Candesartan Approved For Heart Failure Tx

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The recent approval of candesartan for a heart failure indication reflects the key findings of one of the three international trials comparing candesartan with placebo in patients with heart failure.

In February, the Food and Drug Administration approved the angiotensin receptor blocker (ARB) for treating patients with heart failure (New York Heart Association class II or IV and a left ventricular ejection fraction [LVEF] of 40% or less), "to reduce the risk of death from cardiovascular causes and to reduce hospitalizations for heart failure." In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)–Alternative trial, the risk of cardiovascular death or hospitalization for heart failure, the primary end point, was reduced by 23% among those on candesartan after a median follow-up of 34 months, compared with those on placebo—a highly statistically significant effect.

This trial, one of three in the CHARM program, enrolled 2,028 patients with symptomatic heart failure and an LVEF less than or equal to 40%, who were on standard heart failure treatments but were intolerant of ACE inhibitors. At baseline, 85% were on diuretics, 46% on digoxin, 55% on -blockers, and 24% on spironolactone. There were 334 events in the 1,013 patients on candesartan, vs. 406 events in the 1,015 on placebo.

Supporting the approval of this indication, according to the FDA, were the results of CHARM-Added, which enrolled more than 2,500 patients with NYHA class II-IV heart failure and LVEFs at or below 40% who were on an ACE inhibitor. In this trial, adding candesartan to standard treatment, including a -blocker, reduced the risk of cardiovascular mortality by 15%, compared with placebo, and significantly improved in heart failure symptoms, as assessed by NYHA functional class.

An approval for use in heart failure patients on ACE inhibitors is likely to follow. (See accompanying story.)

Candesartan, marketed as Atacand by AstraZeneca Pharmaceuticals LP, is the second ARB approved for heart failure; the first was Diovan (valsartan), approved in 2002 for a narrower indication, NYHA class II-IV heart failure in people who cannot tolerate ACE inhibitors. Candesartan was approved for hypertension in 1998.

Using candesartan for these indications will provide an important new tool for treating heart failure, said Christopher Granger, M.D., CHARM–Alternative's principal investigator, in an interview.

In the CHARM program, 4% of those on candesartan had to stop treatment with the drug because of hypotension, versus 2% of those on placebo. Hyperkalemia leading to discontinuation occurred in 2.4% of those on candesartan, versus 0.6% of those on placebo.

The recommended starting dosage is 4 mg/day, with a target dosage of 32 mg once daily, achieved by doubling the dose approximately every 2 weeks, as tolerated, according to the package insert.

Patients need to be monitored closely when the drug is being titrated because some will develop renal insufficiency, hyperkalemia, or hypotension during titration, side effects expected with any drug that affects the renal angiotensin system, said Dr. Granger, who is director of the cardiac care unit at Duke University, Durham, N.C. In the CHARM trials, it was recommended that investigators check serum potassium and creatinine approximately 2 weeks after dose titration.

Dr. Granger was on the executive committee for CHARM and was a consultant to AstraZeneca for this FDA approval and for the meeting of the FDA's cardiovascular and renal drugs advisory committee. ■

FDA Panel Says Candesartan Can Be Used With ACE Inhibitors in HF

Rockville, Md. — The angiotensin receptor blocker candesartan should be approved as a treatment for heart failure in patients who are on an ACE inhibitor, a Food and Drug Administration advisory panel has unanimously recommended.

The FDA's cardiovascular and renal drugs advisory committee backed the approval on the basis of results of one of the three Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trials.

In CHARM–Added, candesartan (titrated to a target dose of 32 mg/day) was compared with placebo in 2,548 patients with New York Heart Association (NYHA) class II-IV heart failure (HF) and a left ventricular ejection fraction (LVEF) at or below 40% who were on an ACE inhibitor and standard therapy. The results showed that adding an ARB to standard treatment that included an ACE inhibitor added an incremental benefit in this population: The relative risk of cardiovascular mortality or HF hospitalization—the primary end point—was reduced by 15% in those on candesartan during a median follow-up of 41 months. The benefits were also seen in patients treated with -blockers, which suggested no adverse interactions among -blockers, candesartan, and ACE inhibitors, as was noted in the Valsartan Heart Failure Trial (Val-HeFT), in which HF morbidity was worse in patients on an ACE inhibitor, -blocker, and valsartan, according to the FDA.

The purpose of the panel meeting was to determine, according to the FDA's agenda, "whether CHARM–Added provides compelling evidence that candesartan should, under some circumstances, be recommended for use in patients on an ACE inhibitor."

But a large portion of the meeting was spent discussing whether patients in the trial were on optimal ACE inhibitor doses and whether the same benefits might have been achieved by increasing the dose of the ACE inhibitor.

Although panelists said a forced titration of ACE inhibitor therapy in the study protocol would have been ideal, they said they felt comfortable that the ACE inhibitor doses used fell into the ranges considered adequate or optimal. The "final doses of ACE inhibitor achieved were quite substantial" and in line with the doses seen in other trials of ACE inhibitor therapy, said Blasé Carabello, M.D., professor of medicine at Baylor University, Houston. In addition, an analysis of a subset of patients on high doses of ACE inhibitors "all go in the same direction" favoring the benefit.

The FDA usually follows the recommendations of its advisory panels, which are made up of outside experts. If approved, candesartan (marketed as Atacand by AstraZeneca Pharmaceuticals LP) will be the first ARB approved for use with an ACE inhibitor. Shortly before the panel meeting, the agency approved candesartan for patients with NYHA class II-IV heart failure, and an LVEF at or below 40%, who are not on an ACE inhibitor, to reduce the risk of death from cardiovascular causes and reduce HF hospitalization based on the CHARM–Alternative trial.

Speaking for AstraZeneca at the meeting, John McMurray, M.D., the principal investigator of CHARM–Added, said that 96% of the patients in the trial were taking an "individualized, optimum" dose of an ACE inhibitor at baseline, and about 80% of patients were on one of five ACE inhibitors that were considered preferred because of randomized controlled outcome studies of these drugs, said Dr. McMurray, professor of medical cardiology, Western Infirmary, Glasgow, Scotland.

Speaking on the study's efficacy for AstraZeneca, Marc Pfeffer, M.D., interim chair of medicine at Brigham and Women's Hospital, Boston, and cochair of the CHARM executive committee, said that in CHARM–Added, there was there was no evidence that the beneficial effect of candesartan on cardiovascular death or HF hospitalization, was modified "based on ACE inhibitor dose or choice of ACE inhibitor."

James Hainer, M.D., senior director of clinical research at AstraZeneca, said that as expected, due to a greater degree of renin-angiotensin-aldosterone system inhibition, rates of hypotension, abnormal renal function, and hyperkalemia were greater with candesartan. However, these adverse events did not translate into any increases in all-cause hospitalization and/or mortality, sudden death, renal failure, or ventricular fibrillation, he said.

These risks will be addressed on the label in warnings and precautions about hypotension, renal dysfunction, and hyperkalemia and recommendations for monitoring and reducing risk, and through interactions with major societies and treatment guidelines committees, he said.

Dr. McMurray said that on balance, the risk was "substantially" in favor of candesartan: A cost analysis found that for every 1,000 patients treated with candesartan, there were 1,900 fewer days spent in the hospital for worsening heart failure, he told the panel.

—Elizabeth Mechcatie

Poor Kidney Function Is a Harbinger of Anemia in Heart Failure Patients

New Orleans — Poor kidney function is the strongest indicator for anemia in heart failure patients, according to the results of a large study in HMO patients.

A reduced glomerular filtration rate emerged as the strongest risk factor for developing anemia in 41,754 heart failure (HF) patients free of anemia at baseline, Alan S. Go, M.D., reported at the annual scientific sessions of the American Heart Association.

Anemia was a common occurrence in this HMO population with HF, with an incidence of 9% per year, according to Dr. Go of Kaiser Permanente of Northern California, Oakland. The study featured nearly 83,000 person-years of follow-up.

Chronic renal impairment is extremely common among HF patients. Roughly 40% of patients had a baseline glomerular filtration rate of less than 60 mL/min per 1.73 m^2. The risk of developing anemia during follow-up was proportionate to their degree of baseline renal impairment. Heart failure patients with an estimated GFR of 45-59 mL/min per 1.73 m^2 were 34% more likely to become anemic than were those with a GFR of 60 or more. Those with a GFR of 30-44 had a more than twofold increased incidence of anemia, while patients with a GFR of 15-29 were at more than fourfold increased risk.

Among those patients with a baseline GFR less than 15 mL/min per 1.73 m^2 who weren't on dialysis, the incidence of anemia during follow-up was more than eight times greater than in patients with a GFR of at least 60. In those on dialysis, the rate increased nearly fivefold.

Other independent predictors of the development of anemia in a multivariate analysis included cirrhosis, with an adjusted 2.3-fold relative risk, compared with noncirrhotic patients, and HIV infection, which conferred an 80% increase in risk. African descent and age greater than 70 years were each associated with a 40% increased risk of becoming anemic, he said.

—Bruce Jancin