Distinct mutations in sarcomere proteins have now been shown to result in dilated cardiomyopathy and hypertrophic cardiomyopathy. Identification of these and other genetic defects causing dilated cardiomyopathy holds promise to lead to a better understanding of the mechanisms involved in the initiation and progression of this disease. Genetic testing will in the near future allow early and specific diagnosis of patients, as well as screening of family members.

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Vasopeptidase Inhibition in Patients with Heart Failure

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Neurohumoral activation plays a key role in the initiation and progression of heart failure. Neurohumoral inhibition with angiotensin-converting enzyme (ACE) inhibitors, ß-blockers, and aldosterone antagonists has been shown to decrease symptoms, reduce hospitalizations, and prolong survival in patients with heart failure. Despite the benefits of these agents, alone or in combination, patients with heart failure still face substantial risks. Vasopeptidase inhibitors are a new class of pharmaceutical agents that have been shown to increase the activity of endogenous vasodilators.[1] Vasopeptidase inhibitors inhibit the activity of the enzyme neutral endopeptidase, which degrades the natriuretic peptides (atrial, brain, and calcium-activated), bradykinin, and adrenomedullin. These inhibitors may provide additional benefit in heart failure, since they target the imbalance between endogenous vasoconstrictors and vasodilators in heart failure more than ACE inhibition alone.[2]

Comparison of Vasopeptdase Inhibitor, Omapatrilat, and Lisinopril on Exercise Tolerance and Morbidity in Patients with Heart Failure: IMPRESS Randomized Trial

Rouleau JL, Pfeffer MA, Stewart DJ, et al.
Lancet. 2000;356:615-620.

Omapatrilat is a recently developed drug that provides dual inhibition of neutral endopeptidase and ACE. The recently published IMPRESS clinical trial compared the effects of this vasopeptidase inhibitor to those of the ACE inhibitor lisinopril on functional capacity and clinical outcomes in 573 patients with NYHA class II-IV congestive heart failure.[3] Patients were randomly assigned to receive omapatrilat at a daily target dose of 40 mg or lisinopril at a daily target dose of 20 mg for 24 weeks. This study showed that both agents were well tolerated but that there were fewer cardiovascular system adverse events with omapatrilat. Omapatrilat treatment was associated with more frequent dizziness. One case of angioedema occurred with lisinopril, none with omapatrilat. Time on exercise treadmill tests done at week 12 increased similarly in the omapatrilat and lisinopril patient groups (24 vs 31 seconds, P = .45). There was a significant benefit of omapatrilat in the composite of death, hospitalization, and discontinuation of study drug for worsening heart failure (odds ratio, 0.52, 95% confidence interval [CI], 0.28 to 0.96, P = .035). Of patients randomized to lisinopril, 6.1% developed significant elevations in serum creatinine, compared to 1.8% of those receiving omapatrilat (P = .009). This finding that fewer of the patients given omapatrilat developed impaired renal function than of those given lisinopril is compatible with a protective effect of natriuretic peptides on glomerular filtration rate. The major limitations of this study are that the number of patients studied was small and the length of follow-up was short, so that the results are suggestive of benefit but require further confirmation.

This clinical trial suggests that omapatrilat may have some advantages over ACE inhibitors in the treatment of patients with congestive heart failure. The use of vasopeptidase inhibitors could represent a treatment approach that further reduces the morbidity and mortality in patients with heart failure. The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial, a large multicenter clinical trial comparing the effects of omapatrilat and enalapril on mortality in 4420 heart failure patients, will provide more definitive data.

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