

Trial Halted After Niacin Surpasses Ezetimibe

BY MARY ANN MOON

Extended-release niacin was clearly superior to ezetimibe when combined with statin therapy in patients who had or were at high risk for atherosclerosis in a prospective, open-label study.

Niacin caused the regression of carotid intima-media thickness, a surrogate marker for atherosclerosis progression, while ezetimibe caused no significant change in the first clinical trial to directly compare the two secondary agents in combination with a statin.

In addition, fewer adverse cardiovascular events developed with niacin than with ezetimibe during 14 months of follow-up. Perhaps most important, “we found an unexpected paradoxical relationship of a greater degree of atherosclerosis progression in patients with larger, ezetimibe-induced reductions in LDL cholesterol level,” wrote Dr. Allen J. Taylor, director of advanced cardiac imaging at Washington Hospital Center in Washington, and his associates in the ARBITER6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies) study. The findings were published online (N. Engl. J. Med. 2009;doi:10.1056/NEJMoa0907569) and presented concurrently at the annual at the annual scientific sessions of the American Heart Association.

The study, sponsored by Abbott, the maker of the extended-release niacin used in the trial, was designed to randomly assign 363 patients to receive either extended-release niacin or ezetimibe (Zetia, Merck–Shering-Plough Pharmaceuticals) in addition to statin therapy.

The study was halted early when an interim analysis showed a clear advantage with niacin, and the trial included complete data from only 208 of the patients.

Critics have charged that this “premature” termination was “unfortunate and may exaggerate any potential benefit of niacin therapy” because “more than 40% of the patients did not undergo the measurement at 14 months of the carotid intima-media thickness (the primary end point),” Dr. Roger S. Blumenthal and Dr. Erin D. Michos of Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, said in an editorial comment.

“A larger sample size may have either strengthened the provocative results regarding the major adverse cardiovascular events or, alternatively, reduced any evidence of meaningful clinical differences,” they wrote (N. Engl. J. Med. 2009; doi:10.1056/NEJMe0908838).

The ARBITER6-HALTS trial enrolled 363 men and women, including 279 with known atherosclerotic coronary or vascular disease. In addition, there were 84 patients with a coronary heart disease risk equivalent such as diabetes (38 patients), a 10-year Framingham risk score of 20% or more (26 patients), and/or a high coronary calcium score (20 patients).

The study subjects (80% male, mean age 65 years) were randomly assigned to receive the maximum tolerated dose of extended-release niacin up to 2,000 mg/day or 10 mg of ezetimibe daily. All

had already been taking a statin for a mean of 6 years, usually simvastatin or atorvastatin.

Niacin bested ezetimibe in improving both mean and maximal carotid intima-media thickness on ultrasonography at both 8 months and 14 months, Dr. Taylor and his colleagues said.

In addition, the rate of major adverse cardiovascular events was significantly lower with niacin (1%) than with ezetimibe (5%). Both of these benefits were consistent across all subgroups studied, without regard to gender, the presence or absence of diabetes, or baseline HDL cholesterol levels.

A post hoc analysis showed a significant inverse relation between a decrease in LDL cholesterol and an increase in carotid intima-media thickness only in the ezetimibe group. The reason for this paradoxical effect is not yet known, but the researchers proposed that it is biologically plausible: Ezetimibe may have the unintended effect of disrupting the HDL-mediated reverse transport of cholesterol.

“We believe that prudent clinical practice currently favors the avoidance of ezetimibe, with consideration of further restriction on its use in lieu of clinically validated regimens, until its net effect on clinical outcomes can be fully ascertained,” Dr. Taylor and his associates said.

The two patient groups did not differ in quality of life measures at the end of the study. More subjects in the niacin group (63%) than in the ezetimibe group

(33%) withdrew from the study because of adverse drug effects, however.

In their editorial, Dr. Blumenthal and Dr. Michos said that using carotid intima-media thickness as a surrogate for coronary atherosclerosis is “controversial.”

It is unknown whether arresting the progression of carotid intima-media thickness, or even reversing it, is consistently associated with a reduction in risk of cardiovascular events. “Furthermore, there are therapies other than niacin that retard the progression of carotid intima-media thickness (i.e., estrogen and thiazolidinediones) but do not reduce the incidence of cardiovascular events,” they noted.

“The putative negative effects of ezetimibe (i.e., increase in the carotid intima-media thickness) espoused by the authors are unsubstantiated. In the 111 patients in the ezetimibe group with data reported in the study, the carotid intima-media thickness at 14 months was not significantly different from the thickness at baseline,” Dr. Blumenthal and Dr. Michos added. They cited “the premature termination of the ARBITER6-HALTS trial, the small number of patients studied, and the limited duration of follow-up” as reasons to not rush to change the current clinical approach to lipid lowering.

Rather, they said they “would support the use of niacin as the preferred adjunctive agent to be used in combination with the maximal dose of a potent statin in persons who have low levels of HDL cholesterol and established cardiovascular disease.” More clinical trials are currently underway.

Dr. Taylor reported receiving lecture fees from Abbott. Dr. Blumenthal and Dr. Michos reported no relevant conflicts of interest. ■



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DR. TAYLOR

Ambrisentan Benefits Class I-II Pulmonary Hypertension

BY DOUG BRUNK

SAN DIEGO — Following 2 years of treatment with ambrisentan for pulmonary arterial hypertension, patients with World Health Organization functional class I and II symptoms at baseline had a lower risk of clinical worsening and death, compared with those who had WHO class III and IV symptoms at baseline.

Patients in both subgroups also experienced improvements in 6-minute walk distance from their baseline rates.

Those are key findings from the longest-term study to date of ambrisentan (Letairis) in patients with pulmonary hypertension. The agent was approved in 2007 as a once-daily treatment for patients with WHO functional class II or III symptoms to improve exercise capacity and delay clinical worsening.

“This medication seems to work long term,” lead investigator Dr. Fernando Torres said in an interview during a poster session at an international conference of the American Thoracic Society. “Not only is it working at 2 years, but most of the patients are still on monotherapy. We did not have to add a second medication to keep them doing clinically well.”

Dr. Torres and his associates conducted a long-term extension study in 287 patients who participated in the Placebo-Controlled, Efficacy and Safety Study of Ambrisentan in Patients With Pulmonary Arterial Hypertension (ARIES)-1 and ARIES-2 trials. Patients who received ambrisentan in previous studies remained on the current dose, while patients who received placebo in previous studies were randomized to ambrisentan 5 mg

or 10 mg daily.

At baseline, the mean age of the 287 patients was 50 years, and 82% of patients were female; 123 patients had WHO I and II symptoms, and 164 patients had WHO III and IV symptoms. By the second year, 20 patients with WHO I and II symptoms had discontinued the trial, as did 53 patients with

WHO III and IV symptoms.

By year 2, 13% of patients with WHO I and II symptoms had no clinical worsening of disease, compared with 39% of patients with WHO III and IV symptoms, a difference that was statistically significant, reported Dr. Torres, director of the pulmonary hypertension program at the University of Texas Southwestern Medical Center, Dallas.

Patients with WHO I and II symptoms had more fa-

vorable long-term survival, compared with those who had WHO III and IV symptoms (95% vs. 83%), which was statistically significant.

The most common clinical worsening events were hospitalization for pulmonary arterial hypertension (9% in those with WHO I and II symptoms vs. 27% in those with WHO III and IV symptoms), the addition of prostanoid therapy (5% vs. 13%), and death (4% vs. 15%).

The most common adverse events resulting in death were right ventricular failure (1% in those patients with WHO I and II symptoms vs. 4% in those patients with WHO III and IV symptoms) and pulmonary hypertension (0% vs. 2%).

The majority of patients in both subgroups remained on monotherapy through year 2 (85% with WHO I and II symptoms, compared with 72% with WHO III and IV symptoms). “Most of these patients seem to be stable using just one medication,” Dr. Torres said.

He also reported that by year 2, the 6-minute walk distance was improved in both subgroups, and the change from baseline appeared to be slightly better for patients with WHO I and II symptoms at baseline.

A chief limitation of the study, Dr. Torres said, is that it lacked a placebo group, because it would be unethical to keep patients on placebo for that long.

He disclosed that he is a paid researcher, consultant, and adviser to the makers of Letairis, Gilead Sciences, which funded the study. ■

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