This article was sponsored by Kowa Pharmaceuticals America, Inc.

Optimizing Statin Therapy by Avoiding Clinically Relevant Drug Interactions

For decades, statins have been used for the treatment of hyperlipidemia and prevention of primary and secondary cardiovascular events.[1] Nearly one-third (31.8%) of individuals 55 to 64 years of age use prescription cholesterol-lowering medications, most commonly statins. Many of these individuals are also being treated for other conditions.[2,3] As such, there is widespread use of statins in patients taking multiple medications, and it is therefore important to consider the possible risks involved in polypharmacy, including the potential for clinically relevant drug interactions between statins and concomitant medications.

TABLE 1: STATIN DOSE LIMITATIONS FOR HIV AND HCV PROTEASE INHIBITORS[9]

Statin	Interacting protease inhibitor(s)	Prescribing recommendation
Atorvastatin	Tipranavir + ritonavir Telaprevir	Avoid atorvastatin
	Lopinavir + ritonavir	Use with caution and use with the lowest atorvastatin dose necessary
	Darunavir + ritonavir Fosamprenavir Fosamprenavir + ritonavir Saquinavir + ritonavir	Do not exceed 20 mg atorvastatin daily
	Nelfinavir	Do not exceed 40 mg atorvastatin daily
Fluvastatin	No data available	
Lovastatin/ simvastatin	HIV protease inhibitors Boceprevir Telaprevir	Contraindicated
Pitavastatin	Atazanavir ± ritonavir Darunavir + ritonavir Lopinavir + ritonavir	No dose limitations
Pravastatin	Darunavir + ritonavir Lopinavir + ritonavir	No dose limitations
Rosuvastatin	Atazanavir ± ritonavir Lopinavir + ritonavir	Do not exceed 10 mg once daily

HCV = hepatitis C; HIV = human immunodeficiency virus.
Adapted from FDA website. http://www.fda.gov/Drugs/DrugSafety/ucm293877.htm.

Pharmacologic Basis for Statin-Related Interactions

Of all medications metabolized, approximately 3 out of every 4 rely on the cytochrome P450 isoenzymes for metabolism, and approximately half of these rely on CYP3A4/5 isoenzymes.[4,5] Because many commonly used statins rely on this same metabolic pathway,[4,6] use of a statin with medications that inhibit isoenzymes such as CYP3A4 may lead to supratherapeutic statin levels and may increase the risk of statin-related adverse events, such as myalgia, myositis, and, in rare cases, rhabdomyolysis.[7,8]

The FDA released a public safety announcement highlighting this risk for those statins that are sensitive in vivo cytochrome P450 3A4 (CYP3A4) substrates. Regarding other medications metabolized, strong CYP3A4 inhibitors are predicted to significantly increase overall exposures to certain statins. For example, itraconazole, a strong CYP3A4 inhibitor, increases maximal concentrations of simvastatin up to 13-fold and lovastatin exposure up to 20-fold, with the potential interaction to result in rhabdomyolysis.[9] Hence, other CYP3A4 inhibitors may significantly increase lovastatin and simvastatin exposures based on metabolic dependency on the CYP450 system. Statins may also inhibit CYP3A4, exposing patients to supratherapeutic levels of other medications.[4,7]

Key Statin-Related Interactions

Pursuant to an FDA safety advisory communication released in 2011, restrictions, limitations, and contraindications were added to the labeling of simvastatin and simvastatin-containing agents. A later FDA communication, released in 2012, advised against use of statins in combination with human immunodeficiency virus or hepatitis C protease inhibitors (Table 1[9]). Following these communications, the FDA added several contraindications and dose restrictions to the labeling of many statins (Table 2[10]).[9-11] Additionally, for patients taking commonly prescribed antihypertensive medications, the dose of simvastatin must be limited. Patients taking verapamil or diltiazem should take no more than 10 mg of simvastatin daily, and in patients taking amlodipine, simvastatin should not be administered at a dosage greater than 20 mg daily.[11] Use of simvastatin or rosuvastatin with warfarin may affect coagulation parameters, such as prothrombin time (PT) and international normalized ratio (INR), further complicating therapy.[11,12]

Unlike most other statins, pitavastatin (Livalo) is only minimally metabolized by the CYP450 system, has no clinically relevant interactions with strong CYP3A4 inhibitors, has no contraindication, restriction or limitation in patients taking protease inhibitors, and does not significantly affect coagulation parameters (ie, PT/INR) in patients taking warfarin.[4,13] It has no dose-limitation restriction when used with calcium channel blockers. Key clinically relevant drug interactions with pitavastatin include a contraindication for use with cyclosporine and limitation of the pitavastatin dose to 1 mg daily in patients taking erythromy-

Please see Brief Summary of full Prescribing Information adjacent to this article.

TABLE 2: LABEL UPDATES FOR SIMVASTATIN AND SIMVASTATIN-CONTAINING PRODUCTS[10]

Previous simvastatin label	New simvastatin label
Avoid simvastatin with itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone	Use of simvastatin is contraindicated with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, and danazol
Do not exceed simvastatin 10 mg daily with gemfibrozil, cyclosporine, or danazol	Do not exceed simvastatin 10 mg daily with verapamil or diltiazem
Do not exceed simvastatin 20 mg daily with amiodarone or verapamil	Do not exceed simvastatin 20 mg daily with amiodarone, amlodipine, or ranolazine
Do not exceed simvastatin 40 mg daily with diltiazem	N/A
Avoid large quantities of grapefruit juice (>1 quart daily)	

HIV = human immunodeficiency virus.
Adapted from FDA website. http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm.

cin. As with other statins, due to class-wide effects, fibrates, niacin (≥1 gram daily), and colchicine should be used with caution, and gemfibrozil should be avoided.[13]

Assessing Statin-Related Interactions

In the largest Internet-based survey to date on statin use, of more than 10,000 individuals, which included 1220 former statin users and 8919 current statin users, drug interactions that involved statins occurred in more than 8 of every 10 respondents (84%). For each participant with an interaction, an average of 3 other products interacted with the statin, including prescription medications, OTC products, and dietary supplements. Nearly three-fourths (74%) of these respondents never spoke with their physician about the possibility of these drug interactions.[6]

Although a causal relationship between drug interactions and adverse events (AEs) leading to treatment discontinuation was not evaluated in this survey, in this population of patients with unaddressed drug interactions, 1 of 4 current statin users and more than half (60%) of former users reported experiencing muscle-related AEs. In former statin users, AEs, including muscle pain and weakness, were responsible for nearly two-thirds (62%) of statin discontinuations.[6]

Considering that patients prescribed statins who do not take them have nearly 3 times greater mortality risk than patients who take statins as prescribed, treatment discontinuation may have important clinical consequences.[14] In the modern treatment era, statins with fewer drug interactions are available; they are worth consideration because their interaction burden is lower than other medications in this class while still providing potent efficacy.[4]

Role of the Pharmacist

In addition to advising and counseling patients about the importance of adherence to statin therapy to reduce the risk of negative cardiovascular outcomes, pharmacists are instrumental in recognizing and managing drug interactions to achieve treatment regimen harmonization for patients. To achieve this desirable end, pharmacists should not only alert prescribers to drug interactions, but also provide recommendations for alternative therapy to help resolve these drug interactions whenever possible.

In discussing these interactions with prescribers, rather than focusing only on the increased risk of rhabdomyolysis with statins and interacting medications, pharmacists should emphasize the risk of drug interactions leading to statin-related AEs and statin discontinuation. Approximately 8 in 10 patients taking statins are using an average of 3 interacting medications. These interactions may increase the risk of AEs such as myalgia, weakness, myositis, and myopathy.[6,7] Harmonizing treatment regimens may help patients continue taking statins. By applying their specialized knowledge about the subtle but clinically significant differences between individual statins, pharmacists can help align patients with the most appropriate statin and associated dose to help achieve improved long-term outcomes.

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