BP Lowered in Phase II Trial

Hypertension *from page 1*

giotensin-2 receptor blocker in addition to one or more drugs from other classes.

Participants in the multicenter, double-blind, 10-week, phase II trial were randomized 2:1 to once-daily darusentan or placebo. The darusentan group began on 10 mg/day, titrating up at 2-week intervals to 50, 100, 150, and finally 300 mg per day as tolerated.

The primary study end point was reduction from baseline sitting systolic blood pressure (SBP) with darusentan minus the change with placebo, an outcome measure chosen because elevated SBP is the usual cause of failure to control blood pressure. The placebo-corrected change in SBP from a baseline mean of 149 mm Hg was 7.3 mm Hg with darusentan at 8 weeks and 11.5 mm Hg at 10 weeks. Comparable SBP lowering was obtained in women and men, in patients younger or older than 65 or even 75 years, and in patients with or without diabetes or chronic kidney disease.

Patients with more severe resistant hypertension as shown by baseline use of four or more antihypertensive medications seemed to obtain greater benefit from darusentan, Dr. Weber noted. Their mean placebo-corrected reduction in SBP at 10 weeks was 18.0 mm Hg, compared with 8.7 mm Hg in patients taking exactly three other antihypertensive drugs.

The placebo-corrected reduction in mean 24-hour SBP with darusentan by ambulatory blood pressure monitoring was 9.2 mm Hg. This reduction was coupled with a 7.2 mm Hg placebo-adjusted decrease in mean 24-hour diastolic blood pressure. "I've always felt change in mean 24-hour blood pressure is the most robust way of looking at results," the physician added.

It's not every day that the door swings open on an entirely new potential class of highly effective antihypertensive drugs, and the standing room–only audience reacted enthusiastically to the darusentan results.

Audience member Dr. Elijah Saunders, professor of medicine at the University of Maryland, Baltimore, zeroed in on the racial disparity in outcome. Given the recent evidence that hypertensive African Americans have higher endothelin levels than whites, he observed, one would expect an even better response to darusentan in blacks than whites. Yet the placebo-corrected SBP reduction with darusentan was a mere 5.0 mm Hg in black patients, compared with 13.5 mm Hg in whites.

Dr. Weber agreed this result is counterintuitive but cautioned not to make too much of it. The study included fewer than 30 black patients. In addition, some of the other drugs patients were on could affect endothelin levels, further muddying the waters.

What's really required to learn whether darusentan's efficacy varies by race is a study of the endothelin receptor antagonist as monotherapy. That's not immediately in the cards. Next up will be a large phase III trial of darusentan in resistant hypertension.

Dr. Weber is a consultant to Myogen Inc., which sponsored the phase II trial. ■

Big Gains in BP Control Seen Since JNC-7

BY BRUCE JANCIN
Denver Bureau

CHICAGO — Hypertension control has improved markedly in the United States since spring of 2003—and the JNC-7 guidelines deserve most of the credit, James Jackson, Pharm.D., said at the annual scientific sessions of the American Heart Association.

The improvement in blood pressure control since release of JNC-7 (the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) in spring 2003 has been particularly impressive in hypertensive patients with diabetes. But there remains much room for further improvement on this score, as fewer than one-third of such patients in the JNC-7 era have their blood pressure controlled to goal, added Dr. Jackson of Xcenda, a Palm Harbor, Fla.–based health outcomes research and consulting company.

Physicians have taken to heart the JNC-7 message to prescribe more aggressively. More hypertensive patients are on two or three antihypertensive drugs than was the case just prior to JNC-7. But by far the most dramatic change in prescribing has been the nearly threefold increase in the percentage of patients on fixed-dose combination therapy, he noted.

To study JNC-7's effect on blood pressure control rates and treatment patterns, he and his coinvestigators accrued

a random national sample of hypertensive subjects drawn from 23 managed care organizations and physician groups. The pre–JNC-7 group consisted of 15,359 patients followed during June 1998–March 2003; the post–JNC-7 cohort comprised 2,012 patients followed during December 2003–April 2006.

The proportion of all hypertensive patients with good blood pressure control rose from 39% in the pre–JNC-7 period to 53% after the JNC-7 release. The percentage of diabetic hypertensive patients treated to goal nearly doubled during the same time span, from 17% before JNC-7 to 29% afterward.

In the pre–JNC-7 era, 45% of hypertensive patients for whom medication was prescribed received a single agent; after JNC-7 that figure dropped to 37%. Meanwhile, the use of dual therapy climbed from 31% to 37%, and three or more antihypertensive drugs were used in 20% of patients, up from 17% before JNC-7.

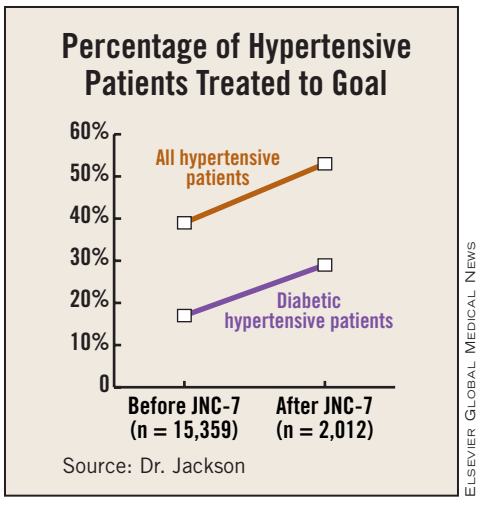
The most widely utilized class of antihypertensive drugs since JNC-7 has been diuretics, prescribed for 33% of patients.

The use of ACE inhibitors declined from 31% before JNC-7 to 24% afterward. Angiotensin-2 receptor blockers took up the slack during this period, as the proportion of patients on this class of drugs rose from 8% to 13%, said Dr. Jackson.

Roughly one-quarter of patients were on a β-blocker for control of hypertension, a proportion that did not change over the study period. Meanwhile, the use of calcium channel blockers declined significantly from 27% before JNC-7 to 24% afterward, Dr. Jackson continued.

The use of fixed-dose combinations has increased more than that of any other antihypertensive agents since release of JNC-7. Before JNC-7, 11% of hypertensive patients were on a fixed-dose combination; since JNC-7 this figure has jumped to 27%.

Dr. Jackson's study was supported by Novartis Pharmaceuticals Corp. ■



The CHF subanalysis of THE-PRINCE study included a total of 206 patients with CHF. In this group, only 9.7% of patients who received LOVENOX® experienced VTE, compared with a rate of 16.1% among those who received UFH. These results showed with 95% certainty that LOVENOX® was at least as effective as UFH (*P*=0.0139 for equivalence). In addition, LOVENOX® was associated with significantly fewer injection-site hematomas, not a surprising result in light of its once-daily dosing regimen compared with the 3 daily injections necessitated by prophylaxis with UFH.[10]

Bleeding and injection-site hematoma are not the only drawbacks to UFH as a VTE prophylaxis strategy. A recent meta-analysis of 5 studies has shown that there is a higher incidence of heparin-induced thrombocytopenia (HIT), with UFH compared to LMWH.[11] HIT is a rare but potentially fatal and extremely costly complication of heparin therapy.[12]

Patients With CHF Will Benefit From More Widespread Appropriate VTE Prophylaxis

MEDENOX and THE-PRINCE showed that appropriate pharmacologic prophylaxis according to the ACCP guidelines results in significantly reduced incidence of VTE in hospitalized medical patients in general and among CHF patients specifically. LOVENOX® is at least as efficacious as UFH in these populations, and has advantages in safety and convenience.

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IMPORTANT SAFETY INFORMATION

LOVENOX® (enoxaparin sodium injection) cannot be used interchangeably with other low-molecular-weight heparins or unfractionated heparin, as they differ in their manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage.

When epidural/spinal anesthesia or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low-molecular-weight heparins or heparinoids are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of postoperative indwelling epidural catheters or by the concomitant use of drugs affecting hemostasis. Patients should be frequently monitored for signs and symptoms of neurological impairment (see boxed WARNING).

As with other anticoagulants, use with extreme caution in patients with conditions that increase the risk of hemorrhage. Dosage adjustment is recommended in patients with severe renal impairment. Unless otherwise indicated, agents that may affect hemostasis should be discontinued prior to LOVENOX® therapy. Bleeding can occur at any site during LOVENOX® therapy. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site (see WARNINGS and PRECAUTIONS).

Thrombocytopenia can occur with LOVENOX®. In patients with a history of heparin-induced thrombocytopenia, LOVENOX® should be used with extreme caution. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm3, LOVENOX® should be discontinued. Cases of heparin-induced thrombocytopenia have been observed in clinical practice (see WARNINGS).

The use of LOVENOX® has not been adequately studied for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves (see WARNINGS).

LOVENOX® is contraindicated in patients with hypersensitivity to enoxaparin sodium, heparin, or pork products, and in patients with active major bleeding.