Combo Antihypertensives Should Be First Line

Nearly half of patients on two agents met diastolic goals compared with a third of those on monotherapy.

BY MITCHEL L. ZOLER
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NEW YORK — Combination antihypertensive therapy must be used more aggressively as the first-line treatment for patients, especially those with diabetes, Dr. Joel M. Neutel said at the annual meeting of the American Society of Hypertension.

"We know that we need combination therapy to get patients to their goal blood pressure, but in practice [physicians in the United States] are very reluctant to titrate multiple drugs," said Dr. Neutel, medical director of clinical pharmacology at the Orange County Research Center in Tustin, Calif. "We need to be much more aggressive with combination therapy, and use even three or four drugs to get patients to their goal. All the evidence shows that there is no increase in adverse effects with more aggressive treatment."

The added value of a two-drug combination compared with monotherapy was documented by the results from two separate studies reported by Dr. Neutel at the meeting. One study examined adding the calcium channel blocker amlodipine to treatment with either quinapril or losartan. The second study looked at the effect of adding the angiotensin II receptor blocker (ARB) irbesartan to the diuretic hydrochlorothiazide (HCTZ).

Dr. Neutel acknowledged that the results from many prior studies had already proved the added efficacy and safety of combination therapy, but he stressed the importance of adding to this evidence base.

"With more reports, we hope that physicians will be more willing to use combination therapy and use it as first-line therapy," he said.

Only about half of U.S. patients with diagnosed hypertension are on medical treatment, and within that fraction only about one-third have their blood pressure controlled to their goal level. Among patients with diabetes, fewer than 20% are at their goal pressure, which was set at less than 130/80 mm Hg in the National Heart, Lung, and Blood Institute's Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

The first study enrolled diabetic patients with a systolic pressure of 140-170 mm Hg and a diastolic pressure of 90-110 mm Hg who were not on any treatment. Patients with a pressure of more than 135/80 mm Hg who were uncontrolled on either monotherapy or combination therapy were also included.

Patients were initially treated with either 20 mg/day of the ACE inhibitor quinapril or 50 mg/day of the ARB losartan. After 4 weeks, the daily dosages were titrated to 40 mg quinapril or 100 mg losartan. After another 4 weeks, patients were randomized to treatment with either 5 mg/day of amlodipine or placebo. After 6 weeks, the amlodipine dosage was increased to 10 mg/day.

The primary end point was the percentage of patients whose blood pressure was below 130/80 mm Hg after 6 weeks of treatment on the final, titrated regimen. This goal was met by 27.5% of the 211 patients in the combination-therapy group, and by 12.5% of the 200 patients treated with just one drug, a statistically significant difference. The combination regimens were as safe as monotherapy, with no excess incidence of adverse effects, Dr. Neutel reported.

The second study randomized nondiabetic patients to either combination therapy with 150 mg/day irbesartan plus 12.5 mg/day HCTZ, or to monotherapy with the ARB irbesartan alone at a dosage of 150 mg/day. After 1 week, the dosage received by all patients was doubled, to 300 mg irbesartan plus 25 mg HCTZ or to 300 mg of irbesartan alone. The primary end point was the percentage of patients with a diastolic pressure of less than 90 mm Hg after 5 weeks of treatment.

This goal was reached by 47% of the 423 patients in the combination arm, and by 33% of the 206 patients in the monotherapy group, a statistically significant difference. The study's secondary end point was the percentage of patients with a pressure of less than 140/90 mm Hg, which was reached by 35% of patients on combination therapy and by 19% of those on monotherapy. The adverse-effect profile and severity was similar in the two treatment groups, Dr. Neutel said. ■

Aliskiren Plus a Diuretic Controls 24-Hour Blood Pressure

BY MITCHEL L. ZOLER
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NEW YORK — A new oral antihypertensive drug, the renin inhibitor aliskiren, was effective when given with a diuretic, and it 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.

The hope is that aliskiren and other renin inhibitors may prove as effective as agents from the 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.

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 from this trial, 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.

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 also included a placebo group, and treatment was continued for 8 weeks. This study was also 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.

Combination regimens of aliskiren and hydrochlorothiazide led to larger reductions in blood pressure than either drug alone. 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, president of Fundapres and chief of the hypertension section at Dr. Cosme Argerich Hospital in Buenos Aires.

Treatment-related adverse effects were reported in 12% of patients who received 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, with the largest increases seen in patients who received both antihypertensive drugs. But the data also showed that aliskiren was effective at blocking renin activity (see chart). ■

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)	+1,211%	–62%
Placebo	+30%	+1%

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

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