In This Issue

Heart of the Matter

BiDil for Everyone

BY SIDNEY GOLDSTEIN, M.D.

With the approval of BiDil for the treatment of heart failure in African Americans, the Food and Drug Administration has essentially excluded the use of this combination of isosorbide dinitrate and hydralazine in non–African Americans.

In the African-American Heart Failure Trial (A-HeFT), BiDil decreased mortality in 1,050 exclusively African American patients with New York Heart Association class III and IV heart failure randomized to the drug or a placebo. Most impressively, this benefit occurred in the presence of concomitant therapy with ACE inhibitors and β-blockers within 10 months (N. Engl. J. Med. 2004;351:2049-57).

A major question remains whether this approval should indicate that its use be limited to African American patients only or extended also to all patients. Now that it is approved, it will almost certainly be used in heart failure patients regardless of race. The two drugs are readily available as generic preparations in any pharmacy.

Much has been made of the observation that the antihypertensive effects of ACE inhibitors are less in African Americans than in whites. In addition, the mortality benefit observed in African Americans, compared with whites, in the Vasodilator Heart Failure Trial (V-HeFT I) provides additional foundation for A-HeFT. If a differential blood pressure response was the cause of improved response in A-HeFT, there is little evidence for that. Very minimal decreases of systolic (0.7 mm Hg) and diastolic (1.6 mm Hg) pressure in diastole were seen in the BiDil-treated patients.

It has been suggested that the benefit of BiDil may be related to the antioxidant effect of hydralazine. This theory is supported in part by observation that African Americans may be deficient in nitric oxide, a major source of oxidant metabolism. A lack of nitric oxide at the cellular level as a result of a decrease in endothelial nitric oxide synthase (eNOS) is thought to be a potential putative process of heart failure. If African Americans with heart failure were more deficient in eNOS, they could be more likely to benefit from chronic therapy with BiDil. However, if not, one would expect the effect to be the same, regardless of race.

Some aspects of the therapy are puzzling. The drug was rather poorly tolerated, with only 68% of the BiDil patients staying on the drug, compared with 89% in the placebo group during the 10 months of follow-up. Much of this was presumably due to headache and dizziness, which occurred in 48% and 29% of the patients, respectively. In addition, long-term hydralazine use has been reported to result in a lupus-like syndrome with arthritis at doses greater than 200 mg/day, particularly in patients with renal dysfunction. The dose used in A-HeFT was 225 mg/day. Unfortunately, the duration A-HeFT was short, owing to its observed benefit.

The A-HeFT findings provide a new approach to treating heart failure, regardless of race. If the antioxidant hypothesis is correct, its application should not be limited to African Americans. Given that previous clinical trials in heart failure—which, unfortunately, have been dominated by whites—have been applied to all heart failure patients, regardless of race, it is reasonable that the results in A-HeFT should also be applied to all heart failure patients. ■

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