HYPERTENSION

LCZ696, a novel dual inhibitor of neprilysin and the angiotensin II receptor, shows promise in phase II trial

The dual-action agent LCZ696 blocks the angiotensin II receptor (via a valsartan moiety) and inhibits neprilysin (via an AHU377 moiety). In a phase II trial, this drug “demonstrated superior [blood pressure]-lowering efficacy as compared to [valsartan] in patients with hypertension,” says Luis Ruilope, the study’s principal investigator. “These study results demonstrate the potential for managing cardiovascular diseases through enhancement of the beneficial effects of the body’s own natriuretic peptides,” he continues.

Inhibition of neprilysin results in increased concentrations of natriuretic peptides, which inhibit the activity of the renin–angiotensin–aldosterone system and have potent natriuretic and vasodilating properties. Increased plasma levels of these compounds might confer cardiovascular and renal protection in patients with hypertension. Unfortunately, however, inhibition of this enzyme alone does not seem to decrease blood pressure, perhaps because neprilysin degrades vasoconstricting peptides such as angiotensin II.

Omapatrilat, a vasopeptidase inhibitor that inhibits both neprilysin and angiotensin-converting enzyme (ACE), reduces blood pressure to a greater extent than either single-action ACE inhibitors or calcium-channel blockers. Treatment with omapatrilat is associated with an increased incidence of angioedema, however, probably because the three enzymes the drug inhibits (ACE, aminopeptidase P and neprilysin) are involved in the breakdown of bradykinin, a peptide described by Ruilope *et al.* as “the putative mediator of angioedema induced by ACE inhibitors”.

LCZ696 was designed to overcome the problem of angioedema. “Drugs that concurrently inhibit neprilysin and block angiotensin II receptors could offer the cardioprotective benefits of vasopeptidase

inhibitors without [an] increased risk of angioedema,” write the researchers.

Ruilope and colleagues conducted a randomized, double-blind, placebo-controlled study to compare the effectiveness and safety of LCZ696 with that of valsartan in the reduction of blood pressure. The participants were 1,328 patients with uncomplicated mild to moderate essential hypertension (mean sitting diastolic blood pressure 90–109 mmHg at baseline). After a 2-week washout period and a 2-week, single-blind, placebo run-in period, each patient was randomly assigned to 8 weeks of treatment in one of eight groups: 100 mg, 200 mg, or 400 mg LCZ696 daily; 80 mg, 160 mg, or 320 mg valsartan daily; 200 mg AHU377 daily; or placebo. Dosages were chosen so that patients treated with the low, medium, and high doses of LCZ696, respectively, would have the same exposure to the active agents as the patients in the corresponding single-agent groups (which facilitated pairwise comparisons).

Patients treated with LCZ696 showed greater reductions in mean sitting diastolic blood pressure than did those treated with valsartan (an average difference across all groups of 2.17 mmHg). The largest reductions in mean sitting diastolic blood pressures were seen with the two highest doses of LCZ696: 2.97 mmHg reduction in patients treated with 200 mg LCZ696 versus those treated with 160 mg valsartan, and 2.70 mmHg reduction in patients treated with 400 mg LCZ696 versus those treated with 320 mg valsartan. AHU377 treatment slightly reduced mean sitting diastolic blood pressure compared with placebo. Furthermore, since patients who received 200 mg AHU377 daily had equivalent exposure to this agent to those who received 400 mg LCZ696 daily but achieved a smaller blood pressure reduction, the researchers demonstrated that LCZ696 has additive and complementary effects on mean

sitting diastolic blood pressure, through its two modes of action.

Adverse events during the 8-week treatment period were rare, mild and dose-independent. No serious adverse events were thought to be related to LCZ696 administration, and no cases of angioedema were recorded.

Ruilope *et al.* conclude that LCZ696 could be a useful treatment for hypertension and cardiovascular diseases characterized by vasoconstriction, pulmonary overload and neurohormonal activation. The effects of LCZ696 in patients with these disorders should be explored in the future.

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Original article Ruilope, L. M. *et al.* Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet* 375, 1255–1266 (2010)