# Fluvastatin XL Least Likely to Cause Myalgias

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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, in particular, is less likely than other statins to cause these problems, said Dr. Stein, director of the Metabolic and Atherosclerosis Research Center, Cincinnati.

He presented a randomized double-blind placebo-controlled clinical trial restricted to patients forced to discontinue statins other than fluvastatin (Lescol) because of muscle-related side effects.

**Roughly 85% of participants could be maintained on fluvastatin XL without having any muscle-related problems.**

**DR. STEIN**

The results of that investigation showed that roughly 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 experiencing any muscle-related problems.

Moreover, the dropout rate owing to muscle-related side effects in those two arms of the 12-week study was less than 5%, even though 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 instead on mild to moderate muscle pain, cramping, and weakness.

The big randomized trials suggest the prevalence of such problems is 2%-4%, but the experience of many clinicians has been that the true figure in everyday practice is much higher, he said.

In the trial conducted 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 (see box on following page).

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 synergistic 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 at the meeting.

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 of them 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 discontinued statin therapy due to such muscle-related side effects, the physician said.

The impression among physicians 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 ever to look at statin-related muscle side effects in clinical practice. The conclusion: Muscular symptoms

occurred in 10.5% of patients, and the negative impact upon quality of life was far greater than generally appreciated. Thirty-eight percent of patients with muscle-related side effects reported that muscular pain prevented even moderate exertion during everyday activities, Dr. Stein said.

The PRIMO investigation, sponsored by Novartis Pharmaceuticals, showed that 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. In contrast, fluvastatin XL at 80 mg/day was associated with a 5.1% rate (Cardiovasc. Drugs Ther. 2005;19:403-14).

Audience members at the meeting argued that Dr. Stein's trial should have featured an arm involving rechallenge to a previously offending statin.

Dr. Stein rejected that as impractical. Most patients found their muscle symptoms sufficiently unpleasant that they would balk at reexposure. And many had experienced continued muscle problems despite switching to two or three different statins, further complicating rechallenge, he said.

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