

New Class of Drugs Offers Benefits in Heart Failure

Based on a presentation by Edward P. Havranek, MD

Presentation Summary

The side effects of angiotensin converting enzyme (ACE) inhibitor therapy are occasionally found to be intolerable for patients with heart failure. Although these agents are currently the preferred treatment for such patients, new alternatives are needed. As more knowledge about the pathophysiology of hypertension and heart failure becomes available, researchers are becoming acutely aware of the possibility of disease prevention as op-

posed to the prevention of disease progression.

Acute and chronic treatment with one of these new agents, irbesartan, produces a decrease in wedge pressure and mean pulmonary artery pressure, while its effects on systemic arterial pressure are equivocal. There are also no observable changes in heart rate with irbesartan. The history of ACE inhibitor use was reviewed, and data from a recent study using irbesartan were presented.

For more than 10 years, ACE inhibitors have been the cornerstone of treatment for heart failure because they decrease the high mortality associated with this disease," said Edward P. Havranek, MD, associate professor of medicine, University of Colorado, Denver. "Despite the significant advance in treatment these agents represent, there is a need to investigate other vasodilators for use in congestive heart failure," he said, adding that "the angiotensin II receptor antagonists may offer several possible advantages in the treatment of heart failure."

Angiotensin I can be converted to angiotensin II by proteases whose activity is not blocked by ACE inhibitors. The clinical significance of angiotensin II produced by these pathways is not

known, but it may be significant in heart failure treatment.

Dr. Havranek emphasized that ACE inhibitors are occasionally not well tolerated. About 5% of all treated patients and 15% of heart failure patients may discontinue ACE inhibitor therapy because of side effects, primarily intractable cough.¹

Benefits of Angiotensin II Receptor Antagonists

According to Dr. Havranek, the angiotensin II receptor blockers offer distinct advantages in the treatment of patients who have heart failure. Not only do they provide a complete and sustained blockade of angiotensin II at the receptor level, but results of clinical trials show that these agents have been

well tolerated so far and have not caused the intractable coughing occasionally experienced by patients receiving ACE inhibitor treatment.¹

Irbesartan is an orally active, selective antagonist of the angiotensin II type I receptor, Dr. Havranek explained, as he presented preliminary data on the tolerability and clinical effects of treatment with irbesartan from a multicenter study.

In this study, eligible patients had congestive heart failure; were classified as being New York Heart Association physical status II, III, or IV; had ejection fractions of 40% or less; and were aged 18 years or older. Diuretic therapy was to be stabilized for at least 2 days before study entry, whereas pulmonary capillary wedge pressures had to be 14 mmHg or more. Cardiac index was 3.0 L/min/m² or less in all patients.

During the lead-in period, all vasodilators except nitrates were withdrawn and substituted with placebo. The second phase of the study consisted of an assessment of 24-hour hemodynamic responses to a single dose of either placebo or irbesartan, Dr. Havranek explained. The dose of irbesartan given during this phase was 12.5, 37.5, 75, or 150 mg. A total of 160 patients successfully completed this initial assessment phase and went on to the long-term treatment phase, during which they were randomized to receive one of the four doses of irbesartan daily for 12 weeks.

Wedge Pressure/Artery Pressure Effects

Significant decreases in pulmonary capillary wedge pressures were seen during the first 12 hours with the 75- and 150-mg doses of irbesartan but not with the 12.5- or 37.5-mg doses, Dr. Havranek reported. The mean change was 4 mm to 5 mm, which occurred between 2 and 12 hours after the first irbesartan dose.

This effect on wedge pressure was maintained after 12 weeks of treatment, Dr. Havranek said, and the three highest doses producing significant and consis-

tent improvements in pulmonary capillary wedge pressures of approximately 4 mm to 5 mm compared with baseline pretreatment values. "Furthermore," he added, "this improvement remained significant at 24 hours after dosing."

Beneficial effects on pulmonary artery pressures were also observed. The two highest irbesartan doses—75 mg and 150 mg—produced statistically significant decreases in mean pulmonary

The two highest irbesartan doses—75 mg and 150 mg—produced statistically significant decreases in mean pulmonary artery pressures compared with placebo after the initial dose. At the end of the full 12 weeks of therapy, the three highest doses, including the 37.5-mg dose, were found to have caused a significant decrease in mean pulmonary artery pressures compared with the lowest dose.

artery pressures compared with placebo after the initial dose. At the end of the full 12 weeks of therapy, the three highest doses, including the 37.5-mg dose, were found to have caused a significant decrease in mean pulmonary artery pressures compared with the lowest dose, Dr. Havranek reported.

However, the effects of the drug on mean arterial pressures did not appear to be dose-related, because all four doses of irbesartan produced a slight reduction in mean arterial pressure compared with placebo, and the amount of reduction was similar among patients, regardless of which dose of irbesartan they received.

Changes in ejection fractions were small and not statistically significant, Dr. Havranek noted. In addition, irbesartan had no significant effects on heart rate, either in the acute or the long-term

chronic phase of treatment. "This indicates that there is no reflex tachycardia associated with acute or chronic use of this agent," he said.

Few Adverse Events

Patients who received either the 75- or 150-mg dose of irbesartan were less likely to be discontinued from the study protocol than patients receiving the 12.5-mg or the 37.5-mg doses at any time during the 12-week period due to a worsening of their heart failure during chronic treatment, Dr. Havranek reported. "This finding supports the assessment that higher doses of irbesartan prevent worsening heart failure," he said.

Another important finding was that no dose-related trends existed in the incidence of adverse events. Adverse events did occur and included significant hypotension in 6.4% of the 160 patients, renal insufficiency in 1.4%, and

hyperkalemia in 4.6%. The total mortality rate due to all causes among the study patients was 1.4%.

"In addition to its beneficial hemodynamic effects, irbesartan significantly prevented worsening heart failure, and it had a tendency to increase left ventricular ejection fraction, although this increase was not statistically significant, Dr. Havranek said. "irbesartan was well tolerated in all the doses used," he concluded.

... REFERENCES ...

1. Larochelle P, Flack JM, Marbury TC, Sareli P, Krieger EM, et al. Effects and tolerability of irbesartan versus enalapril in patients with severe hypertension. Irbesartan Multicenter Investigators. *Am J Cardiol* 1997;80:1613-1615.