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A NOVEL LCZ696 DRUG THERAPY VERSUS ENALPRIL IN THE TREATMENT OF HEART FAILURE

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ABSTRACT

LCZ696 (sacubitril valsartan) is a first-in-class angiotensin receptor neprilysin inhibitor that has been developed for the use of heart failure correspondingly neprilysin is an enzyme that contributes to the breakdown of the biologically active natriuretic vasodilator peptide (ANP) and several other vasoactive compounds. Neprilysin inhibitor has been proved to be a therapeutic target for several compounds that have been tested in cardiovascular disease. Although ecadotril, candoxatril, and omapatrilat were initially tested in hypertension and/or heart failure, lack of efficacy and side effects led to discontinuation of their development. LCZ696 is a compound composed of 2 molecular moieties in a single crystalline complex, the angiotensin receptor blocker valsartan and a neprilysin inhibitor, pro-drug phase 2 trial in heart failure with preserved ejection fraction which demonstrated greater efficacy than enalapril in a phase 3 trial in heart failure with reduced ejection fraction, therefore LCZ696 posses superior efficacy in the management of heart failure compared to the enalpril by decreasing the rate of morbidity and mortality and its mechanism is to inhibit or suppress the renin- angiotensin-aldosterone(RAAS) axis and augment the endogenous natriuretic peptide system.

KEYWORDS: LCZ696,Neprilysin,Enalpril, Heart failure.

INTRODUCTION

Chronic HF is a progressive condition characterized by, reduced cardiac output and decreased tissue oxygen delivery. These hemodynamic abnormalities result in activation of the RAAS and sympathetic nervous system to maintain vital organ perfusion.[1] Initially, this serves as an acute compensatory response, but prolonged activation contributes to the patho-physiology of HF, resulting in progressive cardio renal abnormalities, including myocardial

hypertrophy, fibrosis and apoptosis, increased systemic vascular resistance, and increased sodium and water retention.[1 -2]

Patho- physiology of heart failure

Heart failure is a clinical syndrome that results when the heart is unable to provide sufficient blood flow to meet metabolic requirements or retain blood venous return systemically,traditionally it is defined as the inability of heart to pump sufficient amount of blood carrying oxygen necessary to cover the metabolic needs of the body in the presence of adequate venous return, thus focus mainly on the reduction in cardiac output, pathological processes that involves diminished cardiac output leading to heart failure cases includes injury to the myocardium from a variety of consequences that includes coronary artery disease, hypertension, cardiomyopathies, valvular heart diseases and congenital heart diseases, and diabetes of which coronary artery disease is most frequently responsible. Systolic ventricular dysfunction due to pressure or volume overload that damages myocardium is characterized by diminished contractility and hence decrease in the ejection fraction less than 40% of cardiac output hitherto disturbance in diastolic ventricular function associated with restricted filling is characterized by elevated chamber stiffness, decrease contractility and therefore heart failure. Diastolic dysfunction in an enlarged heart is always associated with an impairment of systolic ventricular function and is, then, relegated to a subordinate role. Possible mechanisms for loss of contractility include structural changes as well as alterations in excitation-contraction coupling and impaired diastolic ventricular function encompass, in addition to altered calcium flux, structural changes such as fibrosis and hypertrophy and factors such as asynchrony and abnormal loading conditions.[3, 4]

Treatment strategies adopted in heart failure

The physiological compensatory mechanism tends to maintain adequate blood pressure and cardiac output so that blood flow distribution is in favor of the heart and brain and away from non vital organ like skin, musculature and visceral organs hence homeostatic balance struggle to recruit the compensatory mechanisms justified as hypertrophy of the cardiac muscle is mediated by controlling hypertension to prevent HF especially with sodium restriction and thiazide, reduces the incidence of HF by approximately 50%, even among very elderly patients. Diuretics, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors appear more effective than calcium channel blockers and doxazosin. Hydroxy methylglutaryl coenzyme A (HMG CoA) reductase inhibitors reduce the incidence of HF by approximately

20% among patients with hypercholesterolemia and coronary artery disease. ACE inhibitors reduce HF incidence by 37% among patients with reduced systolic function and by 23% among patients with coronary artery disease and normal systolic function.[5,6] Diuretics are superior to calcium channel blockers and, at least in the short term, angiotensin-converting enzyme inhibitors in preventing HF in hypertensive individuals.[7] new insights have been gained into the pathophysiology of contraction of hypertrophied myocardium and changes of adrenergic receptors in the myocardium due to chronically increased cardiac sympathetic tone.[8] The compensatory neuro-humoral (RAAS) system cause excessive vasoconstriction as well as sodium and water retention resulting in an undesired elevation of preload and after load which, in turn, further worsens the heart failure thereafter this compensatory mechanism progressively deteriorate and finally destined to decompensation, based upon physiological compensatory mechanisms pharmacological therapeutic intervention is build up to counter the extension of heart failure that includes diuresis, suppression of the overactive neuro hormonal systems, and potentiating and augmentation of NP systems to ameliorate cardiac function is the most focused site for the therapeutic intervention despite significant understanding of the underlying patho physiological mechanisms in heart failure, this disease causes significant morbidity and mortality.[9,10]

Inhibition of RAAS and augmentation of NP system

The RAAS system become overactive following heart failure, the consequences of activation of RAAS and sympathetic nervous system, established potential target site in the therapeutic of HF outcomes. A growing body of experimental and clinical evidence indicates that the natriuretic peptide (NP) system, which mediates beneficial cardio renal effects, is also impaired in HF[11] This suggests that approaches designed to up regulate NPs and/or enhance their biological activity may be of therapeutic benefit, particularly in combination with RAAS blockade[5]

The angiotensin receptor blocker valsartan and a neprilysin inhibitor pro drug has been tested in hypertension, phase 2 trial in heart failure with preserved ejection fraction, and has demonstrated greater efficacy than enalapril. The efficacy is due to its dual ability, one to inhibit the renin-angiotensin-aldosterone axis and and other to augment the endogenous natriuretic peptide system providing distinctiveness in the mechanism of cardiovascular disease.[12]

Effectiveness of drug therapy in HF

HF reduces patient quality of life and increases the financial burden in the healthcare system, with frequent costly hospitalizations and a 5-year mortality rate of approximately 50%[13] While survival rates have improved for HF with reduced ejection fraction (HFrEF) due to more widespread use of drugs that block and suppress the renin–angiotensin–aldosterone system (RAAS) but residual mortality rates remain high. For patients with HF with preserved ejection fraction (HFpEF) no therapy has proven to be effective at reducing morbidity and mortality[14] therefore, urgent need for new therapies to prevent and treat HFrEF and HFpEF is anticipated without any sensitive side effects.

Potential novel effective therapy in heart failure

Heart failure remains a syndrome with a very high mortality rate and a poor quality of life. For patients with heart failure and a preserved ejection fraction (HFpEF), no drugs have shown to improve mortality and morbidity, and therefore novel drugs are highly needed. LCZ696,a first in class angiotensin receptor neprilysin inhibitor (ARN i), might be an interesting novel drug for the treatment of heart failure, studies have shown promising effects of a combination drug with a neutral endopeptidase and an angiotensin-converting enzyme inhibitor (omapatrilat) for the treatment of patients with heart failure. However, the occurrence of angioedema prevented the drug from further development therefore a novel drug lcz696 on the process for the development not having all these side effects with greater efficacy over Enalpril.[15]

Efficacy of LCZ 696 versus Enalpril in the pharmacological management of heart failure

Chronic heart failure with reduced ejection fraction (HF-REF) who received LCZ696 lived longer without being hospitalized for heart failure than those who received standard care with ACE-inhibitor enalapril. Based on the compelling efficacy and primary endpoint[16, 17] LCZ696 is superior to valsartan alone in reducing blood pressure. Preliminary results from a Phase II trial showed that LCZ696 reduced NT-proBNP to a greater extent than valsartan alone, and in addition LCZ696 had beneficial effects on symptoms. With these promising first results, the results of ongoing further studies in heart failure are eagerly awaited. LCZ696 was superior to currently recommended doses of enalapril and has profound implications for the care of patients with chronic heart failure demonstrating compelling evidence that supports LCZ696 as a new cornerstone in the management of chronic heart failure."[18, 19]

LCZ696, a twice a day pill for heart failure, is a first in class medicine that acts in multiple ways on the neuro-hormonal systems of the heart, blocking receptors exerting harmful effects while simultaneously promoting protective mechanisms,[20,21] known as an ARNI (Angiotensin Receptor Neprilysin Inhibitor). LCZ696 is thought to reduce the strain on the failing heart, promoting the ability of the heart muscle to recover and thus superior in efficacy.

Since 25 years, Angiotensin-converting–enzyme (ACE) inhibitors(Enalpril)have been used as a main player for the pharmacological treatment of heart failure and a reduced ejection fraction, as it had shown to posses diminished risk of death by 16% among patients with mild-to-moderate symptoms. and improved quality of life in two trials on prolonged treatment.[22,23] The effect of angiotensin-receptor blockers (ARBs) on mortality has been inconsistent,[24,4] and thus, these drugs are recommended primarily for patients who have tolerability towards the side effect (primarily cough, and angioedema) on ACE inhibitors. Subsequent studies showed that the use of beta-blockers and mineralo-corticoid-receptor antagonists, when added to ACE inhibitors, resulted in incremental decreases in the risk of death of 30 to 35% and 22 to 30%, respectively.[25-30]

Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin.[31-33] Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling.[29,30] Combined inhibition of the renin–angiotensin system and neprilysin had effects that were superior to those of either approach alone in experimental studies,[34,35] but in clinical trials, the combined inhibition of ACE and neprilysin was associated with serious angioedema.[36,37] LCZ696, which consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan, was designed to minimize the risk of serious angioedema.[38,39] In small trials involving patients who had hypertension or heart failure with a preserved ejection fraction, LCZ696 had hemodynamic and neurohormonal effects that were greater than those of an ARB alone.[40,41]

CONCLUSION

The NP system has been shown to play an important cardiac and renal protective role. As a result it has been hypothesized that enhancing NPs may be beneficial in HF. Neprilysin inhibition enhances NP levels by reducing their enzymatic degradation. However, the utility

of neprilysin inhibition requires management of the activation of the RAAS, which occurs with neprilysin inhibition alone. LCZ696, the first ARNI in clinical development, meets this requirement since the compound enhances the actions of the NP system by inhibiting neprilysin while concurrently suppressing the activity of the RAAS by blocking the angiotensin AT_1 receptor.

Results from the clinical trial program of LCZ696 show that LCZ696 improves hemodynamics and cardiorenal biomarkers. Ongoing studies will determine whether these effects translate to improvements in outcomes of patients with chronic HF with either reduced or preserved LVEF. Additional studies of the NPs and of LCZ696 will be needed to further elucidate the mechanisms of its potential cardiorenal protection and the clinical relevance of the metabolic effects of the NPs.

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