Hypertension

Angiotensin receptor neprilysin inhibitor LCZ696: a novel targeted therapy for arterial hypertension?

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The need for novel antihypertensive therapies represents a continuous challenge. LCZ696 is a first-in-class angiotensin receptor neprilysin inhibitor that has been shown to enhance endogenous natriuretic peptide (NP) actions on neurohormonal activation. This effect seems to be additive to that of the renin–angiotensin–aldosterone system (RAAS) suppression, as impressively suggested in the PARADIGM HF study. LCZ696 has been shown to be effective in reducing blood pressure in several small studies; however, its effectiveness and safety remain to be proved in larger studies. This review summarizes the role of RAAS and NP system in the pathophysiology of hypertension and reviews the current data on the antihypertensive effects of LCZ696.

Keywords

LCZ696 • Neprilysin • Natriuretic peptides • Hypertension • Aortic stiffness

Introduction

Hypertension constitutes a major risk factor for cardiovascular mortality, myocardial infarction, heart failure, stroke, atrial fibrillation, and peripheral arterial disease, with one billion people affected worldwide.1,2 The incidence and prevalence of arterial hypertension are predicted to increase considerably as a result of spreading obesity and ageing population, ultimately leading to 1.5 billion people affected by the year 2025.3 In the absence of other cardiovascular risk factors, an increase of 20 mmHg in systolic blood pressure (SBP) or 10 mmHg in diastolic blood pressure (DBP) doubles the risk of cardiovascular disease.4,5

Despite the recent advances in antihypertensive therapy, the need for new treatments, especially for the management of resistant hypertension, is still present. It has become apparent that the various mechanisms implicated in the pathophysiology of essential hypertension may not always be completely neutralized by the currently available therapies.4 Moreover, suppression of such mechanisms may frequently lead to activation of compensatory pathways and establish escape mechanisms.

Renin–angiotensin–aldosterone system inhibition

In the last 30 years, the introduction of agents capable of inhibiting the renin–angiotensin–aldosterone system (RAAS) brought a major breakthrough in the treatment of arterial hypertension.7 The efficacy of the angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), aldosterone inhibitors, and renin inhibitors rendered the suppression of the RAAS as one of the principal antihypertensive strategies.

The endogenous angiotensin-II (AT-II), which is formed through different paths (escape phenomenon) during RAAS inhibition, explains its actions as a vasoconstrictor and stimulant of aldosterone synthesis.8 AT-II receptor blockers prevent angiotensin’s linkage to angiotensin-I (AT-I) receptors, thus counteracting vasoconstriction, sympathetic activation, oxidative stress, and the release of inflammatory factors and aldosterone.9

The role of natriuretic peptides

The natriuretic peptide system (NPS) is a hormone family that elicits natriuretic, diuretic, vasorelaxant, and anti-mitogenic effects, all of
which are largely directed to the homeostasis of blood volume and blood pressure. The NPs constitute a complex mechanism of three peptides (atrial, brain, and C-NPs). Atrial NP (ANP) is predominantly released in response to atrial distension; brain NP (BNP) is synthesized and secreted by the ventricles, whereas C-NP is predominantly localized in the central nervous system and the endothelium and is considered to be a non-circulatory NP. Production of both ANP and BNP increases in left ventricular overload and hypertrophy, congestive heart failure, and arterial hypertension. In these cases, the ventricle becomes the primary site of synthesis for both peptides, and BNP levels are 10–50-fold higher compared with ANP. BNP has a more potent natriuretic effect and exerts longer duration of action compared with ANP.

The cardiac NPs play an important role in controlling the arterial pressure and intravascular volume through interaction with the ANP receptor, activation of particulate guanylyl cyclase, and enhanced production of 3′,5′ cyclic guanosine monophosphate (cGMP). NPs can inhibit the RAAS and demonstrate anti-fibrotic and anti-hypertrophic effects. Acute administration of ANP has been shown to induce natriuresis, diuresis, and systemic hypotension in mammals. This hypotensive effect is primarily related to a decrease in intravascular volume and is further sustained by an attenuated autonomic reflex response in heart rate and vascular resistance. Moreover, studies in animals with high ANP levels after chronic administration have demonstrated sustained reduction of arterial blood pressure mediated primarily by lower peripheral resistance. These results have been attributed to the negative effects of ANP on the cardiovascular sympathetic tone, resulting in reduced peripheral resistance.

Current evidence supports that NPs are only increased in subjects with stage II hypertension and above. Subjects with stage I hypertension have been shown to have lower levels of mature circulating forms of BNP, such as NT-proBNP1-76 and BNP1–32, compared with normotensives. In a large general population of adults with pre-hypertension and stage I hypertension, it was shown that BNP deficiency is associated with lack of activation of other cardiac NPs, such as ANP, indicating an impaired cardiac endocrine function in the early stages of hypertension.

Angiotensin receptor neprilysin inhibitor

The NP receptor C plays a major role in NP removal by binding, internalization, and subsequent degradation. BP breakdown is also facilitated by extracellular metalloproteinases and the neutral endopeptidase neprilysin (NEP), also known as membrane metalloendopeptidase. NEP catalyses the degradation of numerous other endogenous peptides such as bradykinin, substance P, adrenomedullin, and glucagon, whereas it has also shown to contribute to the breakdown of angiotensin.

The vasodilatory and natriuretic effects of the NPs, combined with the decreasing vasoconstrictor and anti-natriuretic action of the RAAS suppression, represent a solid pathophysiological basis for the treatment of hypertension and especially resistant hypertension.

As such, ‘omapatrilat’ was the first drug of a new family of antihypertensive agents with dual neprilysin-ACE inhibition to be studied. Omapatrilat was proven superior to enalapril in a large-scale clinical trial, at the expense of increased incidence of severe angiooedema. This was attributed to the combined bradykinin enhancement arising from suppression of neprilysin, which normally participates in the degradation of bradykinin, and ACE inhibition, which is another mechanism of bradykinin enhancement.

Angiotensin receptor neprilysin inhibitor LCZ696

The safety issues of vasopeptidase inhibitors moved research towards another combination, that of an NEP inhibitor with concomitant A-II receptor-blocking effects. LCZ696 [Japanese-adopted name (JAN); sacubitril valsartan sodium hydrate] is a novel, first-in-class angiotensin receptor neprilysin inhibitor (ARNI), which consists of the ARB ‘valsartan’ and the NEP inhibitor prodrug ‘Sacubitril (AHU377)’, which in turn is metabolized to the active NEP inhibitor LBQ657 by enzymatic cleavage of its ethyl ester. The molar ratio of AHU377 and valsartan in LCZ696 is that of 1:128.

The pharmacokinetics and pharmacodynamics of LCZ696 were investigated in a single-dose study, in which valsartan and AHU377 were absorbed rapidly, reaching peak plasma concentrations within 1.7–2.2 and 0.5–1.1 h respectively. Conversion of AHU377 to LBQ657 was also rapid, with peak plasma concentrations reached within 1.9–3.5 h after administration of LCZ696. The maximal concentration and area under the curve (AUC) (concentration vs. time curve) of LBQ657 were approximately proportional to the LCZ696 dose. Valsartan demonstrated a maximal concentration and a linear AUC, but this was not proportional to LCZ696 dose. In the multiple-dosing part of the study, peak concentrations of AHU377, LBQ657, and valsartan were rapidly achieved, demonstrating prompt dissociation of LCZ696 and absorption of its components. In addition, comparison of AUC and maximal concentration showed no accumulation of AHU377 or valsartan and minimal accumulation of LBQ657. The bioavailability study demonstrated that systemic exposure to valsartan following 400 mg of LCZ696 was equivalent to the administration of 320 mg of valsartan. Of note, the systemic exposure to valsartan, when administered as a compound of LCZ696, was 40% higher when compared with that of valsartan alone. This could be related to its presence in the ionic form rather than the free acid form in LCZ696. Increased levels of ANP and GMP were the expected result of NEP inhibition. Markers of the RAAS blockade, such as plasma renin activity, renin, and A-II levels, were also elevated; however, RAAS activity was not shown to be further suppressed secondary to NEP inhibition. Finally, in the healthy population of the study, no hypotensive effects were seen, likely due to normal compensatory mechanisms.

LCZ696 was tested against valsartan in a randomized double-blind multicentre study, which included 1328 patients, aged 18–75, with mild-to-moderate hypertension. Patients were assigned to 8 weeks of treatment in one of the eight groups: 100, 200, and 400 mg of LCZ696; 80, 160, and 320 mg of valsartan; 200 mg of AHU377; or placebo. The study investigated three pairwise comparison doses of LCZ696 and valsartan (100 vs. 80, 200 vs. 160, and 400 vs. 320 mg) of equivalent pharmacokinetics and pharmacodynamics. The primary outcome was lowering of mean DBP during the 8-week treatment, whereas secondary outcomes included lowering of mean sitting SBP and change in sitting pulse pressure (PP). Significant reductions were seen with 200 mg LCZ696 vs. 160 mg valsartan [−2.97 mmHg, 95% confidence
interval (CI) −4.88 to −1.07, \( P = 0.0023 \) for mean sitting DBP and −5.28 mmHg, 95% CI −8.28 to −2.28 for mean sitting SBP] and 400 mg LCZ696 vs. 320 mg valsartan (−2.71 mmHg, 95% CI −4.61 to −0.80, \( P = 0.0055 \) for mean sitting DBP and −6.01 mmHg, 95% CI −9.01 to −3.02 for mean sitting SBP). Also 200 mg of AHU377 was superior to placebo only (−2.99 mmHg, \( P = 0.0021 \) for mean sitting DBP and −4.20 mmHg, \( P = 0.0057 \) for mean sitting SBP). Monitoring of ambulatory blood pressure was obtained for 427 patients. Although no differences were seen in mean ambulatory DBP, LCZ696 lowered significantly the mean ambulatory SBP both in the 200 and in the 400 mg cohorts. As a result, similar significant reductions in sitting and ambulatory PPs were demonstrated for 200 and 400 mg of LCZ696.\(^{32}\) A significant increase in plasma ANP and the second messenger of neprilysin cGMP was observed with the two higher doses of LCZ696 and AHU377. Plasma renin concentration increased in both the valsartan and LCZ696 groups. Of note, these neurohormonal increases were dose-independent.\(^{32}\) As commented by the authors of the study, the superiority of 400 mg LCZ696 on both AHU377 and valsartan is indicative of the complementary effects of the dual mechanism of action. Unexpectedly, no correlation of plasma ANP and cGMP with LCZ696 dose and consequently with blood pressure response was observed, although previous studies in healthy individuals have demonstrated such dose-dependent effects.\(^{31,32}\) Likewise, plasma renin concentration was not correlated with blood pressure response; however, similar dissociation has been previously shown with ramipril.\(^{34}\)

In a smaller, 7-day randomized, double-blind, controlled, crossover study in patients over 50 years old, administration of LCZ696 resulted in a constant increase in urinary cGMP which was associated with superior blood pressure control compared with valsartan, without significant increase in natriuresis and diuresis.\(^{35}\) In another randomized, double-blind, placebo-controlled study, LCZ696 proved to be effective in reducing clinic SBP and PP, with also significant reduction in daytime and nighttime ambulatory blood pressures.\(^{36}\) Pooled results of a double-blind trial comprising 848 patients, the majority of whom were obese or overweight, showed that LCZ696 was more effective compared with valsartan in lowering 24 h ambulatory blood pressure, PP, and office SBP and DBP.\(^ {33}\)

The results of a double-blind multicentre clinical trial involving 266 Asian patients with systolic hypertension not controlled by amlodipine were recently presented.\(^ {36}\) A reduction of 13.9 mmHg in mean 24 h ambulatory SBP in the LCZ696, compared with 0.8 mmHg in the amlodipine arm, supports the effectiveness of LCZ696 on both the RAAS and sympathetic nervous system. LCZ696 has been shown to be safe and effective in Asian patients with severe hypertension\(^ {37}\) and has demonstrated superiority against valsartan in hypertensive patients over the age of 65.\(^ {38}\)

Although the abovementioned trials are not particularly large, it is of interest that LCZ696 appears to have potent antihypertensive effects in a variety of hypertensive populations with no observed cases of angioedema or other serious side effects.

However, the most solid evidence of the therapeutic potential of LCZ696 comes from the recent PARADIGM HF study.\(^ {39}\)
In PARADIGM HF, 10,521 patients with symptomatic heart failure (New York Heart Association II–IV) and impaired left ventricular (LV) function (ejection fraction <35%) were randomized to LCZ696 or enalapril for 3 years. Patients had to be on an ACEI or an ARB at a stable dose of at least enalapril 10 mg/day or equivalent for at least 4 weeks and treated with a β-blocker, unless contraindicated, for at least 4 weeks. Patients were randomized in a 1:1 ratio to double-blind treatment with either enalapril 10 mg b.i.d. or LCZ696 200 mg b.i.d. The study showed that LCZ696 was superior to enalapril in reducing death from cardiovascular causes and hospitalization for heart failure (hazard ratio in the LCZ696 group 0.80; 95% CI 0.73–0.87; P < 0.001). The study was prematurely terminated in view of the early demonstrated superiority of LCZ696. LCZ696 demonstrated fewer side effects in comparison to enalapril.

Effects of dual inhibition on central blood pressure
Arterial stiffness has a central role in the pathogenesis of arterial hypertension, and aortic pulse wave velocity is an established predictor of adverse outcomes in a variety of populations.\textsuperscript{40–44} Stiffening of the conduit vessel increases the amplitude of the pressure wave produced by the flow in the central aorta, resulting in high propagation velocity of the pressure waves, resulting in increased central SBP and LV pressure load due to earlier return of the reflected pressure waves to the aorta.\textsuperscript{45,46} A-II demonstrates vasoconstrictive, hypertrophic, and pro-fibrotic effects on the vessel wall.\textsuperscript{47} ACE inhibition enhanced by the vasodilating, anti-fibrotic, and antimitogenic properties of NPs through NEP inhibition appears to be an appealing target towards an effective therapy.\textsuperscript{48} In fact, omapatrilat has been shown to be superior to enalapril in reducing both peripheral and central PPs, which is considered a predictor of increased conduit vessel stiffness and cardiovascular events in hypertensive subjects.\textsuperscript{49} The effects of LCZ696 on central blood pressure and arterial stiffness in comparison to olmesartan are currently being studied in the randomized control trial PARAMETER,\textsuperscript{50} the results of which are expected in 2015.

Current therapeutic dilemmas
Although LCZ696 has been proved to be an effective antihypertensive agent without increasing the risk for angioedema, more data are required with regard to its safety in angioedema-prone populations such as the Afro-Caribbeans. Concerns have also been raised with regard to its pleiotropic actions and more specifically the effects of nephrin in lipid metabolism and the pathogenesis of Alzheimer. NPs enhance triacylglycerol breakdown in adipocytes and release non-esterified fatty acids by fat cells, resulting in the enhancement of fatty acid uptake by the heart and skeletal muscles and increase in oxidative capacity and energy coupling.\textsuperscript{55} Through these actions, they can provide energetic substrate to the heart and augment the sensitivity to insulin. In contrast, lipid mobilization and fat oxidation in skeletal muscles can result in pronounced cachexia, which is frequently observed in patients with heart failure.

Serious concerns have been raised regarding the role of NEPs in the development of Alzheimer’s disease. Nephrin is one of the enzymes involved in the degradation of amyloid β-peptide (Aβ), and therefore NEPs can result in the accumulation of the Aβ peptide in the brain.\textsuperscript{52–54} However, the extent to which LCZ696 crosses the blood–brain barrier is not yet fully understood. On the contrary, the authors of the PARADIGM HF trial argue that improving cardiac and vascular function could have a net benefit for cognitive function.\textsuperscript{59} Furthermore, they suggest that the life expectancy of most patients with heart failure would not allow long-term adverse effects due to Aβ peptide accumulation in the central nervous system. However, this potential side effect becomes more relevant in hypertensive patients, given the need for long-term treatment. Therefore, more studies are required in order to evaluate the risk of development Alzheimer’s disease and provide clear evidence on its impact on morbidity and mortality in patients treated with LCZ696.

Although LCZ696 appears to be a promising future therapy for hypertension, long-term results on its superiority against ACEIs and ARBs is required. The striking results of PARADIGM could be difficult to link to the hypertensive population, as neurohormonal activation is much more important in determining long-term prognosis in heart failure, compared with hypertension.\textsuperscript{55}

Conclusions
Although far from being a causative therapy, enhancement of the NP system is a hopeful approach to treatment of hypertension at any stage. Its antihypertensive action seems to be additive to that of the RAAS inhibitors and could have a positive impact on mortality. However, LCZ 696 needs to be evaluated in large randomized trials of appropriate duration in order to assess long-term outcomes in various hypertensive populations.

Conflict of interest: none declared.

References
