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Scientific Update™

Omapatrilat: A novel vasopeptidase inhibitor for the treatment of heart failure

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The development of heart failure is associated with the activation of several neurohormonal systems.[1,2] Vasoconstrictor, trophic, and antidiuretic neurohormonal systems such as the sympathetic nervous system, the renin-angiotensin system (RAS), and the endothelin system have been well-characterized.[3-5] Several clinical trials have demonstrated that blocking the RAS with angiotensin-converting enzyme (ACE) inhibitors results in improved survival in these patients.[6,7] In recent years, it has become apparent that parallel vasodilator, antitrophic, and diuretic systems exist. Through complex interactive mechanisms, these systems, (including the bradykinins, prostaglandins, nitric oxide, and the natriuretic peptides[1,2,8-10]) counter-regulate the effects of the vasoconstrictor neurohormonal systems so that homeostatic balance can be maintained at the tissue, as well as the systemic level. Neutral endopeptidase 24.11 (NEP) is a membrane-bound metalloenzyme that cleaves endogenous peptides at the amino side of hydrophobic residues. This ectoenzyme is found in the kidney, lung, gut, brain, heart, as well as the peripheral vasculature.[11,12] The vasoactive peptide substrates of NEP include the natriuretic peptides, bradykinin, and substance P.[12,13] Accordingly, inhibition of NEP results in the preservation of natriuretic peptides and bradykinins, potentiating their organ protective actions. Furthermore, simultaneous inhibition of both ACE and NEP should have the advantage of blocking the generation of the vasoconstrictor and trophic peptide angiotensin II on one hand, while preserving the endogenous, biologically active vasodilator and antitrophic peptides on the other. Indeed, studies have demonstrated that simultaneous inhibition of ACE and NEP produces greater hemodynamic and renal effects than either treatment modality alone, suggesting that dual inhibition has potential advantages over the currently used ACE inhibitors.[14,15] The end results of the concomitant inhibition of ACE and NEP are depicted in Figure 1.

Clinical pharmacology of omapatrilat: A vasopeptidase inhibitor

Omapatrilat is a novel vasopeptidase inhibitor (formerly dual metalloprotease inhibitor) with activity against both ACE and NEP. The inhibitory activity is highly specific to the respective enzymes (Ki, rabbit lung ACE = 6.0 nM; Ki, rat kidney NEP = 8.9 nM).

In several animal models of hypertension, omapatrilat has been shown to lower mean arterial blood pressure to a similar or greater degree as ACE inhibitors. In monkeys, omapatrilat potentiated the atrial natriuretic peptide (ANP) induced natriuresis, and urinary sodium and cGMP excretion. In cardiomyopathic hamsters, omapatrilat markedly reduced left ventricular end diastolic pressure, and long-term administration of omapatrilat increased the median survival

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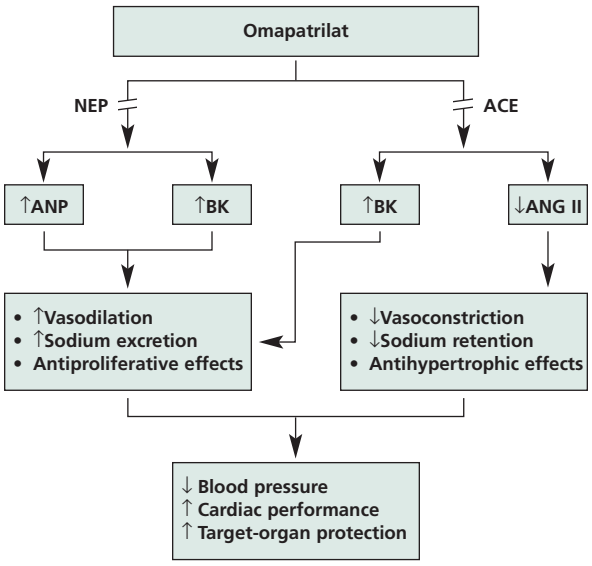
Figure 1: Omapatrilat: The mechanism of action and potential biological effects of combined ACE and NEP inhibition. The net effects are reduced generation of ANG II, increased generation of ANP, and preservation of BK



NEP = neutral endopeptidase
ANP = atrial natriuretic peptide
BK = bradykinins
ANG II = angiotensin II

of these animals by 44%. This was greater than the 23% increase produced by the ACE inhibitor captopril.

The unique pharmacologic properties and the encouraging experimental data of omapatrilat are translated into a potent blood pressure lowering effect when the agent is given to human subjects. To date, over 2000 patients with hypertension have been exposed to omapatrilat at doses ranging from 2.5 to 80 mg per day. Significant declines in peak and trough systolic arterial pressures of >10 mm Hg have been observed with the 2.5, 5, and 10 mg dose.

The neurohormonal effect of vasopeptidase inhibition was examined recently in a study reported at the American Heart Association meeting.[16] In this study, conducted in France, nine mildly sodium-depleted male subjects were randomized in a double-blind crossover design to a single oral dose of omapatrilat 10 mg, or the ACE inhibitor fosinopril 20 mg. Over a 24-hour period, omapatrilat and fosinopril produced a similar degree of reduction in the peak and in the area under the curve values of plasma aldosterone, as well as in the angiotensin II:angiotensin I ratio, a marker of *in vivo* ACE inhibition. These data suggest that in mildly sodium-depleted normal subjects, omapatrilat and fosinopril produced a similar degree of ACE inhibition. Plasma ANP decreased significantly after fosinopril therapy compared to omapatrilat and placebo. However, there was a significant two-fold increase in urinary ANP with omapatrilat compared to fosinopril and placebo. Omapatrilat did not amplify the decline in plasma aldosterone levels, nor did it alter the plasma ANP level, but it did increase the urinary ANP level. It is unclear why plasma ANP level was not increased by omapatrilat although it is possible that it simply reflected a resetting of the release of ANP by concomitant ACE inhibition.

Hemodynamic effects of omapatrilat in patients with heart failure

The first placebo-controlled clinical assessment of omapatrilat in heart failure was protocol BMS CV 137-003. In this multicenter study, the *acute* hemodynamic effects of a single administration of an escalating dose of omapatrilat were assessed in patients with heart failure. The results of this study were presented in the recent American Heart Association scientific meeting.[17] One hundred and thirteen patients with heart failure, New York Heart Association functional class II to IV symptoms, and left ventricular ejection fraction of <40%, were randomized in a double-blind fashion using a four-panel design to omapatrilat (1, 2.5 and 5 mg; 10 mg; 25 mg; 50 mg daily orally, n=80 in total), or matching placebo (n=33 in total). Baseline hemodynamic parameters were comparable in both groups. The primary hemodynamic endpoint was pulmonary capillary wedge pressure (PCWP). Hemodynamic parameters of selected dose expressed as the absolute change from baseline at 4 hours after drug administration are shown in Table 1. Compared to placebo, omapatrilat produced a dose-dependent decline in

Table 1: Acute hemodynamic effects of omapatrilat

		PCWP	CI	MAP	HR
Placebo		-1.8	0	- 2.5	4.8
Omapatrilat	2.5 mg	-3.8	0	- 2.7	0.6
	10 mg	-5.2	0.1	- 7.5	-0.1
	25 mg	-7.2*	0.1	- 8.0*	-3.3*
	50 mg	-8.1*	0.2	-15.2*	0.3

PCWP = pulmonary capillary wedge pressure (mm/Hg)
CI = cardiac index (l/min)
MAP = mean arterial pressure (mm Hg)
HR = heart rate (beats/min)
* p<0.05 versus placebo

PCWP and mean arterial pressure without any significant increases in cardiac output or heart rate. The lack of an increase in heart rate is consistent with animal data and is very encouraging.

The *long- term* hemodynamic effects and safety of omapatrilat were assessed in protocol BMS CV 137-012. The results were recently presented at an Omapatrilat Clinical Investigator Meeting that took place during the American Heart Association meeting. This protocol involved a 12-week administration of a wide range of doses of omapatrilat to patients with heart failure, New York Heart Association class II to IV symptoms, and left ventricular ejection fraction <40%. Because of the duration of the study, the inclusion of a placebo-treated group was not possible. The study was divided into two sequential panels according to the dose of omapatrilat. Panel 1 involved the assessment of 2.5, 5, and 10 mg randomized in a double-blind fashion, whereas Panel 2 involved the assessment of 2.5, 20, and 40 mg of omapatrilat (2.5 mg of omapatrilat contains only ACE inhibitor properties).

Patients underwent two invasive hemodynamic assessments, the first after receiving the first dose of omapatrilat, and the second after taking the final dose of omapatrilat at the end of 12 weeks once-daily oral maintenance therapy with the agent. The results of the 12-week study are described as follows. One hundred and ninety patients were randomized in Panel 1, whereas 179 patients were randomized in Panel 2. In Panel 1, omapatrilat produced a dose-dependent reduction in PCWP (-8 mm Hg for the 10 mg dose at 4-5 hours post-drug administration). These hemodynamic effects were *sustained* at 12 weeks. Furthermore, these beneficial effects were also observed in Panel 2 at both the baseline and 12-week assessment (-9 mm Hg for the 20 and 40 mg dose at 4-5 hours post-omapatrilat). In both Panels 1 and 2, there was a significant dose-dependent decline in systolic arterial pressure (-16 mm Hg at 4-5 hours for both 10 and 40 mg, respectively). Importantly, there was *no* significant change in heart rate. Cardiac index did not increase significantly and there was a trend for left ventricular ejection fraction to increase over the 12-week period (22% at baseline to 27% at 12 weeks for the 40 mg dose; odds ratio 2.3, CI, -0.8, 5.4).

In spite of NEP inhibition, there was no significant increase in either plasma atrial or brain natriuretic peptide levels. Furthermore, there was no significant change in plasma endothelin-1 level, although there was a small but statistically significant increase in plasma norepinephrine level at the 20 mg dose. This may not be clinically relevant. At all doses, a greater percentage of patients reported improvement in New York Heart Association functional class than those who reported worsening of functional class. This difference was most pronounced in the 40 mg group (37% versus 2%). A similar trend was observed in heart failure status based on both physician and patient assessments. Further studies will be needed to confirm the positive results from earlier trials.

Effects of omapatrilat on exercise tolerance in patients with heart failure

The effect of omapatrilat on the exercise tolerance of patients with heart failure was evaluated in the separate pilot study (Protocol CV 137-013). In this protocol, 219 patients with New York Heart Association functional class II (64%) and III (36%) symptoms were randomized in a double-blind fashion to treatment with 2.5, 10, and 20 mg of omapatrilat, or to 20 mg of the ACE inhibitor lisinopril. The primary endpoint was maximum treadmill exercise time on a modified

Table 2: Adverse effects of omapatrilat and lisinopril expressed as the percentage of subjects from Protocol CV 137-013

	Omapatrilat 2.5 mg (n=68)	Omapatrilat 10 mg (n=68)	Omapatrilat 20 mg (n=66)	Lisinopril 20 mg (n=66)
Heart failure	12	10	11	5
Weight gain	3	4	2	2
Dyspnea	10	7	8	9
Sleep disturbances	3	2	0	2
Hypotension	3	6	9	3
Dizziness	12	24	17	12
Diarrhea	4	2	2	0

Table 3: Rate of discontinuation of omapatrilat due to adverse events expressed as percent of subjects

2.5 mg n=190	5 mg n=66	10 mg n=129	20 mg n=124	40 mg n=210	Total N=719
11.6	19.7	17.1	12.1	7.6	12.2

Naughton protocol. The mean ejection fraction of these patients was 27.5% and the baseline exercise time was 587 seconds. After a 12-week treatment period, there were significant increases in exercise time in all groups ranging from +38 seconds in the lisinopril group, to +57 seconds in the 10 mg omapatrilat group. There were, however, no significant differences between the study groups. Likewise, there were no between-group differences in the changes in functional class or heart failure status as assessed by either the patients or physicians.

Clinical safety of omapatrilat

At the time of the writing of this report, over 3000 subjects worldwide have been exposed to omapatrilat. In addition to patients who are actively participating in double-blind trials, over 2000 are currently taking the medication. Data of the rate of side effects reported from the CV 137-013 protocol described above are listed in Table 2. It shows that the incidence of adverse events was relatively low for the different doses of omapatrilat and lisinopril.

The percent of adverse effects that resulted in discontinuation of the drug is listed in Table 3. These data were pooled from Protocol CV 137-012, CV 137-013, as well as an early open-label trial. Table 3 shows that the rate of discontinuation of omapatrilat because of adverse events is relatively low. Furthermore, the overall incidence of cough of 8.1% (data not shown in table) is also low and is not different among the different doses of omapatrilat or lisinopril.

The future development of omapatrilat

Concomitant inhibition of ACE and NEP by vasopeptidase inhibition is a promising novel approach for treatment of patients with heart failure. Studies to-date with omapatrilat indicate that this agent can produce *sustained* potent and beneficial hemodynamic effects without concomitant activation of neurohormones. In a pilot study, omapatrilat improved exercise time to a similar extent as the ACEI lisinopril. Finally, omapatrilat appears to be well-tolerated.

The IMPRESS (Inhibition of Metalloprotease in a Randomized Exercise and Symptoms in Heart Failure, Protocol CV 137-028) study is a large-scale multicenter trial that is assessing the effects of omapatrilat versus lisinopril on exercise tolerance and symptoms in patients with heart failure. Enrollment was completed on July 17, 1998, with over 500 patients randomized. Phase III studies on morbidity and mortality are in the planning stages. It is hoped that vasopeptidase inhibition will be a welcome addition to the armamentarium of treatment modalities for patients with hypertension and heart failure.

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