Valsartan / Sacubitril (LCZ696)
Angiotensin receptor neprilysin inhibitor (ARNI)

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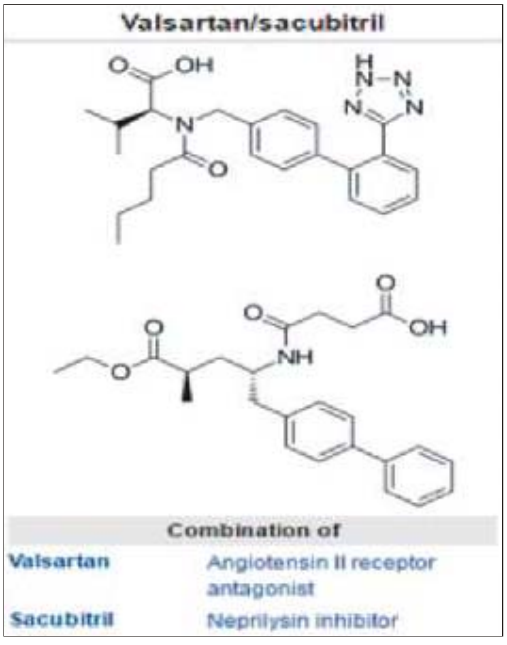
ABSTRACT

Interplay of several endogenous neurohormonal mechanisms like renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, and the natriuretic peptide system play dominant role in pathogenesis of heart failure. This review summarises a novel drug combination of angiotensin receptor blocker valsartan and neprilysin inhibitor Sacubitril, commonly known as angiotensin receptor blocker (ARB) neprilysin inhibitor or ARNI in management of heart failure. Combining ARB and neprilysyn inhibitor is considered as a logical step in management of heart failure.

Valsartan / sacubitril is a combination drug for use in heart failure. It consists of the angiotensin receptor blocker valsartan and the neprilysin inhibitor Sacubitril, in a 1:1 mixture by molecule count. It may be used instead of an ACE inhibitor or an angiotension receptor blocker in people with heart failure with reduced ejection fraction.

Chemistry



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LCZ696 is co-crystallized valsartan and sacubitril, in a one-to-one molar ratio. One LCZ696 complexconsists of six valsartan anions, six sacubitril anions, 18 sodium cations, and 15 molecules of water, resulting in the molecular formula C288H330N36Na18O48·15H2O and a molecular mass of 5748.03 g/mol.The substance is a white powder consisting of thin hexagonal plates. It is stable in solid form as well as in aqueous (watery) solution with a pH of 5 to 7, and has a melting point of about 138 °C (280 °F).

Pharmacology

Mechanism of action :[1,2,3]

Valsartan blocks the angiotensin II receptor type 1 (AT_1). This receptor is found on both vascular smooth muscle cells, and on the zonaglomerulosa cells of the adrenal gland, which are responsible for aldosterone secretion. In the absence of AT_1 blockade, angiotensin causes both direct vasoconstriction and adrenal aldosterone secretion, the aldosterone then acts on the distal tubular cells of the kidney to promote sodium reabsorption which expands extracellular fluid (ECF) volume. Blockade of (AT_1) thus causes blood vessel dilation and reduction of ECF volume.

Sacubitril is a prodrug that is activated to sacubitrilat (LBQ657) by de-ethylation via esterases. Sacubitrilat inhibits the enzyme neprilysin, a neutral endopeptidase that degrades vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Thus, sacubitril increases the levels of these peptides, causing blood

vessel dilation and reduction of ECF volume via sodium excretion.[6] Also combined inhibition will increase levels of Ang 1-7, which has many potential cardiovascular benefits. ***(Fig. 3 and Fig. 4)***

ANGIOTENSIN RECEPTOR BLOCKER NEPRILYSIN INHIBITORS :

Combining an angiotensin receptor blocker (ARB) and a neprilysin inhibitor is a logical step and potential solution to the problem encountered initially with omapatrilat. The angiotensin receptor neprilysin inhibitor (ARNI) sacubitril / valsartan (formerly known as LCZ696) was designed with the aim of inhibiting neprilysin while blocking the adverse effects of RAAS and reducing bradykinin potentiation, which was seen with omapatrilat. As the active metabolite of sacubitril, sacubitrilat (LBQ657), does not inhibit aminopeptidase P, the risk of angio-oedema was expected to be lower than with omapatrilat. Given twice daily, sacubitril / valsartan leads to sustained neprilysin and RAAS inhibition over a 24 h period addressing one limitation of the OVERTURE trial in which omapatrilat was given as a single large dose once daily. That approach may have contributed to the significant early postdose hypotension seen with omapatrilat but did not provide sustained inhibition of ACE and neprilysin over 24 h. The systemic exposure delivered by sacubitril / valsartan 97-mg / 103 mg (200 mg LCZ696) is equivalent to 160 mg of valsartan and neprilysin is almost completely inhibited for up to 12 h.

Metabolism

Sacubitril is converted to active metabolite LBQ657 by esterases; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized (~20%; <10% as a hydroxyl metabolite)

Excretion

Sacubitrilexcreted through Urine (52% to 68%, primarily as LBQ657); feces (37% to 48%, primarily as LBQ657) while Valsartan is excreted through Urine (~13%, parent drug and metabolites); feces (86%, parent drug and metabolites)

Time to Peak

Sacubitril : 0.5 hours; LBQ657 : 2 hours; Valsartan : 1.5 hours

Half-Life Elimination

Sacubitril : 1.4 hours; LBQ657 : 11.5 hours; Valsartan : 9.9 hours

Protein Binding

94% to 97% drug remains protein bound to blood.

Contraindications

Hypersensitivity to sacubitril, valsartan, or any component of the formulation; history of angioedema related to previous ACE inhibitor or ARB therapy; concomitant use or use within 36 hours of ACE inhibitors; concomitant use of aliskiren in patients with diabetes and hypotension are contraindications for its use.

Dosing : Adult

Heart failure : Oral : Patients previously taking >10 mg/day of enalapril or >160 mg/day of valsartan or equivalent dose of another ACE inhibitor or ARB : Initial : Sacubitril 49 mg and valsartan 51 mg twice daily. Double the dose as tolerated after 2 to 4 weeks to the target maintenance dose of sacubitril 97 mg and valsartan 103 mg twice daily. ***Note :*** Concomitant use of an ACE inhibitor is contraindicated; allow a 36 hour washout period when switching from or to an ACE inhibitor.

Patients previously taking low doses of an ACE inhibitor (≤10 mg/day of enalapril or an equivalent dose of another ACE inhibitor) or ARB (≥160 mg/day of valsartan or an equivalent dose of another ARB) : Initialdose : Sacubitril 24 mg and valsartan 26 mg twice daily. Double the dose as tolerated every 2 to 4 weeks to the target maintenance dose of sacubitril 97 mg and valsartan 103 mg twice daily.

Patients **not** currently taking an ACE inhibitor or an ARB : Initial : Sacubitril 24 mg and valsartan 26 mg twice daily. Double the dose as tolerated every 2 to 4 weeks to the target maintenance dose of sacubitril 97 mg and valsartan 103 mg twice daily.

Dosing in Renal Impairment

EGFR ≥ 30 mL / minute / 1.73 m2 : No dosage adjustment necessary.

EGFR < 30 mL / minute / 1.73 m2 : Initial : Sacubitril 24 mg and valsartan 26 mg twice daily

Dosing in Hepatic Impairment

Mild impairment (Child-Pugh class A) : No dosage adjustment necessary.

Moderate impairment (Child-Pugh class B) : Initial : Sacubitril 24 mg and valsartan 26 mg twice daily

Severe impairment (Child-Pugh class C) : Use not recommended (has not been studied).

Administration

Oral: Administer with or without food.

Adverse Reactions[4,5]

About 10% patients have side effects.

Cardiovascular adverse reaction : Hypotension (18%), Orthostatic hypotension (2%).

Endocrine & metabolic adverse reaction : Increased serum potassium (4% to 16%).

Renal adverse reaction : Increased serum creatinine (1% to 16%): Renal failure (5%).

Central nervous system adverse reaction : Dizziness (6%), falling (2%).

Hematologic & oncologic adverse reaction : Decreased hematocrit (≤5%).

Hypersensitivity : Angioedema (black patients : 2%; others : <1%)

Respiratory adverse effects : Cough (9%)

Pregnancy Considerations[6]

[US Boxed Warning]: Drugs that act on the renin-angiotensin system can cause injury and death to the developing fetus. Discontinue as soon as possible once pregnancy is detected.

Monitoring Parameters

Baseline and periodic serum potassium, renal function and blood pressure.

Medical uses :

Valsartan / sacubitril is more useful than ACE inhibitor or an angiotensin receptor blocker in people with heart failure and a reduced left ventricular ejection fraction (LVEF). In those with class 2 or 3 failure who does well with an ACE inhibitor or ARB but still have symptoms, changing to valsartan/sacubitril decreases the risk of death. The drug was approved under the FDA's priority review process.[7]

Novel approach to treat heart failure :

Over activation of Sympathetic nervous system and RAAS is the key in the mortality in heart failure patients. Hence inhibition of these neurohumoural pathways is central to the understanding and treatment of heart failure. Administration of synthetic natriuretic peptides has not improved outcomes in acute HF but modulation of the natriuretic system through inhibition of the enzyme that degrades natriuretic (and other vasoactive) peptides, neprilysin, has proven to be successful. After initial failures with neprilysin inhibition alone or dual neprilysin-angiotensin converting enzyme (ACE) inhibition, the Prospective comparison of angiotensin receptor neprilysin inhibitor (ARNI) with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) trial demonstrated that morbidity and mortality does improve with the angiotensin receptor blocker neprilysin inhibitor sacubitril / valsartan (formerly LCZ696).

Figure 2 : CVS actions of angiotensin (Ang)-(17).

Fig. 2 : Cardiovascular, actions of angiotensin (Ang) - (17). The figure illustrates most of the known cardiovascular actions of Ang-(17). NO indicates nitric oxide; and VSMC, vascular smooth muscle cell.

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