

Keywords:
vasopeptidase
inhibitors,
heart failure,
omapatrilat,
natriuretic
peptides

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Accepted for
publication
2nd September 2002

JRAAS 2002;3:156-9

**Journal of
the Renin-
Angiotensin-
Aldosterone
System**
(Including other
peptidergic systems)

September 2002
Volume 3
Number 3

Vasopeptidase inhibitors in heart failure

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Abstract

Considerable attention has recently focused on the vasopeptidase inhibitors (VPI), a new class of drug that combines angiotensin-converting enzyme (ACE) inhibitor activity with inhibition of natriuretic peptide breakdown. In theory, a drug with these properties may be beneficial both in hypertension and in heart failure. Whilst the efficacy of VPIs in hypertension and clinical studies, the role of VPIs, if any, in heart failure is less clear, since numerous small studies have produced conflicting results. Furthermore, preliminary results from the recently completed Omapatrilat Versus Enalapril Randomised Trial of Utility in Reducing Events (OVERTURE) study have failed to establish the VPI, omapatrilat, as a first line therapy in the treatment of chronic heart failure. We review the literature on VPIs in heart failure and discuss possible reasons for the reported lack of benefit over ACE inhibitors.

Introduction

Heart failure is a major cause of morbidity and mortality in the developed world. Despite the use of diuretics, β -blockers, angiotensin-converting enzyme (ACE) inhibitors and spironolactone, its prognosis remains poor. As the heart fails, a number of compensatory neurohormonal mechanisms are activated, including the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS) and the natriuretic peptides. The ideal drug for heart failure would favourably manipulate a combination of these mechanisms to produce clinical benefit. The vasopeptidase inhibitors (VPIs) have recently been proposed to do this.

The renin-angiotensin-aldosterone system in heart failure

A reduction in cardiac output and fall in blood pressure (BP) results in activation of the RAAS, with increased production of angiotensin II (Ang II) and aldosterone.¹ Ang II is a potent vasoconstrictor with direct effects on the myocardium, leading to hypertrophy, remodelling and fibrosis, whilst aldosterone results in salt and water retention, as well as producing a vasculopathy and stimulating tissue fibrosis.^{1,2} Thus, although activation of the RAAS may initially have beneficial effects, chronic activation is deleterious to the failing heart. ACE is the rate-limiting enzyme in the production of Ang II from angiotensin I. The benefits of inhibition of this enzyme, both in heart failure^{3,4} and in patients without heart failure but at

increased cardiac risk,⁵ have been clearly demonstrated.

The natriuretic peptide system

Three natriuretic peptides have been identified in humans: ANP, BNP and CNP. ANP is produced mainly in the cardiac atria in response to atrial stretch, reflecting volume expansion, whilst BNP is produced and released from the ventricles in response to increased ventricular volume and pressure.⁶ Both peptides possess natriuretic, diuretic and vasodilatory properties, causing increased renal blood flow, increased glomerular filtration rate (GFR), and a shift of fluid from intravascular to extravascular spaces. CNP is released from vascular endothelium in response to shear stress and has vasodilatory properties, although minimal diuretic and natriuretic effects.⁶ All natriuretic peptides possess antimitogenic activity and have been shown to inhibit growth of vascular smooth muscle and endothelial cells. Thus, the effects of the natriuretic peptides counteract the effects of both the RAAS and SNS in chronic heart failure. ANP and BNP levels are elevated even in asymptomatic heart failure and have also been shown to have prognostic value.

Natriuretic peptides are inactivated by two mechanisms: by cell surface clearance receptors and by neutral endopeptidase (NEP), a membrane-bound metalloproteinase enzyme.⁷ NEP is widely distributed in the kidney, lung, gut, brain and heart. As well as catalysing the degradation of natriuretic peptides, NEP also degrades bradykinin, endothelin I, adrenomedullin and Ang II. Inhibition of NEP on its own results in increased natriuretic peptide levels but also in increased levels of Ang II, which is potentially deleterious.⁸ Simultaneous inhibition of ACE and NEP would be expected to exploit the beneficial effects of natriuretic peptides as well as the beneficial effects of inhibiting Ang II production. Drugs which simultaneously inhibit ACE and NEP are called VPIs.

The VPI on which there is most clinical data is omapatrilat. Several studies have already demonstrated its efficacy as an antihypertensive agent, producing particularly large BP reductions of up to 25.6/16.7 mmHg.² Concerns over an increased risk of angioedema with the drug led to voluntary withdrawal of its New Drug Application (NDA) in April 2000. Data from the recently completed Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril (OCTAVE) trial,⁹ which included 25,000 hypertensive patients, has demonstrated

the incidence of angioedema to be 2.17% with omapatrilat, compared with 0.68% with enalapril. On the basis of this result, a NDA for omapatrilat has been submitted to the FDA, the outcome of which is awaited. No application for use in heart failure has yet been made, although this has been the subject of many studies.

Preclinical studies with omapatrilat in heart failure

Numerous animal models have been used in pre-clinical studies of omapatrilat. In sheep models of mild and severe heart failure,¹⁰ omapatrilat produced an acute reduction in mean arterial pressure (MAP) after the first dose, and a sustained reduction in MAP after 5–7 days. ANP and BNP were unchanged after the first dose, but BNP had increased by day 7. In a canine model of mild heart failure,¹¹ omapatrilat was compared with an ACE inhibitor (ACE-I). Omapatrilat caused a reduction in pulmonary capillary wedge pressure (PCWP) and pulmonary artery (PA) pressure, a decrease in distal fractional sodium reabsorption and an increase in urinary sodium excretion and GFR. These effects were accompanied by an increase in ANP, BNP, plasma cGMP and urinary cGMP. The effects on PA pressure, distal fractional sodium reabsorption, urinary sodium excretion and GFR were greater than those seen in the ACE-I group, in which there was no increase in natriuretic peptides. Ang II levels fell equally in both groups.

The administration of a natriuretic peptide receptor antagonist with omapatrilat resulted in a similar increase in ANP and BNP as for omapatrilat alone, but a reduction in GFR and urinary sodium excretion was observed. In a separate canine model of early left ventricular (LV) dysfunction, the haemodynamic effects of omapatrilat were antagonised by natriuretic peptide receptor antagonism, despite an increase in ANP.¹²

Preclinical studies have also looked at the effects of omapatrilat on echo parameters of the left ventricle. In a canine model, omapatrilat resulted in a greater reduction of left ventricular end diastolic volume (LVEDV) and peak diastolic wall stress than did an ACE-I alone or a combination of ACE-I and diuretic.¹³ Two months of VPI therapy also had beneficial effects on cardiac geometry in cardiomyopathic hamsters with heart failure, as well as prolonging median survival time by 31% compared with ACE-I in one study¹⁴ and by 44% in another.¹⁵

Clinical trials with omapatrilat in heart failure

A number of clinical studies have been performed to ascertain whether comparable results are produced in patients with heart failure. The majority of clinical studies of omapatrilat in heart failure included patients with left ventricular ejection fraction (LVEF) \leq 40% and NYHA class II–IV.

One dose-ranging study found significant reductions in PCWP, MAP and systolic vascular resistance (SVR) at doses of omapatrilat greater

than 10 mg.¹⁶ These haemodynamic changes were not associated with an increase in heart rate, but were associated with an increase in ANP and cGMP. There was also a small increase in stroke volume index and cardiac index. However, the study only looked at the effects of the drug up to 24 hours post-dose.

A longer-term study of 48 patients compared 2.5 mg omapatrilat with higher doses up to 40 mg.¹⁷ The dose of 2.5 mg has been shown to have ACE-I activity but no NEP inhibitor activity, and patients receiving this dose were therefore used as a control group. In this study, there was no change in pre-dose plasma ANP levels over 12 weeks, but plasma BNP levels had declined by 12 weeks in all groups. This is not unexpected in the control group, as pure ACE inhibition is known to reduce natriuretic peptide levels. However, the reduction in BNP at higher doses is interesting as, despite this, omapatrilat was still efficacious. Over the 12-week study period, the control group had more hospital admissions for worsening heart failure and a greater need for extra doses of diuretics than did the group receiving higher omapatrilat doses. There was an improvement in NYHA class at 20–40 mg omapatrilat, as well as an improvement in patients' and physicians' subjective score for functional status.

Echo parameters also improved in this study, with a dose-dependent increase in LVEF and a reduction in LV wall stress at the higher doses. In a further study,¹⁸ this group found that 20–40 mg omapatrilat caused a reduction in blood volume, end-diastolic volume (EDV) and end-systolic volume (ESV) and an increase in LVEF by 7.19% after 12 weeks of therapy. This is in contrast with the results of a six month study in 75 patients who received 40 mg omapatrilat or 20 mg lisinopril.¹⁹ Ejection fraction and LV volumes did not improve in either group, but were maintained by both treatments. In a separate study, one year of omapatrilat therapy increased LVEF by 6.3% and wall stress was also reduced.²⁰ Furthermore, the addition of omapatrilat to background heart failure therapy in 369 patients was found to improve LVEF (from 22% to 27%) and reduce the incidence of death, hospitalisation and co-intervention for heart failure from 34% at 2.5 mg to 19% at 40 mg.²¹

The effects of omapatrilat on other non-invasive measures of cardiovascular function have also been investigated. One such study compared the effects of omapatrilat on forearm blood flow, vasodilator response and augmentation index measured by pulse wave velocity.²² Omapatrilat produced an improvement in maximum forearm vasodilator response during reactive hyperaemia, suggesting an improvement in endothelial function, and a reduction in augmentation index, suggesting reduced afterload. Another group compared the effects of six months of omapatrilat or lisinopril in 19 patients with LV dysfunction and found a trend towards an improvement in carotid-femoral pulse wave velocity with omapatrilat, and a trend towards deterioration with lisinopril.²³

A study of the long-term safety of omapatrilat in heart failure compared 20 mg lisinopril with omapatrilat at a dose of 20 mg for 52 weeks or 40 mg for 24 weeks in 1,242 patients.²⁴ Sixty-three percent of patients were in NYHA class II, the remainder being in classes III or IV. Omapatrilat improved the combined endpoint of death or hospitalisation for worsening heart failure in a dose-dependent fashion. There was also less renal dysfunction with omapatrilat and no cases of angioedema.

The Inhibition of Metallo Protease by BMS-186716 in a Randomised Exercise and Symptoms Study (IMPRESS)²⁵ compared 40 mg omapatrilat with 20 mg lisinopril in NYHA II-IV patients with LVEF<40%. Patients had to be taking an ACE-I to be considered for inclusion to this 24-week trial. There were no statistically significant differences between the two groups in the primary endpoint of improvement in maximum exercise tolerance at week 12. Likewise, there were no significant differences in the single endpoints of admissions for heart failure, death from any cause, drug withdrawal, emergency room visits, extra diuretic use or ejection fraction. However, the composite endpoint of death or admission for heart failure favoured omapatrilat ($p=0.052$), as did the composite endpoint of death, admission for heart failure or discontinuation of treatment ($p=0.035$). There was no significant improvement overall in NYHA class, but less worsening and more improvements with omapatrilat in patients within class III or IV at baseline. Renal function deteriorated less with omapatrilat, in keeping with the results of other studies. This renoprotective effect is potentially of interest, as maintained GFR has been reported to be a strong predictor of survival in heart failure patients, beyond that observed with other surrogate endpoints.¹

To date, the most recent study of omapatrilat in heart failure is the Omapatrilat Versus Enalapril Randomised Trial of Utility in Reducing Events (OVERTURE) study,²⁶ the full results of which have not yet been published. This aimed to clarify the effects of omapatrilat on all-cause mortality and CHF hospitalisation and is the largest ever study of a new drug in heart failure. Nearly 6,000 patients were recruited, all of whom had been hospitalised for heart failure within the past year, had an LVEF of <30% and were in NYHA classes II-IV. Median follow-up was 3.9 years. Forty mg of omapatrilat was compared with 20 mg of enalapril. Preliminary reports suggest that there were no statistically significant benefits with omapatrilat over enalapril in either the combined primary endpoint of all-cause mortality and CHF hospitalisation or the secondary endpoints of all-cause mortality or combined death, myocardial infarction (MI), stroke, or revascularisation. There was a statistically significant benefit in the secondary outcome of cardiovascular death or cardiovascular hospitalisation ($p=0.024$). Posthoc analysis of the primary endpoint with the Studies of Left Ventricular Dysfunction (SOLVD) definition for CHF hospitalisations showed a significant 11%

($p=0.012$) benefit with omapatrilat. As in previous trials, there was more hypotension and dizziness with omapatrilat, more angioedema (0.8% compared with 0.5%) and less impairment of renal function.

Despite encouraging results from early studies, doubts remain as to the role of omapatrilat in heart failure. Paradoxically, its efficacy as an anti-hypertensive agent may be one of the reasons for this. Lowering BP in heart failure patients, in whom BP is already tenuous, may ultimately have detrimental effects. Preliminary reports from the OVERTURE investigators suggest that the benefits of omapatrilat were greatest in patients with systolic BP greater than 140 mmHg at recruitment, and that the benefits progressively reduced as systolic BP decreased. In fact, it has been reported that there were no benefits over ACE-I in patients with systolic BP less than 110 mmHg.

Similarly, lowering diastolic BP in patients in whom heart failure is ischaemic in origin may potentially reduce coronary artery perfusion pressure and worsen ischaemia. However, in the majority of trials of omapatrilat, patients with unstable angina or MI within three months were excluded, and these may be the patients in whom low coronary artery perfusion pressure is most likely to cause problems. Furthermore, it is increasingly recognised that many heart failure patients have a combination of both diastolic dysfunction and systolic dysfunction. A large reduction in cardiac filling pressures in patients with a significant degree of diastolic dysfunction may adversely affect cardiac output and therefore limit any clinical benefit which might occur through other potentially favourable mechanisms.

Another possibility for the lack of superiority of omapatrilat over enalapril in the OVERTURE study may be related to the severity of heart failure in the study patients, all of whom were in NYHA class II to IV. It is recognised that renal responsiveness to natriuretic peptides decreases as heart failure worsens, even if natriuretic peptide concentrations in plasma rise.²⁷ Thus, the deleterious effects of the RAAS may outweigh the beneficial actions of the natriuretic peptides in advanced heart failure. Inhibition of the RAAS may be of more importance than manipulation of the natriuretic system in moderate-to-severe heart failure. Indeed, a telling observation is that the benefits of ACE-I occur despite their causing a fall in natriuretic peptides. This begs the question whether VPIs may potentially be more beneficial in early heart failure when natriuretic peptides are activated without activation of the RAAS, i.e. NYHA I patients. These patients have already been shown to benefit from ACE inhibition. Such patients are likely to have higher BPs than patients with severe LV dysfunction and the potential for harm by the hypotensive effects of a VPI would possibly be lessened in this group.

In order to be accepted as routine treatment for heart failure, VPIs would have to be shown to have benefits greater than those of standard heart failure treatment with a similar safety profile. This

has not yet been shown to be the case. Whether they have a place in selected groups of heart failure patients remains to be seen.

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