Novel Antihypertensive Safe, Effective in Phase III Trial

BY BRUCE JANCIN
Denver Bureau

BARCELONA — The investigational antihypertensive agent aliskiren, alone or with add-on hydrochlorothiazide, effectively maintained 24-hour blood pressure control in a large 1-year phase III clinical trial, Dr. Domenic Sica reported at the joint meeting of the European Society of Cardiology and the World Heart Federation.

Moreover, the drug's strong tissue penetration and long half-life meant that rebound hypertension upon discontinuation was a nonissue. When a subset of participants in the 1,625-patient trial were switched double-blind to placebo for a month following 11 months on aliskiren, their blood pressure (BP) increased only gradually and stayed significantly lower than at baseline, added Dr. Sica, professor of medicine and pharmacology and chairman of clinical pharmacology and hypertension at the Medical College of Virginia, Richmond.

Aliskiren (Rasilez) is a novel once-daily oral agent, first in a new class known as direct renin inhibitors. The drug is now under review by the Food and Drug Administration. Novartis, its developer, anticipates marketing approval by next spring as monotherapy and in fixed-dose combination with hydrochlorothiazide (HCTZ), the physician said in an interview.

The company plans to file for European marketing approval by the end of 2006.

Participants had mild to moderate hypertension and were initially randomized to 150 or 300 mg of aliskiren once daily. The 53% whose blood pressure wasn't adequately controlled on 300 mg/day received add-on HCTZ at 12.5 or 25 mg/day as required.

After 1 year, 86% of subjects were classified as responders, meaning their sitting diastolic BP was below 90 mm Hg and/or at least 10 mm Hg lower than baseline. Patients on monotherapy had mean reductions of 17.4 mm Hg systolic and 13.3 mm Hg diastolic BP. Those on combination therapy with HCTZ averaged reductions of 18.7/12.1 mm Hg.

Particularly impressive was the fact that there were essentially no drug-related side effects, Dr. Sica continued. The incidence and type of adverse events didn't differ between patients on 150, compared with 300 mg of the direct renin inhibitor. And during the double-blind month-long treatment withdrawal phase, the side effects of patients switched to placebo were similar to those who remained on aliskiren monotherapy.

Aliskiren has favorably impressed other investigators as well.

"This is going to be a big drug," Dr. Charles Kilo predicted in an interview. "It's going to be the drug of choice, probably in combination with the diuretic, because the side effect profile is that of placebo."

Dr. Kilo, professor of medicine at Washington University, St. Louis, was principal investigator in a 256-patient study he presented at the congress that showed combining aliskiren with ramipril suppressed the undesirable rise in plasma renin typically caused by ACE inhibitor therapy.

In another clinical trial presented at the conference, Mark A. Munger, Pharm.D., reported that adding 150 mg/day of aliskiren to patients whose blood pressure wasn't adequately controlled with 5 mg/day of amlodipine brought their BP down to levels seen in patients switched to amlodipine monotherapy at 10 mg/day—and with far less of the peripheral edema that often limits calcium channel–blocker therapy.

The incidence of peripheral edema was 11.2% in patients on 10 mg of amlodipine, 3.4% with 5 mg amlodipine, and 2.1% with 150 mg aliskiren plus 5 mg amlodipine, according to Dr. Munger, professor of pharmacotherapy at the University of Utah, Salt Lake City.

Dr. Sica said that short-term studies indicate aliskiren has a prominent left ventricular hypertrophy–reducing effect and strong compartmentalization in the kidneys. This suggests the drug might provide clinical benefits beyond simply its BP-lowering effect.

All of the aliskiren studies presented at the congress were funded by Novartis. ■

Aliskiren's Safety Shown in Analysis of Over 7,000 Patients

BY MITCHEL L. ZOLER
Philadelphia Bureau

BARCELONA — Aliskiren, the first drug from a new class of orally active, direct renin inhibitors, was safe and effective for lowering blood pressure in more than 7,000 patients who were enrolled in seven randomized, controlled trials.

Perhaps the most notable finding from this combined analysis was the new drug's safety. During 6-8 weeks of daily treatment with aliskiren, patients in these studies had adverse effect profiles similar to those of the placebo arms, with fewer than 1% of patients having a serious adverse effect or withdrawing from treatment because of adverse effects, Dr. Matthew R. Weir said at a joint meeting of the European Society of Cardiology and the World Heart Federation.

The trial results also showed that treatment with aliskiren led to incremental reductions in diastolic blood pressure in patients who were already treated with an ACE inhibitor (ramipril), a calcium-channel blocker (amlodipine), or a thiazide diuretic. Aliskiren failed to produce additional blood pressure lowering when it was added to an angiotensin-receptor blocker (valsartan). This last result needs to be confirmed in a new study, said Dr. Weir, professor of medicine and chief of the division of nephrology at the University of Maryland in Baltimore.

Aliskiren dosages in the studies ranged from 75 to 600 mg/day. The drug was tested as monotherapy and was compared with placebo in five studies, and it was tested in combination therapy against active controls in two studies.

Patients enrolled in the seven studies had blood pressures at baseline of about 100 mm Hg diastolic and 151-157 mm Hg systolic. After 6-8 weeks of treatment with aliskiren, diastolic pressure fell by an average of 7-8 mm Hg, and systolic pressure fell by an average of 10-11 mm Hg. The effect of aliskiren on blood pressure reduction was dose-dependent, with a plateau reached once the dosage was 300-600 mg/day. The age and gender of patients appeared to have no effect on the degree of blood pressure reduction.

Aliskiren is being developed by Novartis. The company submitted an application to the Food and Drug Administration last April to market the drug as an antihypertensive. Once approved, aliskiren will be marketed as Rasilez. All seven studies included in the analysis were sponsored by Novartis, and Dr. Weir has received honoraria from Novartis.

Once the drug is available, it will be a good choice for both initial therapy and in combination with other antihypertensive drugs, he said. Aliskiren would be an attractive first-line agent given its good safety profile and low rate of interactions with other drugs.

"The major question is whether inhibiting the renin-angiotensin system [with aliskiren] gives us an opportunity to better protect blood vessels and target organs," Dr. Weir said. Studies designed to address this issue are now in progress.

BP Goals Often Unmet in Diabetic Cardiovascular Patients

BY BRUCE JANCIN
Denver Bureau

BARCELONA — Only two in five Americans with type 2 diabetes and cardiovascular disease—and just one in five in European countries—meet current blood pressure goals, Benjamin A. Steinberg reported at the joint meeting of the European Society of Cardiology and the World Heart Federation.

These findings from a huge contemporary international database underscore the urgent need for physicians to do much better at identifying and controlling high blood pressure in this very-high-risk population, Mr. Steinberg stressed in an interview.

During a year-long fellowship to conduct cardiovascular research, Mr. Steinberg, a medical student at Johns Hopkins University, Baltimore, analyzed the CardioMonitor database for 1998-2004. CardioMonitor is an annual survey of outpatients with cardiovascular disease in multiple countries. The survey relies on medical records that are provided by primary care physicians and cardiologists.

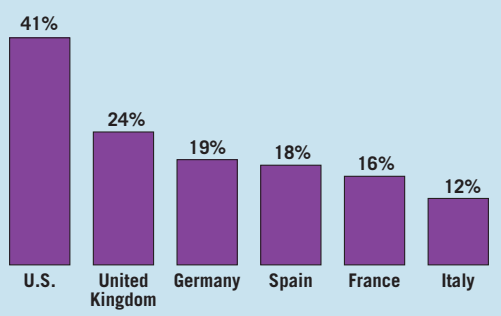
For the years 1998-2004 excluding 2002, when the survey wasn't conducted, the CardioMonitor database included nearly 155,000 patients with cardiovascular disease in the United States and five European nations. A total of 23,139 of them also had type 2 diabetes.

The prevalence of diabetes among cardiovascular patients rose during the years of the study, in some countries quite markedly. For example, the reported prevalence of type 2 diabetes among patients with cardiovascular disease doubled in France and the United Kingdom between 1998 and 2004, while in the United States, it climbed from 15.1% to 20.5%. The prevalence in 2004 was greatest in Germany, at 24.9%. In Spain it was 19.5%, up from 11.8% in 1998, while in Italy the prevalence of type 2 diabetes among cardiovascular patients was just 9.6% in 2004.

The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure VII (JNC-VII) goal of a systolic blood pressure below 130 mm Hg was achieved by only 41% of American diabetic cardiovascular patients. European rates were far lower, Dr. Steinberg continued. (See box.)

The less stringent European Society of Cardiology blood pressure target in place in 2004—a systolic pressure below 140 mm Hg—was met by 72% of American patients, 53% in the United Kingdom, 49% in Spain, 47% in France, 44% in Germany, and 33% in Italy. ■

Europe Lags Behind U.S. in Meeting JNC-VII BP Goal Of <130 mm Hg for Diabetic Cardiovascular Patients



Note: Based on a database of 155,000 patients.
Source: Mr. Steinberg

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