Fixed-Dose Combo Therapy Boosts BP Control

Patients in the as-yet unblinded ACCOMPLISH had the highest overall control rates ever reached in a U.S. trial.

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Fixed-dose combination therapy increased blood pressure control rates from 37% to 76% over 18 months in patients with high-risk hypertension in a large, multinational trial reported at the annual meeting of the American Society of Hypertension.

Control rates were even higher in the U.S. cohort, where 80.5% of patients achieved control to less than 140 mm Hg—an unprecedented rate for a U.S. trial, reported Dr. Kenneth Jamerson, who presented the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial. Significant reductions in systolic blood pressure were seen across all patient populations, including African Americans.

Dr. Jamerson and associates randomized 11,463 patients age 55 years or older with a systolic blood pressure of at least 160 mm Hg or currently on antihypertensive therapy to treatment with either Lotrel, which contains the ACE inhibitor benazepril and the calcium-channel blocker amlodipine, or to benazepril plus the diuretic hydrochlorothiazide (HCTZ).

At 18 months, patients achieved an average decline in blood pressure from 145/80 mm Hg to 132/74 mm Hg. Almost one-fifth of patients went on to achieve a systolic BP of less than 120 mm Hg. The study remains blinded, so blood pressure reductions were not stratified based on treatment. Cardiovascular morbidity and mortality outcomes, the study's primary end point, are anticipated after the trial ends in 2008.

Dr. Jamerson believes the current data will help shift the traditional approach to hypertension management in which clinicians initiate monotherapy then sequentially use additional medications as needed in order to achieve target blood pressure goals.

"For more than 2 decades, too many clinicians have chanted the mantra, 'start low, go slow,' despite having lots of data that multiple drugs are going to be necessary to achieve blood pressure control," said Dr. Jamerson, professor in the department of internal medicine, division of cardiovascular medicine, University of Michigan, Ann Arbor.

"We think we provide substantial evidence to suggest that initial combination therapy is very effective, and think there is substantial evidence here to support broadening the use of combination therapy as an initial therapy."

Although 97% of patients in the study were already taking antihypertensive medication, just 37.5% had their blood pressure controlled at baseline to 140/90 mm Hg—the currently recommended target in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

Dosages were titrated at month 2 to a fixed dose of benazepril 40 mg/amlodipine 10 mg or benazepril 40 mg/HCTZ 25 mg, with the option of adding on other antihypertensive agents at month 3. Overall, 35% of patients used add-on medications, said Dr. Jamerson, who has received grant/research support from Novartis, which sponsored the study and markets Lotrel.

At 18 months, the average systolic BP declined from 153 mm Hg to 137 mm Hg among Nordic patients, from 142 mm Hg to 129 among the U.S. cohort, and from 145 mm Hg to 133 mm Hg among African Americans.

A bit more work needs to be done among patients with diabetes and chronic kidney disease, Dr. Jamerson said. Their respective mean systolic BPs decreased from 145 mm Hg to 131.5 mm Hg and from 149 mm Hg to 136 mm Hg—both short of the JNC 7 goal of 130 mm Hg for these difficult-to-treat populations. Overall, 60% of ACCOMPLISH participants have diabetes, and had a BP control rate of 15%.

ASH President Suzanne Oparil said in an interview that these are the highest overall control rates ever achieved, but at roughly 80% are only slightly higher than the 65% reported in previous hypertension trials. The low systolic BP rates reported in the U.S. cohort may reflect higher values at baseline in the Nordic cohort and a more cautious treatment approach typically used by European physicians.

Dr. Oparil, professor of medicine, physiology, and biophysics at the University of Alabama, Birmingham, took issue with the notion that these results will shift treatment patterns, as the VALUE, or Valsartan Antihypertensive Long-term Use Evaluation trial, already provided clinicians with the lesson that controlling blood pressure quickly is important. "It's not that paradigm shifting because that's what we're preaching anyway," she said.

Some members of the audience suggested that the go-slow approach remains warranted in certain patients such as the elderly because of potential side effects including hypotension. Hypotension was reported in 207 or 2% of patients and 0.4% of these were hospitalized for the condition. Dizziness was reported in 2,144 (19%) patients, peripheral edema in 2,009 (17.6%), and chest pain in 159 (1.4%).

'For more than 2 decades, too many clinicians have chanted the mantra, "start low, go slow."'
DR. JAMERSON

Dr. Jamerson responded by noting that the average age of the ACCOMPLISH cohort was 68 years, but added that the final data will be analyzed to determine exactly how many hypotensive events are drug-related.

The study is powered to show that the combination of benazepril and amlodipine will reduce cardiovascular morbidity and mortality in patients with high-risk hypertension by 15%, compared with the combination of benazepril and HCTZ. Theoretical research suggests that a combination of ACE inhibitors and calcium-channel blockers might confer an additional benefit, as they have been shown independently to increase vascular nitric oxide production, Dr. Jamerson said. ■

FDA Panel Backs Avalide as First-Line Hypertension Therapy

BY ELIZABETH MECHCATIE
Senior Writer

ROCKVILLE, MD. — A Food and Drug Administration advisory panel unanimously recommended that the combination antihypertensive product irbesartan and hydrochlorothiazide (HCTZ) be approved as a first-line treatment for hypertension.

At a meeting on April 18, the Cardiovascular and Renal Drugs Advisory Committee voted 7-0 in favor of approving the fixed-dose angiotensin receptor blocker–diuretic combination product as initial therapy.

The company has proposed that Avalide be indicated as initial treatment of severe hypertension. The panel was asked to comment on the wording of the indication statement that would be included in the label. Several were supportive of wording that Avalide can be considered as initial treatment when control of blood pressure is not likely to be achieved with one drug, or for moderate to severe hypertension.

The product, marketed as Avalide by Bristol-Myers Squibb (BMS), was approved in 1997 for treating hypertension, with a statement in its label that says the combination therapy should not be used until a patient has failed to achieve the desired effect with monotherapy.

The FDA usually follows the recommendations of its advisory panels, which are not binding.

The combination antihypertensives that have previously been approved as first-line treatments are Capozide (captopril and HCTZ), Ziac (bisoprolol/HCTZ), and Hyzaar (losartan/HCTZ).

At the meeting on Avalide, BMS provided the results of two studies. The first, a pivotal trial of 695 patients (mean age was 52) with severe hypertension (an untreated diastolic blood pressure of at least 110 mm Hg or on monotherapy with a diastolic blood pressure of at least 100 mm Hg), compared Avalide with irbesartan monotherapy as initial therapy. The second, a supportive trial, compared Avalide with irbesartan and HCTZ monotherapies in patients with moderate hypertension. The studies used forced titration to 300 mg/25 mg of Avalide, 300 mg of irbesartan, or 25 mg of HCTZ.

In the pivotal trial, 47% of those on Avalide had achieved a diastolic blood pressure below 90 mm Hg at 5 weeks, the primary end point, compared with 33% of those on irbesartan monotherapy, a highly significant difference.

Among black subjects (about 14% of the subjects), 40% of those on Avalide had achieved a diastolic blood pressure below 90 mm Hg at 5 weeks, compared with nearly 15% of those on irbesartan. In diabetic subjects, 33% had achieved blood pressure goal below 140/90 mm Hg, compared with 23% of those on irbesartan at 5 weeks.

Overall, Avalide was safe and well tolerated, and was comparable to irbesartan monotherapy, with no increase in dizziness or syncope and no serious adverse events related to treatment. No deaths were reported, according to BMS.

About 4% of patients in each group experienced dizziness, and headache was reported in 4% of those on Avalide, and 6% of those on irbesartan. Hypotension was reported in 0.6% of those on Avalide, and none of those on monotherapy.

About 2% in each group discontinued treatment for an adverse event. Among the 92 patients 65 and older, Avalide was well tolerated, there were no cases of hypotension or syncope, and dizziness was no more common than in younger patients.

In the supportive study of about 500 patients with moderate hypertension, Avalide was more effective in reducing blood pressure than either irbesartan or HCTZ alone, had a comparable safety profile, and was well tolerated in the elderly, according to BMS.

Several members of the advisory panel said that the company should get more data on the combination as first line treatment in elderly patients and in patients with renal dysfunction.

Approval as a first-line treatment would not affect the patent for Avalide, which expires in 2012, a BMS spokesperson said. ■

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