MEETING HIGHLIGHTS

American Society of Hypertension and American Urological Association

Walter Alexander

American Society of Hypertension, 24th Annual Scientific Meeting

This year’s meeting of the American Society of Hypertension (ASH), which took place from May 6 to 9, 2009, in San Francisco, attracted more than 2,000 hypertension experts. Sessions reviewed in this article cover three clinical trials of fixed-dose combinations (Lotrel, Lotensin, Benicar HCT, Azor) and one single-agent trial of an endothelin receptor antagonist (darusentan) in treatment-resistant hypertension.

The ACCOMPLISH Trial: Amlodipine/Benazepril (Lotrel) and Benazepril/Hydrochlorothiazide (Lotensin)

- Kenneth Jamerson, MD, University of Michigan Health System, Ann Arbor, Mich.
- Moderator, George Bakris, MD, University of Chicago–Pritzker School of Medicine, Chicago, Ill.

Was the improved event rate in ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension) attributable to lower blood pressure (BP) or to the specific drugs or drug classes given? Evidence from a study comparing the ACCOMPLISH regimen of amlodipine besylate/benazepril (AML/BZ, Lotrel, Novartis) with the standard of care, benazepril plus hydrochlorothiazide (BZ/HCTZ) (Lotensin HCT, Novartis), evaluated through 24-hour ambulatory BP monitoring, suggest that it was the drugs, not the reductions in BP.

In this large 11,500-patient trial, cardiovascular events were 20% lower with AML/BZ (Lotrel) than with BZ/HCTZ (Lotensin) among hypertensive patients. While systolic BP reductions were significantly greater with AML/BZ than with BZ/HCTZ, the difference was small (0.9 mm Hg). The hypothesis of Dr. Jamerson’s current analysis of 573 hypertensive patients evaluated through 24-hour ambulatory BP monitoring was that after two years of treatment, there would be no significant differences in mean 24-hour blood pressure between the two treatment groups. Ambulatory BP monitoring, he said, is by far the most reliable and accurate means for testing blood pressure.

The mean age was 68.5 years among the 371 men and 202 women who were enrolled. Mean baseline systolic BP was 142.3 mm Hg in the AML/BZ group and 140.9 mm Hg in the BZ/HCTZ group.

After two years, the mean ambulatory systolic BP over 24 hours was not significantly lower with BZ/HCTZ (~1.6 mm Hg, P = 0.128). No subgroups stood out, Dr. Jamerson said at an

Mr. Alexander is a freelance medical writer living in New York City.

Olmesartan Medoxomil plus Hydrochlorothiazide (Benicar HCT) Safe in Elderly Adults

- Joel M Neutel, MD, Associate Professor of Medicine, University of California–Irvine.

Elderly patients with hypertension achieved significant reductions in systolic and diastolic BP when they were treated according to a stepwise regimen based on olmesartan (Benicar, Dainichi Sankyo). The strategy enabled 67% of patients to achieve the recommended BP goal of below 140/90 mm Hg. Long-term clinical trials have shown greater benefit from treatment in the elderly with uncontrolled systolic and diastolic BP or isolated systolic hypertension than in younger patients, Dr. Neutel said. Only half of elderly patients, however, achieve cuff BP goals of less than 140/90 mm Hg. In addition, age-related increases in systolic BP independently predict cardiovascular mortality in older adults.

The BeniSILVER (Benicar Efficacy: New Investigation Shows olmesartan medoxomil treatment Increasingly Leads Various Elderly populations to safe BP Reductions) study included 176 patients 65 years of age or older with newly diagnosed or uncontrolled hypertension (140/90 mm Hg or above during treatment with an antihypertensive medication). After
a placebo run-in period, participants in the 12-week active-treatment study received olmesartan 20 mg. For patients not achieving mean cuff BP of 120/70 mm Hg or lower, the doses were then titrated upward from 20 mg to 40 mg of olmesartan at week three, with 12.5 mg of HCTZ (Benicar HCT) added at week six and increased to 25 mg at week nine. The primary endpoint of the open-label, blinded-endpoint study was a change in systolic BP from baseline to week 12, as assessed by 24-hour ambulatory BP monitoring.

In this study, the mean age of the patients was 71.9 years (52.3% men) in a mostly Caucasian population (83%). At baseline, the mean systolic BP was 165.5 mm Hg and the mean diastolic BP was 87.7 mm Hg. Baseline BP values, as assessed by 24-hour ambulatory monitoring, were 148.8 and 80.9 mm Hg, respectively.

The change from baseline in 24-hour ambulatory BP monitoring was −25.7 mm Hg for systolic BP and −12.3 mm Hg for diastolic BP (P < 0.0001 vs. baseline). Cuff BP reductions in the office were similar (25.4 and 10.5 mm Hg). Sixty-seven percent of patients achieved the recommended cuff level of below 140/90 mm Hg in the sitting position. Dr. Neutel noted that adverse event rates were low, with drug-related dizziness and hypotension of 3.4% or below. Nine patients (5.1%) discontinued therapy because of treatment-emergent adverse events.

In an interview, Dr. Neutel commented that diuretics address volume-dependent hypertension particularly well in the elderly and that angiotensin-receptor blockers (ARBs) are thought to address age-related vessel stiffness by correcting plasma filtration rates had to show at least “reasonable” renal function (at or above 30 mL/minute per 1.73 m²). If a patient had severe or uncontrolled hypertension, the antihypertensive regimen was expanded to include a renin inhibitor. The goal of treatment was to get rid of “white coat” and placebo effects, we could still get very significant control.”

The intent was also to confirm that the vasodilating effects of the ARB would effectively combat the edema commonly caused by AML. After a run-in placebo period, doses for 185 patients were titrated upward as follows: from amlopidine 5 mg to amlopidine 5 mg/olmesartan 20 mg, to amlopidine 5 mg/olmesartan 40 mg, and to amlopidine 10 mg/olmesartan 40 mg if their BP, while they were seated, was 120/80 mm Hg or more.

After 12 weeks of treatment, systolic and diastolic mean BP, as assessed by 24-hour ambulatory monitoring, dropped by 21.4 and 12.7 mm Hg, respectively (P < 0.0001 for both measures vs. baseline). The baseline systolic BP of 144.8 mm Hg, as assessed by 24-hour ambulatory monitoring, was reduced to 123.5 mm Hg. BP values were consistently reduced throughout the 24-hour interval.

Drug-related adverse events were observed in 7.6% of patients. Edema was reported in only four patients. Three patients (1.6%) withdrew from the study because of adverse events.

Dr. Neutel concluded that the stepwise amlopidine/olmesartan (Azor, Daiichi Sankyo) regimen algorithm reduced mean 24-hour BP and was well tolerated.

A further presentation of data at ASH from the same study by Dr. Punzi showed that 76.8% of patients achieved their BP goal of below 140/90 mm Hg.

The Darusentan 311 Study: Fixed Doses For Treatment-Resistant Hypertension

• Michael Weber, MD, Professor of Medicine, SUNY (State University of New York) Downstate Medical Center, Brooklyn, N.Y.

In patients with treatment-resistant hypertension, darusentan (Gilead), an endothelin receptor antagonist, provides clinically meaningful improvements in BP control compared with placebo. Systolic BP goals were met in about 50% of patients with treatment-resistant hypertension in the Darusentan 311 Study. Between 3 million and 11 million people in the U.S. have hypertension that is resistant to therapy.

Participants (N = 379, with a mean age of 62 years) were not at their goal despite full or maximally tolerated doses of three or more antihypertensive medications. (Goals were defined as 140 mm Hg or below or 130 mm Hg or below for patients with diabetes or chronic kidney disease.) Estimated glomerular filtration rates had to show at least “reasonable” renal function (at or above 30 mL/minute per 1.73 m²).

The co-primary endpoints were the change from baseline to week 14 in trough systolic and diastolic BP. Patients were randomly assigned to receive darusentan at 50 mg, 100 mg, or 300 mg once daily or placebo. Nearly 40% of patients were older than 65 years, about 40% had diabetes, more than 25% had established heart disease, and 25% had chronic kidney disease. At baseline, 99.5% of the patients were taking diuretics, 96% were taking ACE-inhibitors or ARBs, 73.5% were taking calcium-channel blockers, and 65.5% were using beta blockers.

Mean baseline BP values were approximately 151/86 mm Hg.
The REDUCE Trial: Dutasteride (Avodart) and Prostate Cancer Risk Reduction

In the first study of a drug to lower the risk of prostate cancer among men at high risk for the disease, dutasteride (Avodart, GlaxoSmithKline), a 5-alpha reductase inhibitor, significantly reduced their risk of the eventual development of prostate cancer by 23%. The absolute risk reduction after four years of treatment was 22.5%, and the relative risk reduction was 23%.

REDUCE (Reduction by Dutasteride of Prostate Cancer) was a four-year, international, randomized, placebo-controlled study of 8,200 men between 50 and 75 years of age with elevated prostate-specific antigen (PSA) levels and a negative prostate biopsy at baseline. Baseline PSA levels ranged from 2.5 to 10.0 ng/mL (median, 5.9 ng/mL).

The men received dutasteride 0.5 mg daily or placebo. The investigators measured PSA levels throughout the four years. They found 659 cases of prostate cancer in the dutasteride group and 857 in the placebo group.

Inhibition of the type-1 receptor has a pronounced effect on high-grade tumor cells, Dr. Andriole added, noting that dutasteride inhibits both type-1 and type-2 receptors, whereas finasteride (Proscar, Merck), another 5-alpha reductase inhibitor, affects only the type-2 receptor.

At present, no FDA-approved therapies are available for reducing the risk of prostate cancer. Dutasteride is currently approved by the FDA for treating patients with signs and symptoms of benign prostatic hypertrophy (BPH), or prostatic enlargement.

Oxybutynin Chloride Topical Gel (Gelnique) In Women with Overactive Bladder

Treatment with oxybutynin chloride topical gel (e.g., Gelnique, Watson) significantly improved the incidence of daily episodes of urinary incontinence for women with overactive bladder. In 2009, Gelnique was approved to treat men and women with overactive bladder.

“We saw significantly more women achieving complete urinary continence with oxybutynin gel than with placebo,” Dr. Dmochowski said.

Complete continence was defined as no episodes of urinary incontinence recorded in the three-day urinary diary at any time after the study began. In this subanalysis of a phase 3
study, the researchers reported on findings for 704 women, 352 in the oxybutynin-treated group and 352 in the placebo group. The mean age of the patients was 59 years, and 610 patients (87%) were Caucasian. Men were included in the study but not in this analysis.

Subjects were randomly assigned, in a 1:1 fashion, to receive transdermal oxybutynin gel 1 g/day or placebo for 12 weeks. The gel was applied once daily to rotating sites on the abdomen, upper arm or shoulder, and thigh. The primary endpoint was the mean number of daily episodes of urinary incontinence recorded in the ongoing three-day bladder diary.

Dr. Dmochowski reported that 95 women (27%) using the study gel achieved a significantly higher rate of complete urinary continence compared with 55 women receiving placebo (15.6%) \( (P < 0.0001) \).

Dry mouth was the most frequent treatment-related anticholinergic adverse event, appearing more often among actively treated subjects (26 women, or 7.4%) than with placebo (10 women, or 2.8%). None of the patients withdrew as a result of dry mouth.

Pruritus was the most frequently reported application-site reaction, appearing in eight women receiving active treatment (2.3%) and in three women receiving placebo (0.9%). Two actively treated women and one woman using a placebo withdrew primarily as a result of application-site reactions. The investigators reported no serious treatment-related adverse events.

Quick Improvement of Urinary Symptoms Of Benign Prostatic Hyperplasia With Silodosin (Rapaflo)

- Leonard Marks, MD, Clinical Professor of Surgery/Urology, David Geffen School of Medicine, University of California, Los Angeles
- Claus Roehrborn, MD, Professor of Urology, University of Texas–Southwestern Medical School, Dallas

Men who were treated with silodosin (Rapaflo, Watson) for urinary symptoms associated with BPH achieved rapid and significant improvements, according to phase 3 trial results. “In this new analysis, we found that silodosin provided rapid and effective relief of all irritative and obstructive symptoms of BPH,” Dr. Marks said.

Dr. Marks and fellow investigators conducted a post hoc study of pooled data from two identically designed, randomized, placebo-controlled, double-blind clinical trials. These trials included 923 men 50 years of age and older with signs and symptoms of BPH, including peak urine flow rate (Qmax) of between 4 and 15 mL/second and International Prostate Symptom Scores (IPSS) of 13 and higher. Mean flow rate was 8.7 to 8.9 mL/second, and mean IPSS was 21.3. Patients received silodosin 8 mg/day (n = 466) or placebo (n = 457) for 12 weeks.

Investigators evaluated changes in IPSS subscales that measured symptoms of irritation (frequency, urgency, and nocturia) and obstructive symptoms of BPH (incomplete emptying, intermittency, weak stream, and straining). The silodosin subjects achieved statistically significant changes in all IPSS subscales except for nocturia. Compared with placebo, significant improvements in symptoms, except for nocturia, were achieved with silodosin within three or four days of the first treatment \( (P < 0.001) \). The differences between the cohorts remained throughout the 12 weeks \( (P < 0.0001) \).

A second analysis of the same data showed that retrograde ejaculation, a side effect associated with silodosin, was correlated with an improvement in irritative and obstructive urinary symptoms and in peak flow, suggesting a relaxation effect of silodosin in the muscles of the lower urinary tract.

“There appears to be a tradeoff here between this side effect and notable improvement in urinary symptoms,” Dr. Roehrborn commented.

Retrograde ejaculation was reported in 131 of the 466 men (28.1%) receiving silodosin. IPSS and scores of Qmax were similar between the subgroups of silodosin-treated men who experienced the retrograde ejaculation side effect and those who did not. Both subgroups showed significant improvements compared with placebo patients \( (P < 0.02) \) at week 12 in IPSS and Qmax. However, mean improvement in IPSS was somewhat higher among the men who had retrograde ejaculation than those who did not \( (P = 0.39) \) and in Qmax \( (3.1 \text{ mL vs. 2.4 mL}) \ (P = 0.07) \).

“For older men with BPH, it could be an acceptable trade-off, given the rapid relief of urinary symptoms afforded by this treatment,” said Dr. Roehrborn.

Silodosin, a new selective alpha blocker, was approved by the FDA in 2009 to treat patients with signs and symptoms of BPH.