Rosuvastatin Linked to Excess Adverse Events

Use is associated with reports of rhabdomyolysis, proteinuria, nephropathy, and renal failure.

BY MITCHEL L. ZOLER
Philadelphia Bureau

A newly published analysis of the adverse event reports filed during the first year that rosuvastatin was on the U.S. market showed that its use was linked with significantly more adverse events than other statins.

From October 2003 to September 2004, more than 5 million prescriptions for rosuvastatin (Crestor) were filled in the United States. Rosuvastatin use was associated with about 28 adverse events reports of rhabdomyolysis, proteinuria, nephropathy, or renal failure for every 1 million prescriptions filled, a rate two to eight times higher than that for atorvastatin (Lipitor), pravastatin (Pravachol), or simvastatin (Zocor), according to a report published online (Circulation [Epub ahead of print], May 23, 2005. Article DOI number: 10.1161/circulationaha.105.555482. Available from www.circ.ahajournals.org).

But experts differed on the clinical message of these findings.

"This additional safety information is important for both patients and physicians to consider, among other factors, when balancing the risks and benefits in choosing a statin," said Richard H. Karas, M.D., director of the Preventive Cardiology Center and the Women's Heart Center at Tufts–New England Medical Center in Boston, and senior author of the new report.

Dr. Karas and his associates concluded that "it would seem prudent at the current time for health care providers to consider other statins as first-line therapy."

A more skeptical reading of the findings was given by Scott M. Grundy, M.D., who wrote an editorial that accompanied the report (Circulation [Epub ahead of print], May 23, 2005. Article DOI number: 10.1161/circulationaha.105.557652. Available at www.circ.ahajournals.org).

"I don't see any clear-cut evidence to choose one statin over another," he said during a press briefing.

"On the basis of this study, I don't know that rosuvastatin is more dangerous" than other statins, said Dr. Grundy, director of the Center for Human Nutrition at the University of Texas Southwestern Medical Center in Dallas.

Dr. Grundy cited the limitations of adverse event reports as a way to gauge the safety of a drug and to compare safety among drugs.

He also noted that in March 2005, the Food and Drug Administration denied a request to remove rosuvastatin from the U.S. market that had been filed last year by Sidney M. Wolfe, M.D., director of the Public Citizen Health Research Group.

"The FDA had the same database [that Dr. Karas used] and they did not determine that rosuvastatin was more dangerous [than other statins]," Dr. Grundy said at the press briefing.

Dr. Grundy added that "the disagreement is whether the evidence is strong enough evidence to say that there is a difference [among statins]. The new paper says there might be, but the FDA did not reach that conclusion."

The new study analyzed reports for a variety of individual adverse events, such as myopathy and liver effects, as well as for several combinations of events including the primary analysis, which totaled the reports of rhabdomyolysis, proteinuria, nephropathy, or renal failure.

The analysis looked at reports for all statins during the first 12 months when rosuvastatin was available in the United States, as well as reports that were made during the year when each statin was first available. This additional analysis was included because adverse event reports are often more common when a drug is first sold, Dr. Karas said.

The consistent pattern in virtually all of these comparisons was that the number of adverse event reports for rosuvastatin was significantly higher than the number reported for atorvastatin, pravastatin, or simvastatin.

Dr. Karas noted that the adverse events associated with rosuvastatin did not seem to be linked with overdosing, as the average dosage in these reports was 17 mg/day, and more than 60% of patients in the reports received 10 mg/day or less. The approved dosage for rosuvastatin is 5-40 mg/day.

Despite the significantly higher relative risk linked to rosuvastatin use, Dr. Karas as well as the other speakers at the press breifing stressed that the absolute incidence of adverse events was low with rosuvastatin as well as with all other approved statins.

"This paper heightens our sensitivity to the possibility of a signal of increased adverse events with rosuvastatin, but it has limitations," commented Elliott Antman, M.D., director of the coronary care unit at Brigham and Women's Hospital in Boston and senior associate editor of Circulation.

"The overarching issue is to get patients [who need treatment] on statins to help achieve their lipid goals. If rosuvastatin is the statin that is most available to a patient based on insurance reimbursement, then that's perfectly acceptable," Dr. Antman said. ■

Adverse Event Reports for Statins

	Rosuvastatin	Atorvastatin	Pravastatin	Simvastatin
Number of AERs*	145	315	52	381
Number of prescriptions	5,200,000	72,900,000	15,000,000	29,800,000
AERs per 1 million prescriptions	27.9	4.3	3.5	12.8

*AERs = composite total of adverse event reports, including reports of rhabdomyolysis, proteinuria, nephropathy, and renal failure.

Note: Based on data from October 2003 to September 2004, the first year of marketing for rosuvastatin.

Source: http://circ.ahajournals.org/cgi/reprint/circulationaha.105.555482v1

KEVIN FOLEY, RESEARCH

African Americans Fall Short of Achieving LDL Cholesterol Goals

BY MIRIAM E. TUCKER
Senior Writer

WASHINGTON — African American patients with dyslipidemia are less likely than non-Hispanic whites to achieve LDL cholesterol treatment goals, Luther T. Clark, M.D., and his associates reported in a poster at a conference on cardiovascular disease epidemiology and prevention sponsored by the American Heart Association.

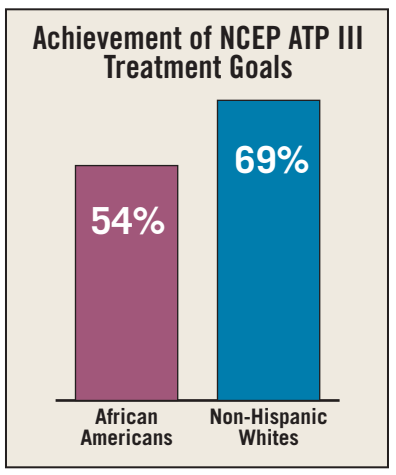
In a national survey of physician compliance with guidelines issued in the third report of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III), African American ethnicity remained a strong predictor of lower success in reaching LDL cholesterol goals, even after adjustment for cardiovascular disease risk factors, said Dr. Clark, chief of cardiovascular medicine at the State University of New York Downstate Medical Center, Brooklyn.

In the study, supported by AstraZeneca PLC, a total of 376 U.S. physicians who were high prescribers of lipid-modifying medications each enrolled 10 or 20 consecutive dyslipidemic patients. Data associated with a single office visit were entered into special software on a personal digital assistant and then uploaded to a central database via the Internet.

The 4,885 patients studied were aged 20-75 years and had been on a diet and/or a stable dose of drug therapy for at least 3 months. Most (80%) were non-Hispanic whites, 8% were African American or black, 4% were Hispanic, and 3% were Asian.

Physician specialties included family practice (40%), general internal medicine (40%), cardiology (15%), and endocrinology (2%).

Most physicians were male (90%), board certified (90%), and office based (99%).



Achievement of NCEP ATP III treatment goals for LDL cholesterol level was significantly lower overall among African Americans than in non-Hispanic whites (54% vs. 69%).

This was true in all risk categories—those with fewer than two cardiovascular risk factors (82% vs. 90%), those with two or more risk factors (59% vs. 77%), and those at highest risk by virtue of having either coronary heart disease (CHD) or a CHD risk equivalent (44% vs. 58%), Dr. Clark and his associates wrote.

The disparity in achievement of LDL goal remained, even after adjustment for age, gender, smoking status, family history of CHD, hypertension, HDL cholesterol category, type of therapy (diet vs. drug), hypertriglyceridemia, obesity, and physician specialty. After the full adjustment, African Americans were less than half as likely (odds ratio 0.48) to have reached their LDL cholesterol goals, they said.

"These findings are disappointing, but not surprising. [They] are consistent with those from other surveys that have shown that CHD risk factors are less well controlled in African Americans," Dr. Clark told this newspaper in a follow-up interview.

Although the reasons are not clear, the fact that the difference persisted after adjustment for both physician specialty and receipt of statins suggests that patient behavior is at least a contributing factor. But physiologic variation may be at work as well.

"Surprisingly little data have been published directly comparing lipid responses to available treatments in African American and non-Hispanic white patients. Therefore, it is also possible that physiologic factors could have played a role in the lower frequency of goal achievement in African Americans," Dr. Clark said. ■