With Statin, Fenofibrate Safer Than Gemfibrozil

Risk for rhabdomyolysis increased significantly when gemfibrozil was combined with most statins.

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NEW YORK — The combination of fenofibrate and a statin appears to be safer than gemfibrozil and a statin, according to an analysis of adverse event reports to the Food and Drug Administration.

In January 1998 through March 2002, the FDA received 0.6 reports of rhabdomyolysis for the combination of fenofibrate plus any statin except cerivastatin per every million prescriptions written for this drug combination, Peter H. Jones, M.D., said at an international symposium on triglycerides and HDL.

During the same period, the FDA received 8.6 reports of rhabdomyolysis for the combination of gemfibrozil plus any statin except cerivastatin per every million prescriptions written for this combination, a rate that is more than 14 times higher than for fenofibrate plus a statin, said Dr. Jones, codirector of the lipid metabolism and atherosclerosis clinic at Baylor College of Medicine, Houston.

Treatment with gemfibrozil appears to boost the maximum concentration and the area under the curve for any concurrently administered statin, an effect that is not seen with fenofibrate, Dr. Jones said.

Statins and gemfibrozil are metabolized by the same liver enzymes, which means that gemfibrozil competes with statins for these enzymes and thus acts as a competitive inhibitor of statin metabolism. Fenofibrate is metabolized by a different set of liver enzymes and hence has little impact on statin metabolism, said Dr. Jones at the symposium, sponsored by the Giovanni Lorenzini Medical Foundation.

The adverse report analysis by Dr. Jones and his collaborator excluded cerivastatin because treatment with that statin was associated with an unusually high number of cases of rhabdomyolysis. Inclusion of patients who were treated with cerivastatin did not affect the safety disparity between fenofibrate and gemfibrozil.

The study found that the FDA received two reports of rhabdomyolysis in patients treated with fenofibrate plus a statin other than cerivastatin out of more than 3.4 million prescriptions for the drug combination written during the 4-year study period. In comparison, 57 reports of rhabdomyolysis were submitted to the FDA regarding patients treated with gemfibrozil plus any statin but cerivastatin out of more than 6.6 million prescriptions written for this combination.

Fenofibrate is metabolized by different liver enzymes and has little impact on statin metabolism.

DR. JONES

Dr. Jones receives research support from Pfizer Inc., which markets gemfibrozil (Lopid), and from Abbott Laboratories, which markets fenofibrate (Tricor). He is also a consultant to Abbott. He does not have a relationship with the companies that market the two other brand formulations of fenofibrate (Antava and Lofibra).

Based on the results of several studies, the combination of a statin and a fibrate (either gemfibrozil or fenofibrate) appears to be very effective for normalizing serum lipid levels in patients who have diabetes, metabolic syndrome, or atherogenic dyslipidemia, which features a high level of serum triglycerides and a low level of HDL cholesterol. However, there are not yet any study results to prove that treatment with a statin-fibrate combination leads to fewer clinical events than treatment with a statin alone. A study designed to address this question is currently in progress.

The usual starting and maintenance dosage of fenofibrate when used in combination with a statin is 160 mg/day, Dr. Jones said. ■

New Treatments in Pipeline Raise HDL in Short, Long Term

NEW YORK — Drug treatments that raise serum HDL cholesterol are already available, but several potentially better, more targeted treatments are moving through the development pipeline, H. Bryan Brewer Jr., M.D., said at an international symposium on triglycerides and HDL.

The new treatments are in a range of development stages, from preclinical animal studies to phase III clinical trials, said Dr. Brewer, director of lipoprotein and atherosclerosis research at the Washington Hospital Center.

Short-term treatments to raise HDL are geared to treating patients with acute coronary syndrome (ACS) who need rapid plaque stabilization. This approach includes infusion of exogenous apolipoprotein A_1, the main protein component of HDL cholesterol, delipidation of HDL, or infusion of an apo A_1 mimetic peptide.

Long-term treatments designed to lower cardiovascular risk are also in the works. The strategies include oral treatment with an apo A_1 mimetic peptide or treatment with an agent that inhibits the cholesterol ester transfer protein (CETP), which is involved in regulating the size of cholesterol particles. Reduced CETP activity is antiatherogenic.

Speaking at the symposium, sponsored by the Giovanni Lorenzini Medical Foundation, Dr. Brewer summarized the progress to date on these treatments:

► **Apo A_1 infusion.** The first of the new wave of HDL cholesterol treatments used a recombinant, variant apo A_1 protein, apo A_1 Milano. Five weekly infusions of apo A_1 Milano given to 36 patients with ACS led to an average drop in atheroma volume of about 1%, a significantly better reversal of atherosclerosis than was seen in a control group of 11 patients (JAMA 2003;290:2292-300). The results of this "landmark" study showed that rapid regression of atherosclerosis was possible and that acute apo A_1 infusions could be given to patients with ACS, Dr. Brewer said. Clinical testing is ongoing.

► **HDL delipidation.** In this process, a patient undergoes plasmapheresis to remove cholesterol from existing HDL particles using an organic solvent. The delipidated HDL is then returned to the patient. This 4-hour treatment can increase cholesterol efflux about 20-fold, said Dr. Brewer. It is scheduled to start clinical testing in late 2005. Dr. Brewer is also chief scientific director for Lipid Sciences Inc., the company that is developing this treatment.

► **Synthetic apo A_1 mimetic peptide.** Researchers have produced an 18-amino-acid peptide that mimics the structure of a portion of the amphipathic, helical peptide that forms apo A_1. In vitro and animal studies indicate that the 18-amino-acid peptide can remove cholesterol from cells without cytotoxicity. Animal studies are continuing with this intravenous agent.

► **CETP inhibitors.** The most advanced of these agents is torcetrapib. In a pilot, uncontrolled study with 19 patients, 120 mg torcetrapib daily for 4 weeks boosted serum HDL by about 50% (N. Engl. J. Med. 2004;350:1505-15). Torcetrapib's clinical efficacy is being tested in a study that will follow atherosclerosis regression using intravascular ultrasound. But, in a controversial move, Pfizer, which is developing torcetrapib, is now studying it clinically only in combination with atorvastatin. Another CETP inhibitor, JTT-705, is being developed by Roche and is also in clinical studies.

► **Oral synthetic apo A_1 mimetic peptide.** The D-4F peptide is similar in concept to the other synthetic apo A_1 mimetic peptide under study, except it is made exclusively from D-amino acids, is not digested, and is orally active. The D-4F peptide is in early-phase human testing. ■

The Need for HDL Treatment Target Remains Debatable Topic

NEW YORK — It's time to set a target for high-density lipoprotein cholesterol in the U.S. lipid guidelines, Ernst J. Schaefer, M.D., said at an international symposium on triglycerides and HDL.

"We should try to target patients to raise their HDL cholesterol, especially if they have established heart disease. We have as much data today for HDL as we had in 1988 when we were asked to set guidelines for LDL," said Dr. Schaefer, professor of medicine at Tufts University in Boston.

But another lipid expert who spoke at the symposium disagreed.

"The time is not yet right for firm HDL guidelines," said Antonio M. Gotto Jr., M.D., dean of the Weill Medical College of Cornell University in New York. "Results from clinical trials must confirm the benefit of treating patients with agents that primarily target HDL cholesterol," he said.

"It's important to treat beyond LDL cholesterol," said Dr. Schaefer, who is also director of the lipid and heart disease prevention clinic and laboratory at Tufts-New England Medical Center. "A substantial fraction of patients don't get treated to increase their HDL. But for every 1% increase in HDL, there is about a 1%-3% reduction in coronary heart disease risk."

Dr. Schaefer said that he was unsure of the best target level for HDL cholesterol. One option is to recommend raising levels to at least 40 mg/dL for men and 50 mg/dL for women.

Another option is to set a minimum goal of more than 40 mg/dL or more than 45 mg/dL for everyone. The existing lipid goals of the National Cholesterol Education Program, the Adult Treatment Panel III, do not set a treatment strategy for patients based on their serum HDL cholesterol level.

Dr. Schaefer reviewed the evidence that documents the prognostic importance of a low level of HDL cholesterol and the risk reduction that occurs when the level of HDL cholesterol is raised. For example, in the Framingham study the strongest predictor of a person's cardiovascular risk was total cholesterol divided by HDL cholesterol.

Existing guidelines in both Canada and Europe say that patients with existing coronary disease should be treated until this ratio drops below 4.0.

Treatment data have documented the efficacy of several drugs to raise serum levels of HDL cholesterol and reduce the risk of cardiovascular disease events. These have included studies using cholestyramine, gemfibrozil, simvastatin, and niacin, Dr. Schaefer said at the symposium, which was sponsored by the Giovanni Lorenzini Medical Foundation.

"There is a consistent pattern that's much stronger statistically [for raising HDL cholesterol] than for [lowering] LDL cholesterol. Increasing HDL cholesterol by even a small amount may benefit patients," Dr. Schaefer said. ■