Treatment with LCZ696 is likely to change first-line treatment of heart failure

LCZ696 – a promising new compound in heart failure treatment

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Summary

LCZ696 is an angiotensin receptor neprilysin inhibitor (ARNI) composed of the angiotensin receptor inhibitor valsartan and the neprilysin inhibitor AHU377. This compound molecule has proven efficiency in mild to moderate arterial hypertension and in heart failure patients with preserved ejection fraction, and has been shown to be superior to enalapril treatment in patients presenting with moderate to severe heart failure due to reduced left ventricular ejection fraction. The present overview will summarise pathophysiological and pharmacological aspects of this compound molecule, discuss results from clinical studies, and provide an outlook on the future role of this molecule in heart failure treatment.

Key words: LCZ696; chronic heart failure

Current treatment of heart failure with reduced ejection fraction

This section summarises current concepts of medical treatment in heart failure with reduced ejection fraction and provides the basis for discussion of the role of LCZ696.

The modern history of therapy for heart failure with reduced ejection fraction began in 1986 when the V-HeFT trial showed the favourable effect of vasodilation treatment [5]. In the following years, the CONSENSUS (1987) and SOLVD-treatment (1991) trials established the beneficial effect of angiotensin-converting enzyme (ACE) inhibition by enalapril by showing that this molecule reduces the absolute risk for mortality by 14.6% in severe heart failure and 4.5% in mild to moderate heart failure (number of patients needed to treat [NNT] to save one life 7 and 22, respectively) [2, 3]. In 1992, the SOLVD-prevention trial extended the benefit of enalapril treatment to asymptomatic patients with reduced left ventricular ejection fraction by evidencing a reduced rate for heart-failure-associated hospitalisation [4]. Angiotensin receptor blockers (ARBs) provide an alternative strategy for vasodilation in heart failure (fig. 1). These molecules interfere with the binding of angiotensin II at its type 1 receptor, whereas ACE inhibitors block conversion of angiotensin I to angiotensin II (see fig. 1). So far, ARBs remain recommended as alternative therapy in patients intolerant of an ACE inhibitor [5]. However, noninferiority of ARBs to ACE inhibition is apparent only with high-dose treatment [6]. Until the advent of the results of the EMPHASIS-HF trial, ARBs were considered to be the recommended first-choice add-on therapy in patients with heart failure and a left ventricular ejection fraction (EF) ≤49% and who remained symptomatic despite optimal treatment with an ACE inhibitor and beta-blocker. In the EMPHASIS-HF trial, however [7], eplerenone led to a larger reduction in the morbidity and mortality endpoint than was seen in the ARB “add-on” trials CHARm Added and Val-HeFT [8, 9]. Furthermore, mineralocorticoid-receptor antagonist (MRA) treatment reduced all-cause mortality both in EMPHASIS-HF (NNT: 51) and in the Randomized Aldactone Evaluation Study (RALES) (NNT for 2 years: 9) whereas ARB “add-on” treatment does not [4]. The other cornerstone of treatment in heart failure with reduced ejection fraction is down-regulation of increased sympathetic nervous system activity. Three key trials [10–12] randomised nearly 9,000 patients with mildly to severely symptomatic heart failure to placebo or beta-blocker treatment (bisoprolol, carvedilol, or metoprolol succinate CR/XL). Each of these three trials showed that, within 1 year of treatment start beta-blocker therapy reduces both mortality (NNT to save 1 life: 14–23) and the rate of heart failure hospitalisation when added to conventional therapy including ACE inhibition in >90% of the study patients. In addition, beta-blocker treatment improves self-reported patient well-being as shown in the MERIT-HF [13].

Natriuretic peptides and the renin-angiotensin system

Atrial and B-type natriuretic peptides (ANP, BNP) are hormones that play an important role in fluid homeostasis. Both peptides are secreted in response to an increase in wall tension, with ANP predominantly...
synthesised and secreted in the atria whereas BNP is released from the ventricles. Both natriuretic peptides promote natriuresis and diuresis, induce vasodilation, and oppose acute effects of volume overload by inhibition of the renin-angiotensin-aldosterone system and the sympathetic nervous system (fig. 2). Because of these effects, the natriuretic peptide system has been a target of potential therapeutic strategy in heart failure. Since results from trials investigating the effect of exogenous administration of natriuretic peptides in heart failure are inconsistent, pharmacological inhibition of natriuretic peptide degradation has been a focus of clinical research in recent years.

Nephrilysin is a neutral endopeptidase that catalyses the degradation of ANP and BNP. The AHU377 moiety of LCZ696 targets nephrilysin and interferes with the catalytic breakdown of ANP and BNP. However, inhibition of nephrilysin will not only augment the naturally occurring natriuretic peptides but also increase the levels of circulating bradykinin, substance P, adrenomedullin, endothelin and angiotensin II. The latter is a potent vasoconstrictor which provides the rationale for a compound molecule with dual action, on nephrilysin as well as the renin-angiotensin system. In any case, nephrilysin plays no role in the breakdown of the N-terminal of proBNP (NT-proBNP), therefore NT-proBNP levels remain representative for the amount of secreted pro-BNP (fig. 2).

Omapatrilat was the first molecule simultaneously acting both on the renin-angiotensin and the natriuretic peptide system by blocking enzymatic activity of the angiotensin-converting enzyme and of the vasopeptidases nephrilysin and aminopeptidase. This compound drug made it into clinical trials because of superior effects in experimental studies to either approach alone [14, 15]. Beneficial effects were present in patients with hypertension [16], and in initial studies in patients with heart failure [17]. However, an outcomes trial comparing omapatrilat 40 mg with enalapril 10 mg twice per day did not demonstrate benefit from omapatrilat in reducing the combined risk of death or hospitalisation in patients with moderate to severe heart failure [18]. In addition, the 0.8% incidence of angioedema in the heart failure outcome trial prompted withdrawal of omapatrilat from regulatory consideration. In fact, all three enzymes targeted by omapatrilat are involved in the inactivation of bradykinin, which is considered as the predominant mediator of angioedema [19].

LCZ696 is the first molecule of new class of compound molecules blocking simultaneously the renin–angiotensin system via its ARB (valsartan) moiety and slowing the degradation of natriuretic peptides via its AHU377 moiety that interferes with the vasoepetidase nephrilysin. Because of this dual action this new class of pharmacological agents is called angiotensin receptor nephrilysin inhibitors (ARNIs). After ingestion, LCZ696 is broken into two components, the nephrilysin prodrug AHU377 and valsartan (fig. 2), and AHU377 is subsequently metabo-
Clinical studies with LCZ696

Mild to moderate arterial hypertension

In mild to moderate hypertension, LCZ696 with its dual action leads to more efficient lowering of diastolic blood pressure in patients with mild to moderate arterial hypertension when compared with an equivalent dose of valsartan [20]. The average reduction in mean sitting diastolic blood pressure was −2.97 mm Hg (p = 0.0023) for 200 mg LCZ696 versus 160 mg valsartan, and −2.7 mm Hg (p = 0.0055) for 400 mg LCZ696 versus 320 mg valsartan. LCZ696 was well tolerated in this study and no cases of angioedema were reported; only three serious adverse events occurred during the 8-week treatment period, of which none was related to the study drug, and no patients died.

PARAMOUNT

PARAMOUNT was a phase II, randomised, parallel-group, double-blind multicentre trial in heart failure patients with preserved left ventricular ejection fraction (≥45%), in New York Heart Association (NYHA) class II–III and with a NT-proBNP concentration of ≤400 pg/ml [21]. Participants were randomly assigned (1:1) to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily; treatment duration was 36 weeks. The primary endpoint was change in left ventricular wall stress measured as NT-proBNP level at baseline and 12 weeks. NT-proBNP was significantly reduced at 12 weeks in the LCZ696 group compared with the valsartan group. After 36 weeks of treatment, there was likewise a significant reduction in the left atrial volume (p = 0.003) and in left atrial dimension (p = 0.034) in the LCZ696 group, with the most apparent reduction present in patients without atrial fibrillation at baseline. LCZ696 was well tolerated with adverse effects similar to those of valsartan; 22 patients (15%) on LCZ696 and 30 (20%) on valsartan (p = 0.14) had one or more serious adverse events. Whether the reduction in left ventricular wall stress and the structural changes translate into improved outcomes will be tested prospectively in the PARAGON study, which is starting enrolment in autumn 2014.
Future role of LCZ696

In the PARADIGM-HF trial, the mean (± standard deviation) doses in the LCZ696 and enalapril groups were 375 ± 71 mg and 18.9 ± 3.4 mg, respectively, with the latter dose being above the dose shown to reduce mortality in severe and mild to moderate heart failure (16.6 mg and 18.4 mg, respectively, for CONSENSUS, and SOLVD). LCZ696 was superior to enalapril in reducing the primary endpoint and the secondary endpoint of cardiovascular death; therefore, LCZ696 has the potential to replace ACE inhibitor treatment as first-line treatment in heart failure, all the more so as many patients with heart failure receive low (and potentially subtherapeutic) doses of ACE inhibitors and ARBs [24].

Prespecified subgroup analysis in the PARADIGM-HF showed a nominally significant interaction between NYHA class at randomisation and the effect on the primary endpoint (p = 0.03). However, no such interaction was observed between NYHA class and the secondary endpoint death from cardiovascular cause (p = 0.76). Separation of NYHA classes into patients with NYHA I/II and III/IV, suggests favourable interaction of LCZ696 with NYHA class I/II patients for the primary and secondary endpoint, whereas no interaction was obvious for patients in NYHA class III and IV. The absence of a significant interaction of LCZ696 with severe heart failure resembles results from clinical trials in which exogenous natriuretic peptides were administered [25] and requires further investigation. There was also no interaction between enalapril treatment and NYHA class III and IV with respect to the primary endpoint and cardiovascular death, despite of a strong and consistent interaction of this ACE inhibitor with mortality in the CONSENSUS trial and many other ACE inhibitor trials performed in patients with heart failure [26]. It remains to be shown whether this observation is due to contemporary heart failure treatment with a beta-blocker (292.9%) and treatment with mineralcorticoid receptor antagonist (254%). It is important to note that a total 12% of patients did not complete the run-in period because of adverse events (most frequently cough, hyperkalaemia, renal dysfunction or hypotension). Overall, the incidence of adverse events was higher for patients receiving enalapril than for those receiving LCZ696 (table 1). Altogether, the safety profile suggests that LCZ696 administration should be applicable to a broad spectrum of patients with heart failure, including those who are currently taking an ACE inhibitor or ARB, or who are likely to be able to take such an agent without having unaccepted side effects.

## Conclusion

Heart failure affects nearly 150,000 individuals in Switzerland, and its prevalence is increasing progressively owing to an aging population. Current heart failure treatment has already achieved large improvement in the reduction of morbidity and mortality. Based on the results of the PARADIGM-HF study, treatment with LCZ696 is likely to change first-line treatment of heart failure because of significant improvement of survival and reduced rehospitalisation rates. Nevertheless, even in the intervention arm of PARADIGM-HF, the mortality rate among patients with heart failure remains about 20% over 2 years, highlighting the reality that this newest entry hardly concludes the compelling story of heart-failure treatment.

## Disclosures

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## References

The full reference list is available in the on-line version of this article.

### Table 1: Adverse events during randomized treatment comparing study groups from the ONTARGET and the PARADIGM-HF trial.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ONTARGET</th>
<th>ONTARGET</th>
<th>PARADIGM-HF</th>
<th>PARADIGM-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ramipril</td>
<td>Telmisarten</td>
<td>LCZ696</td>
<td>Enalapril</td>
</tr>
<tr>
<td>Discontinuation (n, %)</td>
<td>(n = 8,576)</td>
<td>(n = 8,542)</td>
<td>(n = 4,187)</td>
<td>(n = 4,212)</td>
</tr>
<tr>
<td>Hypotension (n, %)</td>
<td>2,099 (24.5%)</td>
<td>1,962 (23%)</td>
<td>977 (23.3%)</td>
<td>1,094 (26%)</td>
</tr>
<tr>
<td>Cough (n, %)</td>
<td>149 (1.7%)</td>
<td>229 (2.7%)</td>
<td>760 (16.7%)</td>
<td>447 (10.6%)</td>
</tr>
<tr>
<td>Angioedema (n, %)</td>
<td>360 (4.2%)</td>
<td>93 (1.1%)</td>
<td>474 (11.3%)</td>
<td>601 (14.3%)</td>
</tr>
<tr>
<td>Hyperkalaemia (n, %)</td>
<td>283 (3.2%)</td>
<td>287 (3.4%)</td>
<td>855 (20.4%)</td>
<td>960 (22.9%)</td>
</tr>
</tbody>
</table>
REFERENCES

Online appendix


4 McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Boehm M, Dickstein K, et al. The Task Force for the Diagnosis and Treatment of Acute and Chronic HF 2012 of the European Society of Cardiology. Developed in collaboration with the HF Association (HFA) of the ESC. Eur Heart J. 2012;33:1787–1847.


