Lcz696 an Innovation for Heart Failure

COMMENTARY

Abstract

Heart failure (HF) is a crescent, solemn and multiple etiology worldwide health problem, which, besides potentially fatal, decreases the life quality of the affected people, mainly the elderly. Despite having obtained drugs that help in the disease development control, have been sought new alternatives for better management of these individuals. The LCZ696, a neprilysin inhibitor (sacubitril) associated with an ARB (valsartan) has shown significant improvements in patients' morbidity and mortality, which puts it as a good and interesting option for the treatment of heart failure.

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Heart failure (HF) is a global health problem with an estimated prevalence of over 5.8 million in the USA and over 23 million worldwide [1]. It represents the most common cause of hospitalization in elderly patients (≥ 65 years) and its incidence has a growing trend mainly due to the aging of the population [2, 3]. Although heart failure increases the risk of death, nonfatal worsening of symptoms is the most common problem encountered by patients, who experience progressive impairment of functional capacity and quality of life [4, 5]. The important advances in the treatment of HF accomplished over the past decades in terms of drug and device therapy have resulted in a significant improvement in the prognosis in patients with chronic HF [6, 7].

Chronic heart failure is associated with a complex pattern of neurohormonal activation that contributes to the relentless progression of this fatal syndrome [8, 9]. The activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) cause cardiac remodeling, leading to progressive cardiac dilatation and to dysfunction of the failing heart [10].

The activation of detrimental neurohormonal pathways contributes to the clinical progression of heart failure [8]. Several peptides (ie, natriuretic peptides, bradykinin, and adrenomedullin) can attenuate vasoconstriction and sodium retention, and retard cardiac and vascular hypertrophy and remodeling, and thus act to ameliorate many of the pathophysiological abnormalities of heart failure [5, 11-13]. Biologically active NPs are degraded by the enzyme neutral endopeptidase or neprilysin; consequently, neprilysin inhibition represents an important pharmacological approach to augment the salutary actions of NPs [14-16].

Simultaneous blockade of RAAS and neprilysin through dual-acting ACE and NEPi (vasopeptidase inhibitors) has been evaluated a decade ago, but further development was halted because of increased rates of angioedema, presumably caused by accumulation of bradykinin in at-risk patients [16-18].

LCZ696, which consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan, was designed to minimize the risk of serious angioedema [19-21], is a single molecule entity consisting of 2 molecular moieties in a 1:1 molar ratio of valsartan, an ARB (angiotensin receptor blockers), and the NEP (neutral endopeptidase) inhibitor prodrug AHU377 [22-23].

In August of 2014, the New England Journal of Medicine published the Prospective Comparison of angiotensin receptor-neprilysin inhibitor (ARNI) with angiotensin-converting-enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study, which compared the combination of an ARB þ neprilysin (LCZ696) head-to-head against an ACEI (enalapril) [21, 23].

The magnitude of these advantages of LCZ696 over ACE inhibition was highly significant and clinically important, particularly since the drug was compared with a dose of enalapril that has been shown to reduce mortality, as compared with placebo [21, 24, 25].

The 20% reduction in cardiovascular deaths with LCZ696 relative to enalapril seen during the trial was attributable primarily to reductions in the incidence of both sudden death and death due to progressive heart failure. There was no discernible impact of LCZ696 relative to enalapril on the incidence of non-cardiovascular death [26].

Because of its greater vasodilator effects, treatment with LCZ696 was associated with a higher rate of symptomatic hypotension, but there was no increase in the rate of discontinuation because of possible hypotension-related adverse effects [21].

The precise mechanism by which LCZ696 influences cardiovascular mortality is uncertain, and requires further study. Understanding the precise mechanism of benefit of LCZ696 in heart failure may provide important insights into the pathophysiology of heart failure and should be a priority for future study [26].

The Heart Failure has great worldwide impact, directly affecting the morbidity and mortality of the population, especially in the elderly. Understanding complex mechanism that generates Heart Failure in the body and act as new drugs, in particular LCZ696, currently known as the Association of Valsartan/Sacubitril, is essential for the treatment we optimize and improve the quality of life of the patients. With the recent publication of a large trial, the efficacy of LCZ696 compared to enalapril, a drug already established in the treatment of Heart Failure, was clear and encouraging, and led to the beginning of a new perspective in the treatment of this pathology. New research should arise and probably elucidate possible remaining doubt, and probably confirmed the real effect of LCZ696 concretely.

References

1. Bui A., Horwich T., Fonarow G. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol*, 2001, 8, 30-41.
2. Hunt S., Abraham W., Chin M. Focused update incorporated into the ACC/AHA 2005 Guidelines for the diagnosis and management of heart failure in adults. *Circulation*, 2009, 119, e391-e479.
3. Kaplinsky, E. PARADIGM-HF trial: will LCZ696 change the current treatment of systolic heart failure? *Journal of Geriatric Cardiology*, 2015, 12, 470-473.
4. Butler J., Braunwald E., Gheorghiade, M. Recognizing worsening chronic heart failure as an entity and an end point in clinical trials. *JAMA*, 2014, 312, 789-790.
5. Packer, McMurray, JV., S. Desai., Gong., Lefkowitz, MP., Rizkala, AR., Rouleau, JL., Shi, VC., Solomon, SD., Swedberg., Zile., Andersen., Arango, JL. Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure. *Circulation*, 2015.
6. McMurray J., Adamopoulos S., Anker S., Auricchio A., Böhm M., Dickstein K. Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J.*, 2012, 33, 1787-847.
7. Filippatos, G., Farmakis, D., Parissis., Lekakis. (2015) Drug therapy for patients with systolic heart failure after the PARADIGM-HF trial: in need of a new paradigm of LCZ696 implementation in clinical practice. *BMC Medicine*, 2015, 13(35).
8. M, P. Evolution of the neuro hormonal hypothesis to explain the progression of chronic heart failure. *Eur Heart J.*, 1995, 16, 4-6.
9. K, S. Importance of neuroendocrine activation in chronic heart failure. Impact on treatment strategies. *Eur J Heart Fail*, 2000, 2, 229-233.
10. Macdonald, P. S. Combined Angiotensin Receptor/Neprilysin Inhibitors: A Review of the New Paradigm in the Management of Chronic Heart Failure. *Clinical Therapeutics*, 2015, 37(10).
11. Cataliotti A., Tonne J., Bellavia D., Martin, F., Oehler E., Harders, G., Campbell J., Peng K., Russell S., Malatino L., Burnett JJ., Ikeda Y. Long-term cardiac pro-B-type natriuretic peptide gene delivery prevents the development of hypertensive heart disease in spontaneously hypertensive rats. *Circulation*, 2011, 123, 1297-1305.
12. Tondangu, D., Hittinger L., Ghaleh, B., Le Corvoisier P., Sambin, L., Champagne S., Badoual T., Vincent F., Berdeaux A., Crozatier B., Su J. Chronic infusion of bradykinin delays the progression of heart failure and preserves vascular endothelium-mediated vasodilation in conscious dogs. *Circulation*, 2004, 109, 114-119.
13. Nakamura, R., Kato J., Kitamura K., Onitsuka H., Imamura T., Cao Y., Marutsuka, K., Asada, Y., Kangawa K., Eto, T. Adrenomedullin administration immediately after myocardial infarction ameliorates progression of heart failure in rats. *Circulation*, 2004, 110, 426-431.
14. Ando S., Rahman M., Butler G., Senn B., Floras, J. Comparison of candoxatril and atrial natriuretic factor in healthy men. Effects on hemodynamics, sympathetic activity, heart rate variability, and endothelin. *Hypertension*, 1995, 26(6), 1160-1166.
15. von Lueder T., Atar D., Krum H. Current role of neprilysin inhibitors in *Hypertension* and heart failure. *Pharmacol Ther*, 2014, 144, 41-49.
16. von Lueder, TG., Wang, BH., Kompa, AR., Huang., Webb., Jordaan., Atar., Krum. (2015) Angiotensin Receptor Neprilysin Inhibitor LCZ696 Attenuates Cardiac Remodeling and Dysfunction After Myocardial Infarction by Reducing Cardiac Fibrosis and Hypertrophy. *Circ Heart Fail*, 2015.
17. Kostis, J., Packer M., Black H., Schmieder R., Henry D., Levy E. (2004) Omapatrilat and enalapril in patients with *Hypertension*: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens*, 2004, 17, 103-111.
18. Packer M., Califf, R., Konstam M., Krum H., McMurray, J., Rouleau, J., Swedberg, K.*/Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation*, 2002, 106, 920-926.
19. Gu J., Noe A., Chandra P. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). *J Clin Pharmacol*, 2010, 50, 401-414.
20. Hegde L., Yu C., Renner T. Concomitant angiotensin AT1 receptor antagonism and neprilysin inhibition produces omapatrilat-like antihypertensive effects without promoting tracheal plasma extravasation in the rat. *J Cardiovasc Pharmacol*, 2011, 57, 495-504.
21. McMurray, JJV., Packer., Desai, AS., Gong., Lefkowitz, MP., Rizkala, AR., Rouleau, JL., Shi, VC., Solomon, SD., Swedberg., Zile, MR. Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure. *The new england journal of medicine*, 2014.
22. Gu, J., Noe, A., Chandra P. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor neprilysin inhibitor (ARNi). *J Clin Pharmacol*, 2010, 50(4), 401-414.
23. Pham, AQ., Patel., Gallagher. LCZ696 (Angiotensin-Neprilysin Inhibition): The New Kid on the Heart Failure Block? *Journal of Pharmacy Practice*, 2015, 28(2), 137-145.

24. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*, 1987, 316, 1429-35.
25. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*, 1991, 325, 293-302.
26. Desai, AS., McMurray, JJV., Pack., Swedberg., Rouleau, JL., Chen., Gong., Rizkala, AR., Brahim., Claggett., Finn, PV., Hartley, LH., Liu., Lefkowitz., Shi., Zile, MR., Solomon, SD. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *European Heart Journal*, 2015, 36, 1990-1997.

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