapril treatment (21%) group. Similarly, the rates of readmission for HF was significantly lower in the LCZ696 group (9.7% vs. 13.4%; odds ratio: 0.62; 95% confidence interval: 0.45 to 0.87; p=0.006) than the enalapril group [10]. Therefore, LCZ696 has an effect on the reduction in the 30 day HF readmission.

During the PARADIGM-HF trial health related quality of life (HRQL) outcome, the Kansas City Cardiomyopathy Questionnaire (KCCQ) was measured among 7623 patients at 8 months. At the end of 8 months, the LCZ696 group demonstrated a significant improvement in both KCCQ clinical summary score (+0.64 versus −0.29; P=0.008) and KCCQ overall summary score (+1.13 versus −0.14; P<0.001) compared to the enalapril group. These findings show that LCZ696 lead to a better HRQL among LCZ696 patients [11]. Furthermore, the marker of left ventricular wall stress NT-proBNP, was quantified among 2,080 patients of the PARADIGM-HF trial. The levels of biomarker were measured at baseline, 1 and 8 month. At 1 month the median NT-proBNP levels was significantly lower in the LCZ696 than the enalapril group, with a fall of <1,000 pg/ml in (31%) versus (17%) between the treatment groups respectively. However, there was no significant correlation between NT-proBNP levels and primary end point (the first occurrence of cardiovascular death or

HF hospitalization) [12]. Therefore, the fixed dose combination of drug molecule sacubitril/valsartan was given recommendation in the ACC/AHA/HFSA and ESC Guidelines for the reduction of morbidity and mortality [13, 14].

Safety and tolerability of sacubitril/valsartan in HF patients:

Some of the most commonly reported adverse effects (AEs) were hypotension, angioedema, renal impairment and hyperkalemia. The above mentioned AEs were reported in the PARADIGM-HF phase III trial. In the PARADIGM-HF trial, the study drugs was given to the HF patients during the run-in period which comprised of two week run-in phase with enalapril, that was followed by four to six weeks run-in phase with sacubitril/valsartan. The run-in phase of the trial was conducted to ensure the tolerability of study drugs among the HF patients. During the run-in phase of the trial about 1102 subjects discontinued the study after the enalapril run-in phase, and 977 subjects discontinued the study after the sacubitril/valsartan run-in phase. One of the reasons for the discontinuation of the study was due to AEs which included hypotension, angioedema, renal impairment, hyperkalemia, cough and laboratory abnormalities [9]. Some of the contra indications of sacubitril/valsartan include history of angioedema related to previous ACE inhibitor or ARB therapy, concomitant use of ACE inhibitors, concomitant use of aliskiren among diabetic patients and patients exposed to hypersensitivity to any component. The warnings and precautions associated with the drug molecule include fetal toxicity, angioedema, hypotension, impaired renal function, and hyperkalemia. The administration of sacubitril/valsartan is not recommended among pregnant as it can cause harm to the foetus, and lactating women. Cases have been reported that pregnant women taking valsartan resulted in the spontaneous abortion, oligohydramnios, and newborn renal dysfunction [7, 15]. Moreover, the safety and efficacy of sacubitril/valsartan has not been established in the pediatric population, and dose adjustments are required when administered among patients with hepatic and renal impairment.

Current regulatory status:

The US FDA approved the innovative drug sacubitril/valsartan for the treatment of CHF (NYHA Class II-IV) with reduced ejection fraction on July 7, 2015. The drug molecule was later launched in the European market in the year 2015. Based on the clinical trial data submitted for the drug approval, the FDA has requested for further studies that will evaluate the incidence of angioedema in black patients treated with sacubitril/valsartan in comparision to controls. The drug manufacturer has also been told to conduct a multicenter, randomized, double-blind, active-controlled trial, that will evaluate the effect of sacubitril/valsartan in comparision with valsartan on the cognitive function among CHF patients with reduced ejection fraction. The drug molecule is more popular in the European countries when compared to the USA, due to the barriers imposed by the medical insurance companies and the drug cost [16]. Prior to the FDA approval, the Canadian HF guidelines had placed recommendation for sacubitril/valsartan. The Canadian guidelines approved the use of sacubitril/valsartan over ACE inhibitors and ARBs among patients with LVEF<40%, elevated BNP, HF hospitalization within the past year [17].

Upcoming sacubitril/valsartan HF trials:

would include 40 trials so as to generate additional data on the symptom reduction, efficacy, QOL benefits and real world evidence on the treatment of sacubitril/valsartan for HF. Some of the trials have already begun and some are on the way. Some of the most prominent and major trials include: PARAGON-HF, PARADISE-MI, TRANSITION and PIONEER [18-21] (Table 1). Due to the non existence of evidence for the safety and efficacy of sacubitril/valsartan in the pediatric population, a study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of LCZ696 followed by a 52-week study of LCZ696 compared with enalapril in pediatric HF patients is ongoing [22].

II. Conclusion

Sacubitril/valsartan an ARNI has been approved for the treatment of HF with reduced ejection fraction in USA, Europe and Canada. The drug has demonstrated an excellent safety, tolerability and efficacious profile, and has shown long-term benefits in HF patients with reduced ejection fraction. The therapeutic effect of the drug has been effective in reducing the risk of cardiovascular death and hospitalization among HF patients with reduced ejection fraction. However, additional data is required to assess the safety, efficacy and tolerability profile of the drug in diverse populations inclusive of the paediatric and black population. More clinical trials are required to establish its usage among patients with HF and preserved ejection fraction and in chronic kidney disease (CKD).

References:

[1]. Denolin H, Kuhn H, Krayenbuehl HP, Loogen F, Reale A. The definition of heart failure. Eur Heart J., 4(7), 1983, 1983, 445–8.
[2]. Chaturvedi V, Parakh N, Seth S, Bhargava B, Ramakrishnan S, Roy A, et al. Heart failure in India: The INDUS (INDia Ukieri Study) study. J Pract Cardiovasc Sci, 2, 2016, 28-35.
[3]. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation, 128(16), 2013,1810–52.
[4]. Menendez JT. The Mechanism of Action of LCZ696. Card Fail Rev., 2(1), 2016, 40–6.
[5]. Tyler JM, Teerlink JR. The safety of sacubitril-valsartan for the treatment of chronic heart failure. Expert Opin Drug Saf., 16(2), 2017; 257–63.
[6]. Richardson J, David T, Grace Y, and Guirguis E. A New Mechanism of Action in Heart Failure: Angiotensin-Receptor Neprilysin Inhibition. Journal of Pharmacy Technology., 32(3), 2015, 116-124.
[7]. Highlights Of Prescribing Information. These highlights do not include all the information needed to use ENTRESTO safely and effectively. See full prescribing information for ENTRESTO, 2015. [Internet] Available from: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/entresto.pdf. Accessed 21 November 2017.
[8]. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet Lond Engl., 380(9851), 2012,1387–95.
[9]. 9. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med., 371(11), 2014, 993–1004.
[10]. Desai AS, Claggett BL, Packer M, Zile MR, Rouleau JL, Swedberg K, et al. Influence of Sacubitril/Valsartan (LCZ696) on 30-Day Readmission After Heart Failure Hospitalization. J Am Coll Cardiol., 68(3), 2016, 241–8.
[11]. Lewis EF, Claggett BL, McMurray JJV, Packer M, Lefkowitz MP, Rouleau JL, et al. Health-Related Quality of Life Outcomes in PARADIGM-HF. Circ Heart Fail. 10(8), 2017, pii: e003430.
[12]. Zile MR, Claggett BL, Prescott MF, McMurray JJV, Packer M, Rouleau JL, et al. Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure. J Am Coll Cardiol., 68(22), 2016, 2425–36.
[13]. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J., 37(27), 2016, 2129–200.
[14]. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol., 68(13), 2016, 1476–88.
[15]. Highlights Of Prescribing Information. These highlights do not include all the information needed to use DIOVAN safely and effectively. See full prescribing information for DIOVAN, 1996. [Internet] Available from: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/diovan.pdf. Accessed 21 November 2017.
[16]. Chaplin, S. Sacubitril/valsartan for chronic heart failure: its future potential. Prescriber., 27, 2016, 26–34. doi:10.1002/psb.1514.
[17]. Moe GW, Ezekowitz JA, O'Meara E, Lepage S, Howlett JG, Fremes S, et al. The 2014 Canadian Cardiovascular Society Heart Failure Management Guidelines Focus Update: anemia, biomarkers, and recent therapeutic trial implications. Can J Cardiol., 31(1), 2015 3–16.
[18]. ClinicalTrials.gov. Novartis Pharmaceuticals. Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF) [home page on Internet]. C2017 [updated 2017 Nov 17; cited 2017 Nov 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT01920711?term=NCT01920711&rank=1
[19]. ClinicalTrials.gov. Novartis Pharmaceuticals. Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI (PARADISE-MI). [home page on Internet]. C2017 [updated 2017 Nov 17; cited 2017 Nov 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT02924727?term=NCT02924727&rank=1
[20]. ClinicalTrials.gov. Novartis Pharmaceuticals. Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event (TRANSITION). [home page on Internet]. C2017 [updated 2017 Nov 17; cited 2017 Nov 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT02661217?term=NCT02661217&rank=1
[21]. ClinicalTrials.gov. Novartis Pharmaceuticals. Comparison of Saocubitril/valsartaN Versus Enalapril on Effect on ntpRo-bnp in Patients Stabilized From an Acute Heart Failure Episode. (PIONEER-HF). [home page on Internet]. C2017 [updated 2017 Nov 17; cited 2017 Nov 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT02554890?term=NCT02554890&rank=1
[22]. ClinicalTrials.gov. Novartis Pharmaceuticals. Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LCZ696 Followed by a 52-week Study of LCZ696 Compared With Enalapril in Pediatric Patients With Heart Failure. [home page on Internet]. C2017 [updated 2017 Nov 17; cited 2017 Nov 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT02678312?term=NCT02678312&rank=1

*Melvin George. "The Utility of Sacubitril/Valsartan in Heart Failure." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.12 (2017): 83-86