Resistant Hypertension Responds to Novel Drug

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CHICAGO — The investigational drug darusentan achieves impressive blood pressure reduction in patients who remain hypertensive despite full-dose therapy with three or more concurrent antihypertensive agents, Dr. Michael Weber said at the annual scientific sessions of the American Heart Association.

In the first-ever clinical trial of the oral type-A–selective endothelin receptor antagonist as adjunctive therapy in treatment-resistant hypertension, darusentan also proved "extraordinarily well tolerated" with the exception of an increase in peripheral edema, a side effect intrinsic to the pharmacology of the entire drug class, according to Dr. Weber, professor of medicine and associate dean for research at State University of New York, Brooklyn.

He reported on 115 patients whose blood pressure remained elevated despite baseline use of three full-dose antihypertensive drugs in 65 cases and at least four drugs in 50 others. All were on a diuretic and ACE inhibitor or angiotensin-2 receptor blocker in addition to one or more drugs from other classes.

Systolic blood pressure lowering was comparable in men and women, in patients younger or older than 65, and in those with or without diabetes or kidney disease.

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," he added.

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 that this result is counterintuitive but he cautioned that those present should not 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.

Endothelin receptor antagonists need to be studied as monotherapy in order to learn whether darusentan's efficacy varies by race, but that's not immediately in the cards. Next up will be a large phase III trial of darusentan in resistant hypertension.

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