

Benefits of Omapatrilat in Patients with Heart Failure

Rouleau JL, Pfeffer MA, Stewart DJ, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *Lancet* 2000;356:615–20.

Study Overview

Objective. To determine whether omapatrilat, a vasopeptidase inhibitor, improves clinical and physiologic outcomes in patients with congestive heart failure when compared with lisinopril.

Design. Double-blind, randomized clinical trial. Analysis was by intention to treat.

Setting and participants. Patients with New York Heart Association (NYHA) class II to IV heart failure were recruited from 113 centers in the United States and Canada. Patients were randomized if they had an exercise tolerance test (using a modified Naughton protocol) lasting between 2 and 12 minutes. Other inclusion criteria were decreased left ventricular ejection fraction, seated systolic blood pressure ≥ 90 mm Hg, and maintenance on a stable (> 4 weeks) dose of angiotensin-converting enzyme (ACE) inhibitors. Patients were excluded if they had a history of uncontrolled hypertension, acute coronary events, or coronary revascularization procedures in the previous 3 months; a serum potassium less than 35 mmol/L or greater than 53 mmol/L, creatinine greater than 22.1 mg/dL, or transaminase levels more than double the upper limit of normal; leukocyte count less than $3.0 \times 10^9/L$, neutrophil count less than $1.5 \times 10^9/L$, or platelet count less than $120 \times 10^9/L$.

573 patients were included in the study. Mean age was 64 ± 10 years. Patients were mostly male (79%) and white (83% versus 9% African American), with NYHA class II (63%) or III (36%) disease. Most patients' heart failure resulted from either ischemic cardiomyopathy (66%) or idiopathic dilated cardiomyopathy (24%). All but 7 patients were taking ACE inhibitors at baseline, while 2 patients in each group had been taking angiotensin II-receptor blockers. Most patients took diuretics (81%) and digoxin (67%), some took long-acting nitrates (29%) and β blockers (30%), and a few took calcium channel blockers (3%).

Intervention. All patients discontinued ACE inhibitors or angiotensin II-receptor blockers immediately before starting their study medication. They then received either lisinopril titrated over 3 weeks to 20 mg/day (successfully in 94% of patients, the rest receiving lower doses) or omapatrilat titrated to 40 mg/day (successfully in 88%, the rest receiving lower

doses). Patients remained on diuretics or digoxin if they had been previously taking these medications. β blockers were continued if they had been administered to patients for at least 6 months, and calcium channel blockers were continued if they were used for control of atrial fibrillation. Patients were not allowed to take angiotensin II-receptor blockers, vasodilators other than nitrates, or inotropic agents other than digoxin over the study period.

Main outcome measures. The primary endpoint was change in exercise duration from baseline to 12-week follow-up. Secondary clinical endpoints included combined measures of death and hospital admission for worsening heart failure as well as death and any worsening of heart failure requiring intervention (eg, hospital admission, emergency room visit, withdrawal from study).

Main results. No significant difference in exercise treadmill test (ETT) times was seen between the lisinopril and omapatrilat groups at 12-week or 24-week follow-up. The combined endpoint of death and deteriorating condition requiring intervention favored omapatrilat (6% versus 10%, $P = 0.035$; hazard ratio [95% confidence interval], 0.52 [0.28 to 0.96]). Another combined endpoint, death or admission for worsening heart failure, showed similar results that did not reach statistical significance (5% versus 9%; 0.52 [0.27 to 1.02]). Data on other adverse outcomes (ie, side effects) did not clearly favor either drug.

Conclusion

While omapatrilat and lisinopril appear to achieve similar outcomes on exercise tolerance and have comparable side effects, omapatrilat may further reduce morbidity and mortality from heart failure.

Commentary

In general, this was a well-designed trial of moderate size. Two main statistical issues should be noted: First, the trial was designed and powered to evaluate ETT performance; second, Rouleau and colleagues assessed a very large number of outcomes (many of which were not summarized above). When the ratio of measurements to participants is relatively high, the pre-set level of statistical significance should be lowered or the P value assessment

should be adjusted. If either had been done, none of the study results would have reached statistical significance. Nevertheless, solid physiologic groundwork exists supporting the use of vasopeptidase inhibitors, of which omapatrilat is the first to reach this stage of clinical trials [1,2]. Given the strong trend toward improved outcomes with omapatrilat, it appears likely that this agent will soon assume a prominent place in the treatment of patients with heart failure.

Applications for Clinical Practice

Currently, omapatrilat is not licensed for use in the United States. Rouleau et al note that a much larger phase III ran-

domized clinical trial is underway to identify the drug's role more definitively. Clinicians and guideline writers should follow these developments closely in order to ensure the highest quality of care for their patients.

References

1. Burnett JC Jr. Vasopeptidase inhibition: a new concept in blood pressure management. *J Hypertens Suppl* 1999;17: S37-43.
2. Ikram H, McClean DR, Mehta S, et al. Long-term beneficial hemodynamic and neurohormonal effects of vasopeptidase inhibition with omapatrilat in heart failure. *J Am Coll Cardiol* 1999;32(2 Suppl A):185A.

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