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Perspective

Weighing the Benefits of High-Dose Simvastatin against the Risk of Myopathy

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Statins are the most widely prescribed class of drugs for treating dyslipidemia — in particular, elevated levels of low-density lipoprotein (LDL) cholesterol. Nearly 20 years of research provide convincing evidence that statin-related reductions in LDL cholesterol decrease the risk of major adverse cardiovascular events in people with or without a history of known cardiovascular disease. A meta-analysis including more than 90,000 patients has shown that for every 39 mg per deciliter that statins lower the LDL cholesterol level, the risk of major adverse cardiovascular events is reduced by approximately 25%.[1] The average LDL cholesterol–lowering effect of the highest doses of approved statins are 63% for rosuvastatin (40 mg), 57% for atorvastatin (80 mg), 46% for simvastatin (80 mg), 41% for pitavastatin (4 mg), 40% for lovastatin (80 mg), 34% for pravastatin (80 mg), and 31% for fluvastatin (80 mg).[2]

Despite their cardiovascular benefits, all statins are associated with myopathy, ranging in severity from asymptomatic increases in creatine kinase to muscle aches or weakness to fatal rhabdomyolysis. Recently, concerns have been raised about a disproportionate increase in the risk of myopathy with high-dose simvastatin. This possible association was the subject of a drug-safety communication issued by the Food and Drug Administration (FDA) on March 19, 2010. Since that time, the FDA has completed a comprehensive review of data from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) clinical trial, other large clinical trials of high-dose statins, and the agency's Adverse Event Reporting System (AERS).

The SEARCH trial was a 6.7-year, randomized, double-blind trial comparing the efficacy and safety of 80 mg of simvastatin with those of 20 mg of simvastatin, with or without vitamin B_{12} and folate, in survivors of myocardial infarction. The primary efficacy end point of the trial was the incidence of major adverse cardiovascular events, defined as death from coronary causes, myocardial infarction, stroke, or arterial revascularization.

At the end of the trial, the incidence of major adverse cardiovascular events was 25.7% in

Key Components of Recent Safety-Labeling Changes for Simvastatin

1. Use of the 80-mg dose of simvastatin should be restricted to patients who have been taking it for a long time (e.g., 12 months or more) without signs or symptoms of clinically significant toxic effects on muscle.
2. Patients who are currently taking an 80-mg dose of simvastatin without adverse effects but who need to begin taking an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin with less potential for a drug–drug interaction.
3. Patients in whom the LDL cholesterol goal cannot be achieved with a 40-mg dose of simvastatin should instead be given other appropriate LDL cholesterol–lowering therapy (e.g., a more potent statin that poses a lower risk of myopathy, such as atorvastatin or rosuvastatin).

Drug Interactions Associated with Increased Risk of Myopathy and Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Itraconazole	Contraindicated with simvastatin
Ketoconazole	
Posaconazole	
Erythromycin	
Clarithromycin	
Telithromycin	
HIV protease inhibitors	
Nefazodone	
Gemfibrozil	
Cyclosporine	
Danazol	
Amiodarone	Do not exceed 10 mg of simvastatin daily
Verapamil	
Diltiazem	
Amlodipine	Do not exceed 20 mg of simvastatin daily
Ranolazine	
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 qt daily)

the 20-mg group, as compared with 24.5% in the 80-mg group (relative risk, 0.94; 95% confidence interval, 0.88 to 1.01; P=0.10). In part because of greater use of off-study LDL cholesterol–lowering medication in the 20-mg group, the difference between the two treatment groups in mean levels of LDL cholesterol was 13 mg per deciliter instead of the expected 20 mg per deciliter. Nonetheless, the 6% reduction in the relative risk of major adverse cardiovascular events observed in the SEARCH trial is consistent with the 13-mg-per-deciliter difference in LDL cholesterol levels.[3]

Myopathy — defined as a serum creatine kinase level more than 10 times the upper limit of normal with unexplained muscle weakness or pain — developed in 52 patients in the 80-mg group (0.9%) but in only 1 patient in the 20-mg group (0.02%). Rhabdomyolysis — defined as unexplained muscle pain or weakness with a serum creatine kinase level more than 40 times the upper limit of normal — developed in 22 patients in the 80-mg group (0.4%) but in no patients in the 20-mg group. There were no deaths related to rhabdomyolysis.

It is critical to note that the risks of myopathy and rhabdomyolysis with the 80-mg dose of simvastatin decreased from 5 per 1000 person-years and 2 per 1000 person-years, respectively, during the first 12 months of treatment to 1 per 1000 person-years and 0.4 per 1000 person-years, respectively, after the first 12 months of treatment. This reduction indicates that in patients who are at risk for myopathy with high-dose simvastatin — for instance, those with common variants of *SLCO1B1*, which encodes a hepatic statin transporter — this risk will tend to manifest early in the course of treatment.[4]

Of the statins on the market, simvastatin is particularly prone to drug–drug interactions, in part because it is extensively metabolized by the CYP3A4 enzyme system. Data from the SEARCH trial indicate that much of the increase in risk for myopathy noted in the high-dose simvastatin group was due to the concomitant use of medications such as amiodarone, diltiazem, and amlodipine. Hence, judicious concomitant use of other medications with simvastatin will reduce the risk of myopathy.

The FDA's review of additional data from large clinical trials of high doses of statins indicates that the incidence of myopathy — defined as a serum creatine kinase level more than 10 times the upper limit of normal with or without unexplained muscle weakness or pain —

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though very low for all statins, was approximately 3 times as high with the 80-mg dose of simvastatin as with superior LDL cholesterol–lowering doses of rosuvastatin and atorvastatin. The FDA also conducted analyses of U.S. rhabdomyolysis reports in AERS associated with use of a statin and with an outcome of death, from the date of initial marketing approval of each statin through January 1, 2010. With the caveat that spontaneous adverse-event reporting systems have recognized limitations (e.g., reporting rates are not incidence rates), the rates of reported fatal rhabdomyolysis were higher with 80 mg of simvastatin than with 80 mg of atorvastatin or with 20 mg and 40 mg of rosuvastatin.

Thus, on the basis of the totality of the data, the FDA recommends that the 80-mg dose of simvastatin be used only in patients who have been taking this dose "chronically" (e.g., for 12 months or more) without signs or symptoms of clinically significant muscle toxicity. For these patients, the agency believes that the cardiovascular benefits of high-dose simvastatin outweigh the low absolute risk of myopathy. Patients who require a greater reduction in LDL cholesterol than can be achieved with 40 mg of simvastatin should be given an alternative LDL cholesterol–lowering therapy (e.g., a statin with greater potency that poses a lower risk of myopathy, such as atorvastatin or rosuvastatin).

To help ensure that high-dose simvastatin therapy is not initiated in new patients and that patients receiving any dose of simvastatin do not receive concomitant medications that could increase plasma concentrations of simvastatin to inappropriate levels, the FDA, exercising its authority under the FDA Amendments Act of 2007, has mandated safety-labeling changes for Zocor (simvastatin) and Vytorin (ezetimibe and simvastatin). The key components of the labeling changes are shown in the box. Under its Safe Use initiative, the FDA is working with creators of drug formularies, pharmacy benefit managers, and professional medical societies to increase awareness and implementation of the new safety-labeling changes.

During the next year, the FDA will closely monitor prescription-use data to determine whether the safety-labeling changes and the communication outreach are having their intended effects of limiting new initiation of high-dose simvastatin therapy and guiding appropriate use of concomitant medications with simvastatin. If evidence indicates that these measures are not effective, the agency will consider additional regulatory action, including withdrawal of high-dose simvastatin from the market.

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