Ezetimibe's Rapid U.S. Adoption Called Flawed

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CHICAGO — When data on ezetimibe's missing antiatherosclerotic effect finally received their first airing at a scientific meeting, the consensus conclusion from a panel of cardiologists was that this was a case of a new-drug introduction run amok.

"Amid an aggressive marketing campaign, ezetimibe was rapidly adopted into practice," Dr. Harlan M. Krumholtz said at the annual meeting of the American College of Cardiology. After ezetimibe's entry onto the U.S. market in late 2002, its use "skyrocketed." By 2006, 15% of all U.S. prescriptions for lipid-lowering drugs were either for ezetimibe alone (Zetia) or for the combination of ezetimibe and simvastatin (Vytorin), Dr. Krumholtz said in his talk and in a report that he coauthored (N. Engl. J. Med. 2008 March 30 [Epub doi: 10.1056/NEJMsa0801461]).

"In the United States, ezetimibe supplanted statins to some extent, and this led to reduced use of statins and reduced statin doses," said Dr. Krumholtz, professor of medicine, epidemiology, and public health at Yale University, New Haven, Conn. Ezetimibe "was the next new thing. There was a wave of enthusiasm," with physicians "not thinking critically enough" about its proper role.

"The strongest recommendation we can make is turn back to statins," he said, a message that had unanimous support from the three other experts chosen by the ACC to review and comment on the ezetimibe data at the meeting.

"We underscore optimizing doses of statins," agreed Dr. Patrick T. O'Gara, director of clinical cardiology at Brigham and Women's Hospital, Boston, and another member of the review panel. "Many of us have patients in our practices who started treatment with a lower dose of a statin plus ezetimibe to spare them from taking higher doses of statin that are perhaps much more effective."

"We thought that we could get a lower cholesterol level by adding ezetimibe rather than doubling the statin dose, which was well received by our patients who felt that increasing statin doses increased their risk of severe complications," said Dr. Joseph V. Messer, professor of medicine at Rush University, Chicago, a third member of the ACC's comment panel.

Trouble for ezetimibe began Jan. 14, when Merck/Schering Plough Pharmaceuticals, which markets the drug, issued a press release with the essential findings from the study it sponsored, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial (N. Engl. J. Med. 2008 March 30 [Epub doi: 10.1056/NEJMoa0800742]).

The core findings remained as first announced more than 2 months before: Although treatment of patients with heterozygous familial hypercholesterolemia with a combination of 10 mg ezetimibe and 80 mg simvastatin was substantially more potent than 80 mg of simvastatin alone for reducing blood levels of LDL cholesterol and high- sensitivity C-reactive protein, the combination had absolutely no advantage over the statin alone for slowing the progression of carotid atherosclerosis during 2 years of follow-up of the 720 patients in the study.

The ACC review panel was assembled to go over all of the data starting a few weeks before the meeting, and by the time their assessment was done "the most likely explanation [for the results] that we kept coming back to was that in this study ezetimibe did not work," Dr. Krumholtz said. "It lowered LDL, but it did not retard atherosclerosis." The panel members stressed that they had reached a consensus.

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DR. KRUMHOLTZ

"Ezetimibe is a new drug, a first in its class, with a novel mechanism of action. It was approved only on the basis of lowering LDL. We didn't have results from any clinical outcomes studies. Until we are shown some data that can give us confidence that there is net benefit [from ezetimibe treatment], we need to use it very judiciously. It should have been tested this way early, but it got a pass," he said.

Both Dr. Krumholtz and Dr. O'Gara cited niacin, fibrates, and resins as better-proven agents that can be used first if treatment with a statin isn't tolerated or is inadequate. For now, ezetimibe use should be limited to the relatively small number of patients who still need LDL lowering despite use of all of these other agents.

Another concern of the ACC's panel was ezetimibe's safety, although results from the ENHANCE study and other investigations have so far indicated that the drug is well tolerated and safe. The panelists noted that an 18,000-patient trial of ezetimibe now underway was reviewed at the meeting by the study's data and safety monitoring board, and a decision was made to proceed with the study, an indication that no unexpected excess of adverse events was occurring. Results are expected in 2012.

The results reported last year from a clinical outcomes trial of torcetrapib "really chastened me," Dr. Krumholz said. Torcetrapib had shown potent, positive effects for raising levels of HDL cholesterol while also lowering LDL cholesterol and seemed safe and well tolerated. But then the trial results showed that torcetrapib raised blood pressure in many patients and boosted the study group's mortality rate, which led to the study's early halt.

The fourth panel member was Dr. Rick A. Nishimura, professor of medicine at the Mayo Clinic, Rochester, Minn., and a member of the guidelines task force for the ACC and American Heart Association. Revised lipid-management guidelines that reflect the new findings on ezetimibe could be released by the end of this year, he said.

The day after the ENHANCE report, a statement from the ACC and American Heart Association said: "The study reinforces the need to adhere to current American College of Cardiology/American Heart Association guidelines, which recommend statins to the maximally tolerated dose or to goal as first-line treatment for patients with coronary artery disease."

On the same day, Congress renewed its pressure on the drug manufacturers. (See box.)

Senate Seeks Answers on Vytorin From Manufacturers, American College of Cardiology

One day after the full ENHANCE data were presented at the ACC meeting, Sen. Chuck Grassley sent Merck & Co. and Schering-Plough Corp. executives a letter asking for the names of "key opinion leaders" who advised the companies on development and marketing of their cholesterol-lowering drug ezetimibe/simvastatin (Vytorin). The letter also called for a full accounting of payments made to these medical professionals and of how much was spent in total on advertising and marketing for Vytorin and/or ezetimibe (Zetia).

Sen. Grassley (R-Iowa) is the ranking minority member on the Senate Finance Committee, which has been investigating an alleged delay of the release of pivotal data from the ENHANCE study.

"Delaying the release of the results from the ENHANCE trial not only affected medical decisions, but also imposed financial burdens on patients as well as the federal government," Sen. Grassley said in his letter, adding that since the trial's completion in 2006, the federal government has paid "hundreds of millions of dollars for Vytorin," a drug which now seems to be of limited utility.

ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) showed that in patients with heterozygous familial hypercholesterolemia, a combination of ezetimibe and simvastatin was substantially more potent than simvastatin alone for reducing levels of LDL cholesterol and high-sensitivity C-reactive protein. But the combination had absolutely no advantage over the statin alone for slowing the progression of carotid atherosclerosis during 2 years of follow-up.

According to Sen. Grassley's letter, the Finance Committee staff has unearthed e-mail correspondence between Schering-Plough and Dr. John Kastelein, the ENHANCE primary investigator.

In July 2007, Dr. Kastelein wrote to a Schering-Plough executive, saying, "Is it correct that SP has decided not to present at AHA [the American Heart Association annual meeting], but to await the two other, completely unvalidated, endpoints, which analysis is going to take us straight into 2008??!!??" Dr. Kastelein added, "If this is true, SP must have taken this decision without even the semblance of decency to consult me as PI of the study. I can tell you that if this is the case, our collaboration is over. … This starts smelling like extending the publication for no other [than] political reasons and I cannot live with that."

Just a day later, Dr. Kastelein wrote again to a Schering-Plough executive that he had been "cleared to say that ENHANCE would be presented at AHA" when he was presenting ezetimibe data at meetings he attended on behalf of the company over 6 months. "There is no reason whatsoever to include femorals; you will be seen as a company that tries to hide something and I will be perceived as being in bed with you!"

Sen. Grassley also said he was disturbed by a Merck/Schering-Plough public relations campaign, the "49 plan," which was "designed to wine and dine doctors and convince them to prescribe Vytorin." The campaign budget was at least $3.5 million, said Sen. Grassley, adding, "This seems like a great deal of money for free lunches and dinners."

A Schering-Plough spokeswoman said that the letter from Sen. Grassley is one of a series the company has received from the committee. "We are cooperating fully with the committee, and we stand behind our products, as we have done nothing wrong," Rosemarie Yancosek said in an interview.

The Iowa senator also wrote to the American College of Cardiology, saying that he was hopeful that the college was hewing to its own conflicts-of-interest policies but that he was concerned, noting that ACC had received $5 million from Merck since 2003, $1 million from Schering-Plough, and $5 million from the joint venture.

Soon after the ENHANCE data were released in January, ACC issued a statement saying that "there is no reason for patients to panic" and advising concerned patients to talk to their health care professional. ACC also said that further research was needed to determine Vytorin's usefulness. Sen. Grassley noted that in internal e-mails, both Merck and Schering-Plough officials had pointed to the ACC statement as evidence of Vytorin's effectiveness.

"It would not be unreasonable for an independent third party to conclude that the Merck and Schering-Plough payments to ACC influenced ACC's comments about Vytorin, especially now that experts are calling for doctors to use this drug only as a last resort," Sen. Grassley said in his letter.

—Alicia Ault