Aliskiren Boosts Diuretic's Benefit

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NEW YORK — A new oral antihypertensive drug, the renin inhibitor aliskiren, was effective when given with a diuretic, and also achieved consistent, 24-hour blood pressure control as monotherapy in a pair of studies that together included about 3,000 patients.

The successful pairing of aliskiren with the diuretic hydrochlorothiazide was seen as a step forward for this agent—the first from a novel drug class—because it showed evidence of blocking renin, the rate-limiting enzyme of the renin-angiotensin-aldosterone system. Water depletion by diuretics stimulates renin release from the kidneys, but the activity of this renin surge was effectively blunted by concurrent treatment with aliskiren, according to the combination study.

"It's a proof of principle," Dr. George L. Bakris said in an interview at the annual meeting of the American Society of Hypertension. But despite the encouraging development, a much fuller picture of aliskiren will unfold over the next year as new data are reported on the drug's ability to exert additional effects, such as controlling heart failure and preserving renal function.

The hope is that aliskiren and other renin inhibitors may prove as effective as agents in other drug classes that inhibit the renin-angiotensin-aldosterone system—the ACE inhibitors and the angiotensin-receptor blockers, said Dr. Bakris, director of the Rush University Hypertension Center in Chicago.

An even greater hope is that a drug like aliskiren may have antihypertensive effects and other actions additive to or even synergistic with the effects of drugs from these other classes.

Novartis AG, the company that makes aliskiren (Rasilez), has submitted a licensing application to the Food and Drug Administration for approval to market aliskiren for lowering blood pressure. A decision by the agency is expected in early 2007, said Dr. Steve Zelenkofske, senior medical director for the U.S. aliskiren program.

Clinical research data on aliskiren were first reported last March at the annual meeting of the American College of Cardiology from a study of 672 hypertensive patients who received aliskiren monotherapy.

Additional results involving a subset of 216 patients who underwent ambulatory blood pressure monitoring were reported in a poster at the American Society of Hypertension meeting by Dr. Jerry Mitchell, a researcher with the Texas Center for Drug Development in Houston.

The findings showed that once-daily treatment with aliskiren, which has a 40-hour serum half-life, led to "smooth blood pressure control" with no signs of blood pressure variability and "minimal loss of effect throughout 24 hours," said Dr. Mitchell. "Blood pressure variability is associated with end-organ damage to the heart, kidney, and brain," but aliskiren appeared effective at eliminating early-morning blood pressure surges, he said.

Combination regimens of aliskiren and hydrochlorothiazide led to larger reductions in blood pressure than were seen with either drug alone.

In addition, in the full study of 672 patients, treatment with aliskiren had a safety profile that was similar to the placebo-treated control group. This study was funded by Novartis; Dr. Mitchell reported no other financial relationship with the company.

Combination treatment with aliskiren and hydrochlorothiazide was assessed in a study of 2,776 patients in Argentina, reported Dr. Alberto S. Villamil in a second poster at the meeting. The study involved 15 different treatment groups: Aliskiren monotherapy was administered at dosages of 75, 150, or 300 mg/day, hydrochlorothiazide monotherapy was given at dosages of 6.25, 12.5, or 25 mg/day, and various combinations of both drugs at these dosages were also tested. The study included a placebo group, and treatment was continued for 8 weeks. This study was sponsored by Novartis; Dr. Villamil reported no other financial relationship with the company.

Aliskiren monotherapy lowered blood pressure in a dose-dependent way, with the 300 mg/day dosage producing an average 15.7 mm Hg drop in systolic pressure and a 10.3 mm Hg reduction in diastolic pressure after 8 weeks. This reduction compared with the 14.3/9.4 mm Hg decrease in pressure produced by the highest dose of hydrochlorothiazide monotherapy tested, and the 7.5/6.9 mm Hg average decline in the placebo-treated group.

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The biggest decline was produced by the highest dosage tested—300 mg aliskiren plus 25 mg hydrochlorothiazide—which led to an average pressure cut of 21.2/14.3 mm Hg, reported Dr. Villamil, chief of the hypertension section at Dr. Cosme Argerich Hospital in Buenos Aires.

Treatment-related adverse effects were reported in 12% of patients receiving the highest dosage of aliskiren plus hydrochlorothiazide, compared with a 9% rate in the placebo group.

Perhaps the most intriguing result from this study was reported in a separate poster at the meeting by Dr. David Calhoun, a cardiologist at the University of Alabama, Birmingham. The researchers measured plasma renin levels and plasma renin activity in all participants at baseline and after 8 weeks of treatment.

Plasma renin concentrations rose from baseline in all patients,. The largest increases were in patients who received both antihypertensive drugs. On average, renin concentration rose by 348%, compared with baseline, in patients who took 300 mg of aliskiren daily, by 108% in patients who received 25 mg of hydrochlorothiazide daily, and by more than 1200% in patients who received both dosages simultaneously. (See box.)

But the data also showed that aliskiren was effective at blocking renin activity. Plasma renin activity fell by an average of 54%-65%, compared with baseline, in patients who took any dosage of aliskiren (75, 150, or 300 mg/day) as monotherapy.

And in those patients treated with any of the combined regimens of aliskiren and hydrochlorothiazide, renin activity dropped by an average of 46%-64%. In contrast, patients treated with 25 mg/day of hydrochlorothiazide alone showed increases in plasma renin activity of 72%, and those who received 12.5 mg/day of hydrochlorothiazide alone had a 45% boost in their plasma renin activity.

Combined treatment with aliskiren appeared to give an "enhanced antihypertensive effect and potentially improved end-organ protection through effective suppression of the renin system," concluded Dr. Calhoun and his associates in their poster. ■

Aliskiren Blunts Renin Activity

Treatment	Renin Concentration (change from baseline)	Renin Activity (change from baseline)
Aliskiren (300 mg/day)	+348%	–58%
HCTZ (25 mg/day)	+108%	+72%
Aliskiren plus HCTZ (300 mg/25 mg per day)	+1211%	–62%
Placebo	+30%	+1%

Note: All plasma renin measurements in 2,776 patients were made after 8 weeks of treatment.
Source: Dr. Calhoun

ELSEVIER GLOBAL MEDICAL NEWS

ARB Increases Insulin Sensitivity In Hypertensives

BY ERIK L. GOLDMAN
Contributing Writer

MADRID — Angiotensin I receptor blockade with losartan improves insulin sensitivity independent of its effects on blood pressure in hypertensive individuals at risk for metabolic syndrome, reported Dr. Tonje Aksnes at the annual meeting of the European Society of Hypertension.

Previous studies have shown that blocking the renin-angiotensin system prevents new-onset diabetes to a far greater degree than does pressure control with calcium channel blockers, which suggests that angiotensin receptor blockers (ARBs) have direct effects on glucose metabolism. Calcium channel blockers probably do not have metabolic effects, said Dr. Aksnes of the cardiovascular and renal research centre at Ullevål University Hospital, Oslo.

To test this hypothesis, Dr. Aksnes and colleagues compared two regimens—10 mg/day amlodipine and 100 mg/day losartan plus 5 mg/day amlodipine—in a cohort of 21 subjects with essential hypertension. The patients had a mean age of 59 years and had baseline systolic pressures in the 160-180 mm Hg range and diastolic pressures of 95-110 mm Hg.

All had impaired glucose tolerance or impaired fasting glucose levels, and at least one of the following signs of metabolic syndrome: microalbuminuria, low HDL cholesterol level, elevated triglycerides, waist-to-hip ratio greater than 0.9 for men or 0.85 for women, or body mass index greater than 28 kg/m^2.

After a 4-week run-in period during which all of the patients were given 5 mg/day amlodipine, they were randomised to receive, in addition to the 5 mg/day amlodipine, 100 mg/day losartan or an additional 5 mg/day of amlodipine for 8 weeks. This was followed by a 4-week washout during which all of the patients were again put on 5 mg/day amlodipine alone. For the final phase, the two patient groups were crossed over: Those who were on the ARB during the initial trial phase were switched to the 10-mg calcium channel blocker, and those who were initially on the calcium channel blocker switched to the ARB.

The two drug regimens gave comparable levels of blood pressure control. Amlodipine alone, at a 10 mg daily dosage, reduced mean pressure to 141/88 mm Hg from a baseline mean of 160/96 mm Hg. Losartan reduced pressure to 143/88 mm Hg.

The investigators assessed glucose metabolism by two separate hyperinsulinemic glucose clamp examinations. They found a consistent and significant difference between the two regimens. While the patients were on 10 mg amlodipine alone, they had a mean insulin sensitivity of 4.2 mg/mL per minute. This increased to 4.9 mg/mL per minute while they were on the ARB plus 5 mg amlodipine.

There was no significant difference in HbA_{1c} values between the two treatment regimens. Likewise, blood glucose levels were more or less consistent and unchanged by either treatment. The main impact, it seemed, was on the degree of insulin sensitivity.

"The present data suggest that angiotensin I receptor blockade improves glucose metabolism at the cellular level, beyond what can be expected by the vasodilatation and blood pressure reduction alone," said Dr. Aksnes. ■