

# Statins and Potentially Interacting Medications: A Managed Care Perspective

*Lida Etemad, PharmD, MS*

According to 2001 data from the American Heart Association, 104.7 million Americans (50.7% of the US population) have total cholesterol above 200 mg/dL, mainly caused by elevations in low-density lipoprotein cholesterol.<sup>1</sup> Dyslipidemia is most frequently treated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, otherwise known as statins. Data from the Pharmaceutical Care Network show that statins were the third leading class of drugs in terms of cost per patient per month and percentage of total drug costs in 2001.<sup>2</sup>

Statins have consistently been shown in primary and secondary prevention trials to be highly effective in treating dyslipidemia and reducing the risk of cardiovascular events and are considered first-line drug therapy.<sup>3</sup>

As a class, statins are generally well tolerated. The most commonly reported side effects are mild (such as gastrointestinal upset or discolored urine); serious side effects are reported more rarely.<sup>3</sup> The major clinical concerns relating to statin therapy are myotoxicity (myalgia, myopathy, and rhabdomyolysis) and hepatotoxicity,<sup>4</sup> which generally occur secondary to excessive statin dosing or drug-drug interactions that inhibit statin metabolism. Milder cases are often reversible without serious clinical sequelae on drug discontinuation or reduction of exposure; severe cases are rare but potentially fatal.<sup>5,6</sup>

The statins have distinctive pharmacodynamic and pharmacokinetic properties that result in important differences in safety. The high risk of rhabdomyolysis with cerivastatin led to its withdrawal from the market in 2001,

whereas the risk with all other statins is extremely low (<1 case per million prescriptions).<sup>4</sup> Approximately 60% of cases of statin-related rhabdomyolysis have been attributed to drug-drug interactions.<sup>7</sup>

Because many patients with hyperlipidemia present with concomitant medical problems, such as diabetes, hypertension, and coronary artery disease, statins are often used in combination with other medications. This raises the potential for adverse drug-drug interactions, which can have serious clinical and financial consequences. Clinically, drug-drug interactions may lead to severe toxicity and may force discontinuation of needed pharmacotherapy. Financially, treatment for interaction-induced toxicity and for illness exacerbated by forced interruptions in pharmacotherapy adds substantially to the overall cost of medical care. For all drugs, major adverse reactions and interactions account for 6.7% of hospitalizations, and the per-patient cost of preventable drug toxicity is \$4865.<sup>8</sup>

Most of the statins are metabolized through the cytochrome P450 (CYP) metabolic pathway; atorvastatin (Lipitor), simvastatin (Zocor), and lovastatin (Mevacor, Altacor) via the CYP3A4 isoenzyme, and fluvastatin (Lescol) via CYP2C9. In contrast, pravastatin (Pravachol) and rosuvastatin (Crestor) do not depend on the CYP450 pathway.

CYP3A4 is involved in the metabolism of a large number of medications, many of which bind to the enzyme more strongly than the statins bind to it. A drug whose affinity for CYP3A4 is greater than that of a statin blocks the statin from binding and thereby inhibits its

metabolism. Consequently, simultaneous use of a CYP3A4-dependent statin and other medications that also bind to that enzyme may result in decreased metabolism of the statin and an increased risk of statin-related toxicity.<sup>9-12</sup>

Much information has been reported on the pharmacodynamic and pharmacokinetic implications of concomitant use of CYP450 inhibitors and statins, but research on the economic impact of such interactions has been much more limited. A Canadian study found that patients taking statins in combination with prescription medications that have been shown to increase the serum concentration of statins had higher overall medical and pharmacy costs than statin users who did not receive medications with the potential to interact.<sup>13</sup>

A key concept in assessing the risk of drug-drug interactions in patients taking statins is that the same drug may be a potentially interacting medication (PIM) with one statin but not with another. Thus, a drug that binds strongly to CYP3A4 is a PIM with statins that also depend on that enzyme, but not with statins that do not depend on CYP3A4. For example, cyclosporine, macrolide antibiotics, azole antifungal agents, protease inhibitors, and calcium channel blockers all bind to CYP3A4 with greater affinity than that of atorvastatin, simvastatin, and lovastatin, and can thus inhibit the metabolism of those statins. In contrast, the same drugs will not interfere with the disposition of statins that do not depend on CYP450-mediated metabolism.<sup>10,14-18</sup>

Despite established pharmacy programs designed to prevent exposure to PIMs, the actual frequency of exposure is not known; nor is it clear how often exposure leads to clinical toxicity. One reason for this uncertainty is that much of the data are derived from case reports rather than controlled trials.<sup>19</sup> In addition, there are relatively few data on the economic impact of interaction-related statin toxicity.

In 2003, a retrospective study was initiated to address these issues in a population of managed care enrollees taking statins. Preliminary results of this study indicate that subjects taking statin medications still receive PIMs in high numbers and with an increased cost to the health care system.<sup>20</sup>

Educational programs for medical providers should emphasize the prevalence of PIM exposure with each of the statins and the costs associated with such exposure. As more is learned about other potential benefits of the statins beyond lipid lowering, clinical use of these agents may expand, and these considerations would thus assume increasing importance.

In the following article, Michael B. Bottorff, PharmD, reviews the mechanisms underlying the differential risk of drug-drug interactions involving the various statins, explaining how the likelihood of such interactions is a function of the unique pharmacologic profile of each of these agents. Rational therapeutic decisions aimed at achieving the best clinical and cost outcome should be observant of these principles.

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