MEETING HIGHLIGHTS

American Society of Hypertension
23rd Annual Scientific Meeting and Exposition
Reuben B. David

More than 2,000 blood pressure specialists attended the American Society of Hypertension (ASH) annual meeting in New Orleans from May 14 to 17, 2008. Among key presentations were two large trials on combination therapy and one trial featured in an ASH press briefing on an investigational agent targeting two receptors.

Combination and Dual Receptor Antagonist Treatments

Amlodipine/Olmesartan (Azor) Therapy
- George Bakris, MD, Professor of Medicine, University of Chicago, Chicago, Ill.
- Suzanne Oparil, MD, University of Alabama, Birmingham, Ala.
- Steven G. Chrysant, MD, University of Oklahoma School of Medicine, Tulsa, Okla.
- Dean Kereiakes, MD, Christ Hospital Heart and Vascular Center, Cincinnati, Ohio

Hypertensive patients (n = 1,940) across a broad range of often problematic subgroups were treated effectively with Azor (Daiichi Sankyo), a combination of Pfizer’s calcium antagonist amlodipine (Norvasc) and Daiichi Sankyo’s angiotensin-receptor blocker (ARB) olmesartan medoxomil (Benicar). In a large registration trial using prespecified analyses, Dr. Bakris found that these randomly assigned, double-blind subgroups all benefited from the combination, compared with patients receiving monotherapy. The subgroups consisted of 481 African-American patients; 241 Hispanic/Latino subjects; 1,256 participants with a body mass index (BMI) of 30 kg/m² or more; and 258 diabetic patients. Twelve regimens were as follows: 8 weeks of amlodipine 5 mg/day or 10 mg/day as monotherapy; olmesartan 10 mg/day, 20 mg/day, or 40 mg/day as monotherapy; and each of the six possible combinations of these doses of amlodipine and olmesartan; or placebo.

Dr. Bakris reported that the antihypertensive efficacy of amlodipine/olmesartan was similar among patients with or without diabetes. Patients starting the combination were more likely to achieve the recommended blood pressure (BP) goal of 130/80 mm Hg. Among patients with diabetes, only 10% to 13% achieved that goal, compared with 55% to 60% of non-diabetic participants.

He also said that among obese patients, regardless of BMI, benefits were generally clinically meaningful and greater with the combination therapy, although they were somewhat lower among subjects with higher BMIs. With the highest dose of the combination, systolic BP among patients with higher BMIs was reduced by 20.6 mm Hg and diastolic BP was reduced by 17.9 mm Hg. In patients with BMIs lower than 30 kg/m², systolic BP was reduced by 30.6 mm Hg and diastolic BP was reduced by 20.6 mm Hg. The percentages of patients receiving combination therapy who achieved BP goals at the eighth week also tended to be greater if the BMI was below 30 kg/m² (41%–55%) than if the BMI was higher (28%–52%).

“Olmesartan should reduce the edema associated with amlodipine,” Dr. Bakris stated. Higher edema rates associated with amlodipine monotherapy (40.3% at 10 mg/day) were attenuated in the combination treatment groups (25.2%–28.8%).

Dr. Oparil said that mean reductions in systolic and diastolic BP were significantly greater with amlodipine/olmesartan than with olmesartan alone in African-American patients, except in the case of systolic BP in those treated with amlodipine 5 mg/day and olmesartan 10 mg/day. She emphasized that with amlodipine/olmesartan 10/40 mg/day, the magnitude of BP reductions in the African-American patients (~29 mm Hg/–16 mm Hg) approached that of the non–African-American patients (~31 mm Hg and –20 mm Hg, respectively).

For Hispanic/Latino patients, all combinations resulted in greater systolic and diastolic BP reductions than with monotherapy. In addition, reductions were similar among Hispanic/Latino patients and non–Hispanic/Latino subgroups.

In the BENIFORCE trial (Benicar Efficacy: New Investigative Findings show Olmesartan medoxomil safely and effectively Reduces blood pressure Compared with placEbo), 276 patients with stage 1 or 2 hypertension were randomly assigned to receive olmesartan 20 mg/day or placebo. This dose was then titrated upward at three-week intervals if patients did not reach a target of below 120/80 mm Hg according to the following schedule: olmesartan 40 mg/day (weeks 4 to 6), olmesartan plus hydrochlorothiazide (HCTZ) 40/12.5 mg/day (weeks 7 to 9), and olmesartan/HCTZ 40/25 mg/day (weeks 10 to 12). Patients were maintained on their current medication doses as long as BP was controlled to target levels, stated Dr. Chrysant.

The trial’s primary endpoint was the mean difference in BP reduction between the olmesartan-based regimen and placebo. Systolic BP was reduced by 22.1 mm Hg, diastolic BP was reduced by 12.2 mm Hg. In patients with stage I hypertension

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Dr. Kereakes reported on 148 patients with stage 2 hypertension (systolic: 160 mm Hg and above; diastolic: 100 mm Hg and above). Mean differences from placebo were −22.5 mm Hg systolic BP and −13.2 mm Hg diastolic BP. Overall, for patients receiving olmesartan-based therapy, treatment-related adverse events were not significantly increased.

Commenting on all of these findings, Dr. Bakris said that olmesartan alone “is a very good starting choice for patients with stage I hypertension without diabetes.” He recommended initial monotherapy with a diuretic or calcium antagonist for stage I elderly or African-American patients. For those with stage 2 hypertension, he said, “I start with combination therapy on top of lifestyle modification.”

A Dual Receptor Antagonist (PS433540, DARA)
• Joel M. Neutel, MD, Associate Professor of Medicine, University of California, Irvine

An investigational antihypertensive agent that antagonizes two receptors appears to offer stronger BP reductions than existing monotherapies, according to results of a clinical trial presented by Dr. Neutel. The agent, PS433540 (Pharmacopeia, Inc.), is a dual angiotensin and endothelin receptor antagonist (DARA). Its half-life is about 15 hours, which makes it likely, he said, to be a once-daily agent. Both angiotensin II and endothelin are powerful vasoconstrictors thought to contribute to elevated BP.

Dr. Neutel noted that DARA therapy has been safe and well tolerated in early trials and, at 250 mg, has provided ARB-receptor blockade similar to that of irbesartan (Avapro, Bristol-Myers Squibb/Sanofi-Synthelabo) at 300 mg. At 500 mg, blockade of both types of receptors is believed to be complete.

Inclusion criteria for this first trial among hypertensive subjects were a mean (sitting) systolic BP of between 150 and 179 mm Hg and a diastolic BP below 110 mm Hg. For those participants qualifying, 24-hour ambulatory BP monitoring had to show a mean daytime systolic BP of 140 to 179 mm Hg and a diastolic BP of less than 110 mm Hg. Patients who met these criteria were then randomly assigned to receive DARA 200 mg or 500 mg daily or placebo. Ambulatory BP monitoring was conducted after four weeks of treatment. The primary endpoint was the change in mean systolic BP.

Among 114 patients randomly assigned, 93 were evaluable. Their mean age was 59 years, and approximately 80% were Caucasian. Mean systolic BP was 160 mm Hg, and mean diastolic BP was 94 mm Hg. Changes from baseline for systolic and diastolic BP, respectively, were as follows: placebo, −0.4 mm Hg and +0.3 mm Hg (n = 25); DARA 200 mg, −12.20 mm Hg and −10.5 mm Hg; and DARA 500 mg, −14.3 mm Hg and −9.8 mm Hg.

The pattern persisted, although it was attenuated, for mean nighttime ambulatory BP monitoring: placebo, −2.7 mm Hg (systolic) and −1.6 mm Hg (diastolic); DARA 200 mg, −10.7 mm Hg and −6.8 mm Hg; and DARA 500 mg, −14.3 mm Hg and −9.1 mm Hg (P = not significant).

“These numbers are extremely impressive,” Dr. Neutel said, noting that the DARA reductions far surpassed what is expected for monotherapy treatment. Systolic BP reductions, from a baseline of −14.4 mm Hg during the final two hours of the dosing period for the 500-mg dose, Dr. Neutel said, “clearly demonstrate that this is a once-daily drug.”

Adverse events were experienced by 27% of patients receiving the 500-mg dose and by 26.5% of patients receiving placebo.

“They were no different from placebo despite the tremendous reductions in blood pressure,” he commented.

Peripheral edema, considered a concern with endothelins, was reported in only one patient receiving the higher DARA dose. The other concern about endothelins has been liver abnormalities, and none were reported. The lack of adverse events usually associated with endothelin antagonists, Dr. Neutel speculated, is a result of the specificity of this agent for the endothelin A receptor.

Dr. Neutel concluded, “What you see here is a new class of drug that effectively lowers systolic and diastolic BP in stage I and II hypertensive patients. The magnitude of the treatment effect appears greater than that of existing monotherapies.”

When compared with placebo (P < 0.001).

Seated office BP changes from baseline (systolic and diastolic, respectively), were similarly significant: placebo, −4.2 mm Hg and +1.6 mm Hg; DARA 200 mg, −16.9 mm Hg and −10.5 mm Hg; and DARA 500 mg, −17.3 mm Hg and −9.8 mm Hg.

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