Fluvastatin XL Cuts LDL Level With Less Myalgia

Trial finds drug is well tolerated and less likely than other statins to cause muscle-related side effects.

BY BRUCE JANCIN
Denver Bureau

CHICAGO — Fluvastatin XL, either alone or in combination with ezetimibe, is an effective, well-tolerated, and safe option for lowering LDL cholesterol in patients who can't tolerate other statins because of muscle-related side effects, Dr. Evan A. Stein said at the annual scientific sessions of the American Heart Association.

Statin-associated mild to moderate muscle-related side effects such as myalgias, cramping, and weakness are far more common and debilitating in daily practice than suggested by high-profile, highly selective clinical trials. And fluvastatin XL is less likely than other statins to cause these problems, said Dr. Stein, director of the Metabolic and Atherosclerosis Research Center, Cincinnati.

The data showed 85% of subjects were maintained on fluvastatin XL at 80 mg/day without muscle-related problems.

DR. STEIN

He presented a randomized double-blind placebo-controlled trial restricted to patients forced to discontinue statins other than fluvastatin (Lescol) because of muscle-related side effects. The results showed 85% of participants could be maintained on fluvastatin XL at 80 mg/day or fluvastatin XL 80 mg plus ezetimibe (Zetia) at 10 mg/day without muscle-related problems.

Moreover, the dropout rate owing to muscle-related side effects in the 12-week study was less than 5%, although everyone in the trial had already discontinued another statin for that very reason.

Dr. Stein stressed he was not talking about myopathy and rhabdomyolysis, serious but rare side effects of statin therapy. He focused on mild to moderate muscle pain, cramping, and weakness. The big randomized trials suggest the prevalence of such problems is 2%-4%, but many clinicians say the figure in everyday practice is much higher, he said.

In the trial at 27 U.S. and European centers, 199 patients with a history of intolerance to statins other than fluvastatin due to muscle-related side effects were randomized to 12 weeks of ezetimibe plus placebo, fluvastatin XL plus placebo, or both drugs.

LDL cholesterol lowering with fluvastatin, with or without ezetimibe, was greater than with ezetimibe alone. Muscle-related side effects in the two fluvastatin arms were slightly lower than with ezetimibe. And when such side effects occurred in patients on fluvastatin alone, they began in the first month, whereas with ezetimibe they started any time during the 3-month trial. The combination therapy's effect upon C-reactive protein lowering is difficult to explain but has consistently been seen in other studies of ezetimibe plus various statins, Dr. Stein said.

Mean baseline LDL cholesterol in the study cohort was 175 mg/dL. Eighty percent of subjects were high risk by National Cholesterol Education Program (NCEP) criteria. Fluvastatin XL enabled many to reach their NCEP LDL cholesterol goal, which otherwise would not have been possible because of their muscle problems on other statins. An estimated 1-2 million patients have ended statin therapy due to such side effects, the physician said.

The impression that prevalence of mild to moderate muscle-related side effects to statins is much higher in practice than in clinical trials was recently borne out in an observational study involving an unselected population of 7,924 French patients on high-dose statin therapy.

The study—the Prediction of Muscular Risk in Observational conditions (PRIMO)—was the first to look at statin-related muscle side effects in clinical practice. It found that muscular symptoms occurred in 10.5% of patients. Thirty-eight percent of patients with muscle-related side effects said muscular pain prevented even moderate exertion during everyday activities, Dr. Stein said.

PRIMO, sponsored by Novartis Pharmaceuticals, showed the rate of muscle symptoms was 10.9% with pravastatin at 40 mg/day, 14.9% with atorvastatin at 40-80 mg/day, and 18.2% with simvastatin at 40-80 mg/day. Fluvastatin XL at 80 mg/day was associated with a 5.1% rate (Cardiovasc. Drugs Ther. 2005;19:403-14).

Audience members argued that Dr. Stein's trial should have featured an arm involving rechallenge to an offending statin, though Dr. Stein said most patients found their muscle symptoms sufficiently unpleasant that they would balk at reexposure. Dr. Stein is a consultant to Novartis, which funded the trial. ■

Results of Fluvastatin With and Without Ezetimibe at 12 Weeks

	Ezetimibe	Fluvastatin	Fluvastatin + Ezetimibe
Patients having muscle-related side effects	24.2%	17.4%	14.1%
Patients dropping out of study because of muscle-related side effects	7.6%	4.3%	3.1%
Patients reaching LDL-cholesterol level <100 mg/dL	1.5%	33.3%	67.2%
Patients reaching NCEP LDL-cholesterol goal	10.6%	43.5%	73.4%
Reduction in:			
Level of LDL cholesterol (mean)	15.6%	32.8%	46.1%
Level of C-reactive protein (median)	0%	7.9%	18.6%

Note: Based on a study of 199 patients who had discontinued other statins because of muscle-related side effects.
Source: Dr. Stein

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Medication Combo Trumps Rosuvastatin in Cutting LDL

BY MIRIAM E. TUCKER
Senior Writer

COPENHAGEN — A combination of ezetimibe and simvastatin provides additional lipid-modifying benefits compared with rosuvastatin monotherapy among patients with type 2 diabetes or with metabolic syndrome without diabetes, Dr. Alberico L. Catapano reported at the annual meeting of the European Association for the Study of Diabetes.

"Overall, ezetimibe/simvastatin, a single-tablet, dual-cholesterol inhibitor, offers an effective and well-tolerated lipid-modifying option for the treatment of hypercholesterolemia in patients with type 2 diabetes and metabolic syndrome," said Dr. Catapano, of the department of pharmacological sciences at the University of Milan.

In a post-hoc analysis of data from a multicenter, double-blind, randomized, 6-week study sponsored by Merck & Co., 375 patients with type 2 diabetes, 840 with metabolic syndrome but without diabetes, 1,722 with neither condition, and 22 who could not be placed in a category because of missing data were randomized to one of six treatment groups: ezetimibe/simvastatin (E/S) in doses of 10 mg/20 mg (respectively), 10 mg/40 mg, or 10 mg/80 mg; or rosuvastatin (R) in doses of 10, 20, or 40 mg. All had hypercholesterolemia, defined as an LDL-cholesterol level of 145-249 mg/dL (3.7-6.4 mmol/L) with triglycerides at or below 350 mg/dL (4 mmol/L).

Among the whole cohort of 2,959 patients, significant reductions in LDL cholesterol from baseline were seen among the E/S group at the usual starting, next highest, and maximum dosing levels. (See chart.)

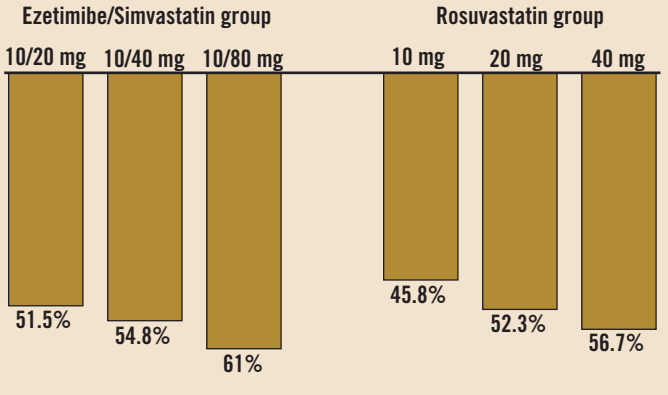
Across all doses, the difference in LDL-cholesterol reduction between E/S and R was significant for the whole cohort (55.8% vs. 51.6%). Consistent with that, LDL-cholesterol lowering was also greater with E/S in the type 2 diabetes patients (58.5% vs. 54.2%), nondiabetics with metabolic syndrome (55% vs. 51.8%), and those with neither (55.6% vs. 51%), Dr. Catapano reported.

Overall, 95.3% of the E/S group, compared with 92.1% of the R group, attained the recommended LDL-cholesterol goals of less than 100 mg/dL (2.6 mmol/L) for the diabetics, 130 mg/dL (3.4 mmol/L) for the nondiabetics with metabolic syndrome, or 160 mg/dL (4.1 mmol/L) for the group with neither. A total of 88.2% of the E/S patients versus 81.9% of the R patients achieved an LDL-cholesterol level of less than 100 mg/dL (2.6 mmol/L), whereas 45.3% vs. 29.5% reached an LDL-cholesterol level of less than 70 mg/dL (1.8 mmol/L). All of these differences were significant, he said.

Reductions in total cholesterol, non-HDL cholesterol, apolipoprotein B, and triglycerides were also significantly greater with E/S; there were no significant differences between the two treatments in HDL cholesterol, or high-sensitivity C-reactive protein.

Both drugs showed similar rates of adverse events (8.1% E/S vs. 7.4% R) and discontinuations because of adverse events (2.2% for both drugs). Proteinuria was higher at baseline in the R group and among those with diabetes, he noted. ■

Greater Reductions in LDL-Cholesterol Level With E/S In Type 2 Diabetes and Metabolic Syndrome Patients



Note: Based on a study of 2,959 patients.
Source: Dr. Catapano

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