Articles

Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial

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Summary

Background We aimed to assess in patients with congestive heart failure whether dual inhibition of neutral endopeptidase and angiotensin-converting enzyme (ACE) with the vasopeptidase inhibitor omapatrilat is better than ACE inhibition alone with lisinopril on functional capacity and clinical outcome.

Methods We did a prospective, randomised, double-blind, parallel trial of 573 patients with New York Heart Association (NYHA) class II–IV congestive heart failure, left-ventricular ejection fraction of 40% or less, and receiving an ACE inhibitor. Patients were randomly assigned omapatrilat at a daily target dose of 40 mg (n=289) or lisinopril at a daily target dose of 20 mg (n=284) for 24 weeks. The primary endpoint was improvement in maximum exercise treadmill test (ETT) at week 12. Secondary endpoints included death and comorbid events indicative of worsening heart failure.

Findings Week 12 ETT increased similarly in the omapatrilat and lisinopril groups (24 *vs* 31 s, p=0·45). The two drugs were fairly well tolerated, but there were fewer cardiovascular-system serious adverse events in the omapatrilat group than in the lisinopril group (20 [7%] *vs* 34 [12%], p=0·04). There was a suggestive trend in favour of omapatrilat on the combined endpoint of death or admission for worsening heart failure (p=0·052; hazard ratio 0·53 [95% CI 0·27–1·02]) and a significant benefit of omapatrilat in the composite of death, admission, or discontinuation of study treatment for worsening heart failure (p=0·035; 0·52 [0·28–0·96]). Omapatrilat improved NYHA class more than lisinopril in patients who had NYHA class III and IV (p=0·035), but not if patients with NYHA class II were included.

Interpretation Our findings suggest that omapatrilat could have some advantages over lisinopril in the treatment of patients with congestive heart failure. Thus use of vasopeptidase inhibitors could constitute a potentially important treatment for further improving the prognosis and well being of patients with this disorder.

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Introduction

Congestive heart failure is characterised by chronic overactivation of sodium-retaining and water-retaining neurohormones.[1] Overactivation of these vasoconstrictor neurohumoral systems also leads to excessive cellular growth, cardiac fibrosis, and cellular toxicity.[1] Attenuating the effects of these neurohumoral systems has been one of the most successful strategies in lowering the morbidity and mortality of patients with congestive heart failure.[2,3] Although the use of angiotensin-converting-enzyme (ACE) inhibitors and β-blockers has been beneficial in this respect, the outlook of these patients remains poor. Therefore, new strategies to improve outlook need to be developed.[2,3]

Human beings have developed several endogenous systems for countering the effects of overactivation of vasoconstrictor neurohormones.[1] One mechanism is endogenous vasodilator systems, which include natriuretic peptides, nitric oxide, and prostaglandins.[1] These peptides vasodilate and promote diuresis and natriuresis and lessen cellular growth.[4–7] In congestive heart failure, endogenous vasodilator systems are activated to try to compensate for chronic activation of vasoconstrictor sodium and water-retaining neurohormones. The vasopeptidase inhibitors, a new class of pharmaceutical agents, have been shown to heighten activity of endogenous vasodilator systems and reduce production of the vasoconstrictor angiotensin II.[8] Vasopeptidase inhibitors inhibit the activity of neutral endopeptidase, an enzyme that metabolises endogenous vasodilator peptides, such as natriuretic peptides (atrial, brain, and calcium-activated neutral protease), adrenomedullin, and bradykinin.[8] Because these inhibitors better redress the imbalance between endogenous vasoconstrictor and vasodilator substances in congestive heart failure than does ACE inhibition alone, they could be more useful in treatment of patients with the disorder.

We did a randomised double-blind trial to compare the effects of omapatrilat with those of lisinopril on exercise tolerance in patients with congestive heart failure. We also assessed side-effects of the treatments, effects on death rate, and comorbid events for worsening heart failure.

Methods

Omapatrilat

Omapatrilat (BMS-186716) is the first of a new class of cardiovascular agents termed vasopeptidase inhibitors. Omapatrilat is an orally active, long acting, selective, competitive inhibitor of neutral endopeptidase (NEP; enkephalinase, neprilysin, EC 3.4.24.11) and angiotensin converting enzyme (ACE; EC 3.4.15.1) with similar K_i