Recommendation for the Management of Chronic Heart Failure with Reduced Ejection Fraction (HFrEF)

Commentary

Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. HF is divided as HF with preserved EF (HFpEF) and HF with reduced EF (HFrEF). HFrEF is defined as the clinical diagnosis of HF and EF ≤40%, and HFrEF criteria include as a) clinical signs or symptoms of HF; b) evidence of preserved or normal LV diastolic function that can be determined by Doppler echocardiography or cardiac catheterization. According to the exercise capacity and the symptomatic status of HF, the New York Heart Association (NYHA) functional classification is used. Angiotensin converting enzyme inhibitor (ACE) and ß blocker and aldosterone antagonist have been a gold standard for treating chronic heart failure. ACEi/ARB and ß blocker and aldosterone antagonist have been a gold standard for treating chronic heart failure. PARADIGM-HF trial has shown not only the significant clinical efficacy, but also a good safety. Adverse reactions included hypertension (14% in the LCZ696 group vs. 9.2% in the enalapril group (p<0.001)), nonserious angioedema (0.2% vs. 0.1%), renal impairment (3.3% vs. 4.5%), p<0.007), hyperkalemia (11.3% vs. 17.3%), and cough (11.5% vs. 13.4%, p<0.001).

The clinical significance of PARADIGM-HF trial

For nearly 25 years, ACEi has been a cornerstone for treating HF. Long-term treatment with enalapril decreased the relative risk
of death by 16% (95% CI 5%-26%; NNT 22) among patients with mild-to-moderate symptoms [2]. The use of beta-blockers and mineralocorticoid-receptor antagonists, when added to ACEIs, resulted in incremental decreases in the risk of death of 34% (95% CI 19%-47%; NNT 26) and 30% (95% CI 18%-40%; NNT 9), respectively [3,4]. The guidelines in many countries put ACEI/ARB and beta-blocker and mineralo-corticoid receptor antagonists as golden standard for the treatment of EFHF. Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin counters the neurohormonal over-activation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling. LCZ696, which consists of the neprilysin inhibitor prodrug sacubitril (AHU377) which is converted enzymatically to the active neprilysin inhibitor LBQ657, and valsartan, decline in renal function (risk ratio 0.68, 95% CI 0.51-0.92, p=0.01) that contributes to vasoconstriction, sodium retention, and adaptive actions of atrial natriuretic peptide (ANP). The magnitude of the benefit of LCZ696 over ACEi was highly significant and up to 20% on the base of ACEi 16% benefit and LCZ696 had a good safety. The recent meta-analysis showed that combined with ACEi or ARB alone, combined NEP-RAAS inhibition resulted in a reduction in risk of decline in renal function (risk ratio 0.68, 95% CI 0.51-0.92, p=0.01) [5]. Therefore, dual inhibition of the renin-angiotensin-aldosterone system and neprilysin inhibition represent a novel approach to treating patients with HF. We maybe predict that the results of more clinical trials will challenge the standard treatment on HFrEF at present. LCZ696 could replace ACEi and ARBs as first-line therapy in the treatment of patients with HFrEF [6].

The Future

Given that PARADIGM-HF’s encouraging results, how the next researches are? First of all, the effect of LCZ696 on in patients with chronic heart failure with preserved ejection fraction (HFpEF) [7]. The PARAMOUNT study served as a hypothesis-generating trial for HFrEF. PARAMOUNT trial showed that comparing with the valsartan group, LCZ696 significantly reduced NT-proBNP (605 pg/ml vs 835 pg/ml, p=0.005) at 12 weeks. At present the large scale PARAGON (Prospective Comparison of LCZ696 with ARB Global Outcome in HF with Preserved Ejection Fraction) trial (NCT01920711) has begun. Second, aortic stiffness- in the Strong Heart study, central systolic pressure was a predictor of left ventricular hypertrophy, whereas pulse pressure was a predictor of vascular hypertrophy [8,9]. The evidence showed that LCZ696 reduced both ambulatory systolic and pulse pressures more than did valsartan. So, the PARAMETER (Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker Measuring arterial stiffness in the Elderly) study (NCT01692301) is comparing LCZ696 with olmesartan in elderly hypertensive patients with a pulse pressure > 60 mm Hg. The endpoints are changes in central aortic systolic and pulse pressures determined noninvasively. Third, renal disease- the evidence shows that RAAS inhibitor slows progression in patients with chronic kidney disease, with and without diabetes. There is being tested prospectively in the UKHARP (UK Heart and Renal Protection) trial, which is comparing LCZ696 with irbesartan in the efficacy and safety, in patients with proteinuric renal disease and an estimated glomerular filtration rate (eGFR) 20-60 ml/min/1.73 m2. LCZ696 is also promising for the treatment of serious and/or resistant hypertension.

Conclusion

In conclusions, the PARADIGM-HF study has an important clinical significance and would change the pattern of HF treatment in the future. LCZ696 may replace conventional RAAS inhibitors in many patients with chronic HFpEF in our clinical practice. The potential value of LCZ696 in HFrEF, in acute HF, in HF patients with the cardio renal syndrome, in the prevention of HF in asymptomatic patients with left ventricular hypertrophy, dilation, and/or dysfunction and in severe hypertension remains to be determined. ARNi will show a vast clinical prospect.

References

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