SJHG Heartbeat

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If You Cannot Go Lower Go Elsewhere

There is nothing wrong with change,
if it is in the right direction.—Winston Churchill

This Heartbeat will discuss the effects of an alert issued by the the Food and Drug Administration in June concerning simvastatin (Zocor). It recommended physicians restrict prescribing high-dose simvastatin because of increased risk of muscle damage. **Physicians should *stop prescribing a new 80-mg dose*** unless the patient has already been taking the drug for 12 months and there is no evidence of myopathy. This includes patients already taking lower dosages of the drug.

The FDA notes that the risks of myopathy and rhabdomyolysis were highest in the first year and that older age and female sex increased the risks.

These changes are based on the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (**SEARCH**) trial.[1] 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.

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 a lot 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.

Interestingly, the risks of myopathy and rhabdomyolysis with the 80-mg dose decreased from 5/1000 person-years and 2/1000 person-years, respectively, *during* the first 12 months of treatment to 1/1000 person-years and 0.4/1000 person-years, respectively, *after* the first 12 months of treatment.

The FDA has requested that more changes be made to the drug's label to include the new dosing recommendations, as well as warnings not to use the drug with various medications that could increase plasma concentration of simvastatin to inappropriate levels. A summary of the recommendations follows.[2]

Summary of Key Components of Recent Drug Labeling Changes for Simvastatin:

1. Use of the 80-mg dose of simvastatin or Vytorin 10/80mg (ezetimibe [Zetia] 10 mg/ simvastatin 80 mg) 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 and Contraindicated with Simvastatin:

Itraconazole
Ketoconazole
Posaconazole
Danazol
Erythromycin
Clarithromycin
Telithromycin
Nefazodone
Gemfibrozil
HIV protease inhibitors
Cyclosporine

Interacting Agents Prescribing Recommendations:

Do not exceed 10 mg of simvastatin daily with:
Amiodarone
Verapamil
Diltiazem

Do not exceed 20 mg of simvastatin daily with:
Amlodipine
Ranolazine

Avoid large quantities of grapefruit juice

Clinical Application:

What does all this mean and what do we do? Unfortunately this becomes a major issue because simvastatin is the most widely prescribed statin and 80 mg is our most potent generic statin dose. Now the FDA, appropriately, is telling us we can't go there to get adequate non-HDL-C lowering (the best surrogate for apoB or LDLp).[3] [4] **Short of using apoB or LDLp, non-HDL-C has replaced LDL-C as the goal of therapy regardless of triglyceride level.**

Physicians aren't going to be comfortable in escalating to branded statins (Crestor 40 mg or Lipitor 80 mg). Add-ons to simvastatin 40 mg, Zetia or Welchol (also only available as branded), won't be much help either because of resistance from the health insurance companies and frequently the necessity for *this widely loved thing* called a 'prior authorization'. Additionally, patients are going to complain because of the higher cost.

We have to educate our patients and be aware that these branded statins are very well tolerated and highly effective in their maximal dosages and associated with

significant event reduction—our ultimate goal.

We prefer the one pill approach with Crestor (rosuvastatin) 40 mg **or Lipitor** (atorvastatin) 80 mg replacing simvastatin 40 mg as opposed to add-ons **because of better proof of outcome benefits** and for better compliance. This approach will result in a greater than 50% reduction in lipids from baseline compared to ~45% with simvastatin 80 mg.

Lastly, since pravastatin 80 mg is equivalent in potency—not drug interactions—to simvastatin 40 mg and we can't even use the higher doses with many of the cardiac medications that we use every day, ***we recommend removing simvastatin from your statin repertoire (KISS)***. We will continue patients on chronic simvastatin at their present dosages as long as they are not taking any interacting medications and don't have symptoms of myopathy.

During the next year, the FDA will closely monitor prescription-use data to determine whether the safety-labeling changes and its communication outreach are effective in limiting new initiation of high-dose simvastatin therapy and guiding appropriate use of concomitant interactive 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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[1] Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg Versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a doubleblind randomised trial. *Lancet* 2010; 376: 1658-69.

[2] Egan A & Coleman E. Weighing the benefits of high-dose simvastatin against the risk of myopathy. *NEJM* July 28, 201; 365:285-87.

[3] Ramjee V, et al. Non–high-density lipoprotein cholesterol versus apolipoprotein B in cardiovascular risk stratification: do the math. *J Am Coll Cardiol* July 26 2011;58:457– 63.

[4] Milani RV, Lavie CJ. Another step forward in refining risk stratification—moving past low-density lipoprotein cholesterol. *J Am Coll Cardiol* July 26 2011; 58:464– 63.