Dyslipidemia

Does Simvastatin Cause More Myotoxicity Compared with Other Statins?

James M Backes, Patricia A Howard, Janelle F Ruisinger, and Patrick M Moriarty

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are well-established agents for the treatment of dyslipidemia and reduction of cardiovascular events. Statins have been widely prescribed since the first agent, lovastatin, was approved in 1987. Currently, more than 13 million patients in the US receive statin therapy. Overall, these agents are generally well tolerated and possess an excellent safety profile.

Presently, 6 statins are available in the US. Clinical data suggest that approximately 5–10% of patients discontinue these agents due to minor adverse effects. A frequent cause of discontinuation for all statins is myotoxicity. Statin-related muscle symptoms can range from common and clinically benign myalgia to rare but life-threatening rhabdomyolysis. Many statin-induced adverse effects are considered dose dependent. Pooled data of atorvastatin and simvastatin trials indicate a 4- to 5-fold increase in adverse effects when daily doses are increased from 40 to 80 mg. Other studies also report unacceptably high rates of adverse events with unapproved daily doses of pravastatin (160 mg).

OBJECTIVE: To review the literature regarding statins and myotoxicity and evaluate these data to determine whether incidence rates are higher with simvastatin.

DATA SOURCES: Literature was identified from a search of MEDLINE (1966–August 2009) and International Pharmaceutical Abstracts (1970–August 2009), as well as references of selected articles. Key search terms included the names of individual statins, rhabdomyolysis, myopathy, myalgia, myotoxicity, statins, and drug interactions.

STUDY SELECTION AND DATA EXTRACTION: All English-language articles discussing statin-related myotoxicity and relevant drug interactions that involved human subjects were examined.

DATA SYNTHESIS: Simvastatin is a commonly prescribed, moderately potent statin. Recent evidence suggests that the risk of severe muscle toxicity with simvastatin may be higher than that with other statins, particularly when used in combination with cytochrome P450 isoenzyme inhibitors. However, the lack of direct comparative clinical trials assessing the risk of myotoxicity among the statins in equivalent doses precludes definitive conclusions. Data sources examining low-to-moderate doses of simvastatin suggest that myotoxicity with this agent is infrequent, with rates similar to those seen with other statins. Conversely, findings from clinical trials using the maximum daily dose (80 mg) and a clinical trials database of varying doses of simvastatin suggest a possible increase in rates of myotoxicity with the 80-mg dose compared with lower doses and a higher incidence rate when compared with maximum doses of other statins.

CONCLUSIONS: Overall, the rates of severe myotoxicity with all statins are low, especially with low-to-moderate doses. However, recent trials for those using simvastatin 80 mg daily suggest a higher incidence of myotoxicity compared with maximum approved doses of other statins. Practitioners should be aware of these possible risks and individualize therapy to limit myotoxicity.

KEY WORDS: drug interactions, myopathy, rhabdomyolysis, statins.
mg), simvastatin (160 mg), and rosvuvastatin (80 mg), suggesting a toxic threshold for adverse events with the class.6-8

Patient intolerance and adverse effects, including myotoxicity, are likely increased with concomitantly administered medications that inhibit statin metabolism. One study indicated that approximately 50% of patients experiencing rhabdomyolysis were also receiving an interacting drug known to increase statin plasma concentrations.9 As a class, statins have many similar properties; however, unique metabolic differences between agents likely make some more susceptible to common drug interactions. The CYP3A4 isoenzyme is required for metabolism of approximately 50% of all medications and is the primary cytochrome P450 isoenzyme in the liver and intestinal wall. Inhibition of this common isoenzyme by concomitant medications will increase plasma concentrations of statins metabolized by the CYP3A4 pathway.10

In addition to drug interactions and the use of high statin doses, there are other risk factors that may predispose patients to myotoxicity. A clinical advisory from the American College of Cardiology/American Heart Association and the National Heart, Lung, and Blood Institute describes the key factors that appear to increase rates of rhabdomyolysis (Table 1).4 In general, the overall medical complexity of the patient is a useful guide for determining the potential for myotoxicity.

Since there are important differences in metabolic pathways and susceptibility to drug interactions with individual statins, it is plausible that the risk for myotoxicity may vary among agents. Previous editorials, a labeling change, and a warning from the Food and Drug Administration (FDA) have raised concerns for potentially greater myotoxicity with simvastatin.11-14 However, long-term prospective studies directly comparing the myotoxic effects of individual statins are lacking. In this article, we attempt to determine from the available literature whether simvastatin does indeed have a higher incidence of myotoxicity compared with other statins.

### Statin Overview

Simvastatin is a widely prescribed, moderately potent statin. The drug is indicated as an adjunct to diet for patients requiring lipid modification and for adolescents with heterozygous familial hypercholesterolemia. It is also indicated for reduction of cardiovascular events and mortality in high-risk patients, regardless of baseline low-density lipoprotein cholesterol (LDL-C) levels. Approved daily doses of 5–80 mg reduce LDL-C (26–47%) and triglycerides (12–40%), while raising high-density lipoprotein cholesterol (HDL-C) by approximately 9%.18 The recommended simvastatin dose, administered in the evening, is 20–40 mg daily; however, for patients at high risk for coronary heart disease, 40 mg daily is suggested. Simvastatin, a nonsynthetic prodrug, is closely related to lovastatin. Both drugs are the fermentation products of *Aspergillus terreus*. The inactive parent compound, simvastatin lactone, is metabolized primarily by CYP3A4 in the intestinal wall and liver. After hydrolysis, this compound forms the active metabolite, simvastatin acid, which undergoes further metabolism by CYP3A4, CYP2C8, and glucuronidation. Simvastatin has a short half-life of 2–3 hours, thereby allowing for approximately 10% greater efficacy when administered in the evening, the time of more active steroid synthesis.15

Atorvastatin, lovastatin, and simvastatin are all dependent upon CYP3A4 metabolism.16-19 Atorvastatin is only partially (20%) metabolized by this isoenzyme, possibly making it less susceptible to interactions with CYP3A4 inhibitors.19 Because lovastatin is closely related to simvastatin and experiences similar metabolism by CYP3A4, this agent is also likely to be prone to interactions and subsequent adverse events. However, lower use of maximal doses (80 mg daily) and less overall utilization likely limit major adverse events with lovastatin. None of the other available statins are metabolized primarily by CYP3A4; however, inhibition of other metabolic pathways can lead to clinically significant drug interactions. One such mechanism is the blocking of statin uptake to the liver by organic anion transporting polypeptides (OATPs).10,20 Pravastatin is minimally metabolized, but like other statins, inhibition of OATPs may ultimately lead to increased plasma concentrations. Similarly, rosuvastatin undergoes minimal metabolism but depends on less common cytochrome P450 isoenzymes (2C9, 2C19) in the gut and liver and may be

| Table 1. Risk Factors for Statin-Induced Myotoxicity⁴ |
|-----------------|-----------------|
| High statin doses | Advanced age (especially those >80 y) |
| Sex—female more than male | Small body frame and frailty |
| Multisystem disease (eg, chronic renal impairment, especially as a result of diabetes) | Hypothyroidism |
| Perioperative periods | Alcohol abuse |
| Grapefruit juice (typically >0.95 L daily) | Concomitant medications |
| amiodarone | azole antifungals (especially itraconazole and ketoconazole) |
| cyclosporine | fibrates (especially gemfibrozil) |
| macrolides (especially clarithromycin, erythromycin, and telithromycin) | nefazodone |
| protease inhibitors | verapamil |

⁴Adapted from Pasternak et al.⁴
prone to interactions with drugs such as gemfibrozil that block biliary excretion. Fluvastatin also appears to be less involved in major drug interactions by relying on CYP2C9 for elimination.\(^{10,20}\)

**Pharmacokinetic Studies**

Drug interactions play a large role in adverse events. It has also been determined that many statin-induced adverse events, including myotoxicity, are generally dose- and plasma concentration–dependent.\(^{9}\) To evaluate the susceptibility of statins to drug interactions and subsequent increases in plasma concentrations, an overview of pharmacokinetic studies is needed.

A number of trials have analyzed the pharmacokinetic effects of a variety of metabolic inhibitors on statin plasma concentrations. The results of these studies suggest that both lovastatin and simvastatin are more susceptible than other statins to CYP3A4 inhibition. Conversely, when interacting agents inhibiting pathways primarily outside of CYP3A4 were evaluated, more consistent pharmacokinetic changes were observed among all statins.

The general methods of most of these studies consisted of a double-blind, placebo-controlled crossover design in a small number (~10–14) of healthy volunteers. Typically, the interacting agent would be administered for a short time (~4 days), with a single statin dose given on approximately day 4. Key pharmacokinetic parameters would then be measured for usually 24 hours. In some studies, especially those involving immunosuppressant agents (eg, cyclosporine), subjects were transplant patients with pharmacokinetic measures performed more extensively after multiple statin doses.

**CYP3A4 INHIBITION**

Marked changes in statin concentrations were observed when the effects of the potent CYP3A4 inhibitor itraconazole on both simvastatin and lovastatin were evaluated.\(^{10,18,21,22}\) Mean increases in area under the curve (AUC) for each agent ranged from 5- to 20-fold, while the AUC for atorvastatin was increased 2- to 4-fold.\(^{19,21,23}\) For statins not extensively metabolized by CYP3A4, including fluvastatin, cerivastatin, pravastatin, and rosuvastatin, minimal (≤1.5-fold increases) or no changes in AUC were observed with concomitant itraconazole administration.\(^{16,21,22,24,25}\)

Similar trends were noted when the effects of less potent CYP3A4 inhibitors on statin metabolism were evaluated. Administration of erythromycin or clarithromycin increased the AUCs of both simvastatin and lovastatin by 4- to 12-fold, whereas atorvastatin AUC increased by 1.5- to 5-fold.\(^{17,21,26,27}\) Again, for all other statins, either no change or minor increases (≤2-fold) in AUC were observed with macrolide administration.\(^{21,28,29}\)

**INHIBITION OF OTHER METABOLIC PATHWAYS**

Considerably less variation in the pharmacokinetic changes of individual statins has been found with the coadministration of drugs known to inhibit metabolic pathways other than CYP3A4. Cyclosporine is thought to increase statin plasma concentrations primarily by inhibiting several membrane transporters, especially OATP1B1.\(^{16,20}\) When administered concomitantly with statins, cyclosporine increased the AUC of all statins by at least 5-fold (range 5–20), with the exception of fluvastatin AUC, which was increased only 2- to 4-fold.\(^{30-38}\) Similarly, gemfibrozil, which is a known inhibitor of CYP2C9, CYP2C8, and glucuronidation, also displayed less variable effects on statin concentrations. All available statins, except fluvastatin, developed AUC increases of approximately 2-fold with concomitant gemfibrozil.\(^{39-44}\) Again, fluvastatin was less impacted by gemfibrozil, with minimal changes in pharmacokinetic parameters.\(^{45}\)

**Literature Review**

**OBSERVATIONAL STUDIES**

Outcomes from most observational studies do not indicate a higher rate of myotoxicity with simvastatin. Black and Jick\(^{46}\) evaluated the United Kingdom General Practice Research Database for documented cases of rhabdomyolysis between 1990 and 1999. Records of 52,000 patients who received 868,700 prescriptions for lipid-lowering therapy were evaluated. This included nearly 25,000 simvastatin users involving approximately 400,000 prescriptions. Additionally, 2935 patients were prescribed both a fibrate and statin concurrently. During this time, only one case of rhabdomyolysis associated with lipid-lowering therapy was observed, which involved a patient using concomitant simvastatin and ciprofibrate. After discontinuation of each agent, the patient recovered uneventfully. The authors noted that a potential limitation to their analysis was the lack of a specific diagnostic code used to identify rhabdomyolysis; instead, nearly all cases were identified from free-text comment fields.

The Japan Lipid Intervention Trial was a nationwide cohort study evaluating the benefits and safety of open-label simvastatin in Japanese hypercholesterolemic patients.\(^{47}\) The study showed very limited myotoxicity with simvastatin, as over 51,000 patients with 175,000 person-years of follow-up reported no cases of rhabdomyolysis and an incidence of musculoskeletal adverse events of less than 1%. However, this was a low-dose study, with nearly all patients receiving only 5–10 mg daily.

Data from managed care health plans across the US were also used to assess hospitalized patients with rhabdomyolysis associated with lipid-altering therapy.\(^{48}\) The treatment of over 250,000 patients with statins and/or fi-
brates between 1998 and 2001 resulted in 24 cases of patients hospitalized with rhabdomyolysis. Combined statin–fibrate therapy accounted for 8 cases, while statin and fibrate monotherapy resulted in 13 and 3 reports, respectively. The incidence rate of rhabdomyolysis was 0.44 per 10,000 person-years of use for the most commonly used statins, atorvastatin, pravastatin, and simvastatin. No significant differences were seen between simvastatin and atorvastatin either as monotherapy or in combination with fibrates. No cases were reported for pravastatin alone or in combination with a fibrate. At the time, this study provided significant insight into the association between lipid-altering agents and myotoxicity, but it does not reflect current prescribing trends and the subsequent potential for myotoxicity.

A more recent assessment using administrative claims from health plan databases was used to determine the incidence rates of adverse events associated with lipid-altering therapy that caused hospitalization. Over 473,000 patients contributed nearly 500,000 person-years of monotherapy and almost 12,000 person-years of combination therapy between 2000 and 2004. A total of 144 hospitalizations secondary to myopathy were identified. The incidence per 10,000 person-years, including rhabdomyolysis, was similar for all currently available statins when administered as monotherapy, but ranged from 1.58 for fluvastatin to 3.49 for simvastatin. Also, a 6-fold increase in muscle disorders was observed when lipid-altering agents were used with a concomitant CYP3A4 inhibitor. A further analysis of the specific cases examining the use of individual lipid drugs with CYP3A4 inhibitors was not included in the study.

The PRIMO (Prediction of Muscular Risk in Observational) survey was a study performed in France involving approximately 8000 patients receiving high-dose atorvastatin (40–80 mg), fluvastatin (80 mg), pravastatin (40 mg), or simvastatin (40–80 mg) daily. A major objective of the study was to determine the occurrence of mild-to-moderate muscle symptoms with individual statins in a usual-care, outpatient setting. Data were collected through questionnaires administered by the patient’s general practitioner. The results indicate that patients receiving simvastatin had the highest rate of muscular symptoms (18.2%), followed by atorvastatin (14.9%), pravastatin (10.9%), and fluvastatin (5.1%). However, due to the observational nature of the study and the imbalance in sample sizes between groups, the authors urged caution when comparing individual statins.

**CLINICAL TRIALS**

Randomized clinical trials are another source for evaluating the myotoxic effects of statin therapy. These data are ideal for capturing all major adverse events; however, the screening process prior to randomization often eliminates many patients with drug interactions or statin intolerance. Because of this, analyses of these data may not accurately reflect what is observed in clinical practice. Additionally, many clinical trials have not clearly defined adverse muscle symptoms or definitions have been inconsistent between studies, further confounding some of these data. As a general rule, the clinical trial definitions for adverse muscle experiences are as follows: (1) myalgia: muscle ache, pain, or weakness with or without creatine kinase (CK) elevation; (2) myopathy: otherwise unexplained elevations in CK 10 or more times the upper limit of normal (ULN), associated with muscle symptoms; and (3) rhabdomyolysis: marked CK elevation substantially more than 10 times the ULN, creatinine elevation usually with cola-colored urine, and possibly other metabolic disturbances (eg, hyperkalemia, metabolic acidosis). It is important to consider these inconsistencies and confounding factors when interpreting data from clinical trials.

Law and Rudnicka systematically reviewed all major placebo-controlled statin trials performed through 2006. These trials included all statins except cerivastatin and rosvastatin. With nearly 180,000 person-years of exposure, statin treatment resulted in 8 cases of rhabdomyolysis, compared with 5 in the placebo groups. Simvastatin was implicated in 6 cases (n = 12,683), atorvastatin (n = 7506) and lovastatin (n = 10,549) were each involved with 1, and no cases were reported in trials using pravastatin (n = 13,990) or fluvastatin (n = 1597). The incidence rate of rhabdomyolysis for patients receiving statins compared with placebo was an additional 1.6 cases per 100,000 person-years. When rates of less severe myotoxicity (ie, myopathy) were evaluated, the incidence among those receiving statin treatment (n = 97) was similar to that with placebo (n = 92).

Nearly all of the studies evaluated by Law and Rudnicka used low-to-moderate statin doses. Because of this, the analyses do not accurately assess the potential myotoxicity observed with higher statin doses. Trials using higher simvastatin doses of 80 mg daily have suggested a higher risk of muscle symptoms (Table 2). In the recently presented SEARCH trial (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine), which evaluated outcomes of simvastatin 20 or 80 mg daily among 12,000 subjects with a previous myocardial infarction, cases of myopathy, defined as muscle symptoms and CK levels more than 10 times the ULN, were significantly greater with the 80-mg dose (53 vs 3). Similar findings were noted in the A to Z trial (Early Intensive vs a Delayed Conservative Simvastatin Strategy in Patients with Acute Coronary Syndromes study). Among approximately 4500 subjects receiving simvastatin, 9 cases of myopathy, including 3 defined as rhabdomyolysis, were reported in those receiving 80 mg compared with none for patients receiving 20 mg daily. When evaluating these data overall with other study find-
ings in the simvastatin clinical trials database (N = 41,050), a clear dose-dependent delineation in muscle toxicity was observed in patients receiving higher doses. The incidence of myopathy or rhabdomyolysis was 0.02%, 0.08%, and 0.53% for 20, 40, and 80 mg daily, respectively.

Trials evaluating high doses of other statins have found less noticeable trends toward increased myotoxicity compared with those observed with simvastatin 80 mg. The PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) study evaluated the daily use of maximum-dose atorvastatin versus moderate-dose pravastatin among patients with acute coronary syndromes. During the mean follow-up of 2 years, no cases of rhabdomyolysis were reported and differences in discontinuation rates secondary to myopathy with high-dose atorvastatin or moderate-dose pravastatin were not statistically significant.

The IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) study compared the effects of simvastatin 20 mg daily with those of atorvastatin 80 mg daily in patients with a history of myocardial infarction. Rates of investigator-reported rhabdomyolysis were similar for simvastatin and atorvastatin. However, patients receiving high-dose atorvastatin were more likely to discontinue therapy due to myalgias (2.2% vs 1.1%; p < 0.001). The authors noted that the low rates of adverse events with simvastatin were readily explained by the fact that approximately 50% of subjects received simvastatin prior to enrollment and were deemed “simvastatin tolerant.”

The results of the TNT (Treating to New Targets) study did not indicate a relationship between muscle symptoms and varying doses of atorvastatin. In this study, researchers evaluated the effects of low- and high-dose atorvastatin among patients with coronary heart disease. Muscle complaints were nearly identical, as cases of rhabdomyolysis and treatment-related myalgia in each treatment group were not statistically different.

Studies using maximum doses of other statins, including the JUPITER study (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) and LIPS (the Lescol Intervention Prevention Study) only produced one case of rhabdomyolysis, which occurred after trial close, and rates of myopathy similar to those with placebo.

### OTHER DATA

The assessment of other data sources, including information from the FDA, indicates a potentially greater asso-

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**Table 2. Reports of Myotoxicity in Major Randomized Trials Using Maximum-Dose Statins**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment (mg)</th>
<th>Subjects (n)</th>
<th>Rhabdomyolysis Cases, n (%)</th>
<th>Myopathy Cases, n (%)</th>
<th>Myalgia Cases, n (%)</th>
<th>Duration (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A to Z trial de Lemos (2004)</td>
<td>simvastatin 20</td>
<td>2232</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>34 (1.5)*</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>simvastatin 80</td>
<td>2265</td>
<td>3 (0.13)</td>
<td>6 (0.26)</td>
<td>41 (1.8)*</td>
<td>4.8</td>
</tr>
<tr>
<td>IDEAL Pedersen (2005)</td>
<td>simvastatin 20</td>
<td>4449</td>
<td>3 (0.07)</td>
<td>11 (0.25)</td>
<td>51 (1.1)*</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>atorvastatin 80</td>
<td>4439</td>
<td>2 (0.05)</td>
<td>6 (0.14)</td>
<td>97 (2.2)*</td>
<td>3.9</td>
</tr>
<tr>
<td>JUPITER Ridker (2008)</td>
<td>rosuvastatin 40</td>
<td>8901</td>
<td>1 (0.01)*</td>
<td>10 (0.1)</td>
<td>142 (16)*</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>8901</td>
<td>0 (0)</td>
<td>9 (0.1)</td>
<td>3735 (15.4)*</td>
<td>3.9</td>
</tr>
<tr>
<td>LIPS Serruys (2002)</td>
<td>fluvastatin 80</td>
<td>844</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
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<tr>
<td></td>
<td>placebo</td>
<td>833</td>
<td>0 (0)</td>
<td>3 (0.4)</td>
<td>NR</td>
<td>4.9</td>
</tr>
<tr>
<td>PROVE-IT Cannon (2004)</td>
<td>pravastatin 40</td>
<td>2063</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
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<tr>
<td></td>
<td>atorvastatin 80</td>
<td>2099</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
<td>2</td>
</tr>
<tr>
<td>SEARCH Armitage (2008)</td>
<td>simvastatin 20</td>
<td>6033</td>
<td>NR</td>
<td>3 (0.05)*</td>
<td>NR</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>simvastatin 80</td>
<td>6031</td>
<td>NR</td>
<td>53 (0.88)*</td>
<td>NR</td>
<td>7</td>
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<tr>
<td>SPARCL Amarenco (2006)</td>
<td>atorvastatin 80</td>
<td>2365</td>
<td>2 (0.08)</td>
<td>7 (0.3)</td>
<td>129 (5.5)*</td>
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<td>7 (0.3)</td>
<td>141 (6.0)*</td>
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<td>TNT LaRosa (2005)</td>
<td>simvastatin 10</td>
<td>5006</td>
<td>3 (0.06)</td>
<td>0 (0)</td>
<td>234 (4.7)*</td>
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<td>atorvastatin 80</td>
<td>4995</td>
<td>2 (0.04)</td>
<td>0 (0)</td>
<td>241 (4.8)*</td>
<td>4.9</td>
</tr>
</tbody>
</table>

A to Z = Early Intensive vs a Delayed Conservative Simvastatin Strategy in Patients with Acute Coronary Syndromes; IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LIPS = Lescol Intervention Prevention Study; NR = not reported; PROVE-IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy; SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TNT = Treating to New Targets.

*Defined as discontinuation due to muscle-related adverse event.
*Occurred after trial closed.
*Defined as muscle weakness, stiffness, or pain (but treatment/placebo not necessarily discontinued).
*Defined as discontinuation due to increased creatinine kinase or myalgias.
*Myotoxicity broadly defined as “myopathy” with creatine kinase levels >10 times the upper limit of normal.
*Not defined.
*Defined as treatment-related myalgia.
ciation between simvastatin and myotoxicity compared with other statins. Shortly after cerivastatin was voluntarily withdrawn from the US market, Staffa et al. analyzed cases of fatal rhabdomyolysis reported to the FDA and numbers of prescriptions dispensed for all statins. Reported rates of fatal rhabdomyolysis per 1 million prescriptions were as follows: fluvastatin 0, atorvastatin 0.04, pravastatin 0.04, simvastatin 0.12, lovastatin 0.19, and cerivastatin 3.16. This indicates much higher rates for cerivastatin but also potentially higher risk of fatal rhabdomyolysis with simvastatin and lovastatin compared with the other agents. However, rigorous comparisons are discouraged because of the crude nature of the reporting system and the lack of actual incidence rates.

The prescribing information for the individual statins appears to reflect each agent’s susceptibility to drug interactions and potential for myotoxicity. While the labeling for all statins contains the warning for possible skeletal muscle effects, the language and recommended dosing limitations with simvastatin is more extensive (Table 3). Initial labeling changes occurred in 2002; in August 2008 the FDA issued a safety alert warning healthcare professionals of the increased risk of rhabdomyolysis with simvastatin and concomitant amiodarone. The alert was issued because of continuous reports of myotoxicity with the combination, despite the previous labeling change. The safety alert indicates that the risk for myotoxicity is dose-related and generally only observed when amiodarone is combined with simvastatin doses exceeding 20 mg daily. Additionally, the mechanism presumed responsible for the interaction is the inhibition of CYP3A4 by amiodarone. A pharmacokinetic study supported this, as it reported marked increases (155%) in the AUC of both simvastatin acid and simvastatin lactone with concomitant amiodarone, whereas no AUC changes were observed with the combination of the non–CYP3A4-metabolized pravastatin and amiodarone.

Evaluation of the individual published case reports seems to further strengthen this association. A literature search produced a total of 8 case reports of severe myopathy or rhabdomyolysis involving amiodarone and simvas-

<table>
<thead>
<tr>
<th>Table 3. Simvastatin and Concomitant Agents Associated with Increased Risk of Myopathy/Rhabdomyolysis</th>
<th>Interacting Agents</th>
<th>Prescribing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin, erythromycin, protease inhibitors, itraconazole, ketoconazole, nefazodone, telithromycin</td>
<td>avoid simvastatin</td>
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</tr>
<tr>
<td>Cyclosporine, danazol, gemfibrozil</td>
<td>do not exceed simvastatin 10 mg daily</td>
<td></td>
</tr>
<tr>
<td>Amiodarone, verapamil</td>
<td>do not exceed simvastatin 20 mg daily</td>
<td></td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>avoid large quantities (&gt;0.95 L daily) of grapefruit juice</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from simvastatin product information.*

Discussion

Heightened awareness of the potential for statins to cause severe muscle toxicity possibly resulting in rhabdomyolysis has been raised through an FDA advisory. Because the advisory focuses on simvastatin and muscle toxicity resulting from drug interactions, concerns have been raised that the overall risk for severe myotoxicity is higher with simvastatin than with other statins. However, the lack of direct comparative clinical trials assessing the risk of myotoxicity among the statins in equivalent doses precludes definitive conclusions.

Numerous pharmacokinetic studies have been performed evaluating the effects of concomitant use of common interacting agents with statins. Findings from these studies indicate that simvastatin is highly susceptible to certain drug interactions, especially CYP3A4 inhibition, generally resulting in more marked increases in plasma concentrations of simvastatin compared with most other statins. The implication of simvastatin in these common drug interactions and the subsequent increase in plasma concentration likely play a major role in the development of myotoxicity.

Overall, the data from both clinical and observational trials suggest that the risk of severe myotoxicity and rhabdomyolysis for all statins is low. Further, the findings from earlier observational studies of large databases do not suggest an increased risk of severe myotoxicity with simvas-

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When the available evidence is evaluated, it appears that several factors have contributed to the emerging concern of a higher risk for severe myotoxicity with simvastatin. First, the more aggressive guidelines from the Adult Treatment Panel III Update (eg, LDL-C <70 mg/dL) have necessitated the use of either potent statins (eg, rosuvastatin, atorvastatin) or higher doses of the less potent agents such as simvastatin. Second, the availability of generic simvastatin in 2006 has caused some organizations to select simvastatin as their preferred statin. This change has exposed more patients to simvastatin and in many cases required the use of higher doses to achieve equivalent lipid lowering.

Until more definitive data are available, patients should be assessed on an individual basis. First, one must consider the degree of LDL-C lowering necessary to achieve therapeutic goals and the dose of statin that is needed. Second, the use of concomitant medications must be taken into account. If drugs known to inhibit CYP3A4 are indicated, consideration should be given to choosing a statin that is not dependent upon this pathway or limiting the dose of statins that undergo CYP3A4 metabolism. Finally, the patient’s baseline risk for myotoxicity should be assessed. For patients with multiple risk factors, consideration should be given to using statins less prone to common drug interactions (eg, pravastatin, flu- vastatin, rosuvastatin), with final selection based on the degree of lipid lowering required. Lastly, additional studies based on contemporary practice and current guidelines are needed to further assess the comparative risks.

Summary

The overall risk of severe myotoxicity with statin therapy is low. Studies evaluating low-to-moderate doses of simvastatin indicate rates of muscle complaints similar to those with other statins. Recent trials using simvastatin 80 mg daily raise concern about potentially higher rates of myotoxicity compared with maximum approved doses of other statins; however, studies directly comparing agents are lacking. Until comparative risks between statins are clearly defined, practitioners should be aware of these potential risks, observe the FDA warning and dosing limitations regarding the use of simvastatin with concomitant CYP3A4 inhibitors, and individually assess overall patient risk by determining the presence of established risk factors for myotoxicity.

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References

1. Mitka M. Expanding statin use to help more at-risk patients is causing financial heartburn. JAMA 2003;290:2243-5.
6. Rosenson RS, Bays HE. Results of two clinical trials on the safety and efficacy of pravastatin 80 and 160 mg per day. Am J Cardiol 2003;91:878-81.
11. Rosenson RS, Bays HE. Results of two clinical trials on the safety and efficacy of pravastatin 80 and 160 mg per day. Am J Cardiol 2003;91:878-81.
34. Spence JD, Munoz CE, Hendricks L, Latchinian L, Khouri HE. Pharmacokinetics of the combination of fluvastatin and gemfibrozil. Am J Cardiol 1995;76:80A-3A.
40. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006;97:52C-60C.
La Simvastatina Causa más Myotoxicidad que Otras Estatinas?
JM Backes, PA Howard, JF Ruisinger, y PM Moriarty


EXTRACTO

OBJETIVO: Revisar la literatura médica para obtener información referente a las estatinas y su miotoxicidad, y determinar si la tasa de incidencia de esta toxicidad es mayor con la simvastatina.


SELECCIÓN DE ESTUDIO Y EXTRACCIÓN DE INFORMACIÓN: Se examinaron todos los artículos en inglés discutiendo la miotoxicidad asociada a las estatinas y sus interacciones con otros medicamentos en humanos. SELECCIÓN: La simvastatina es una estatina de potencia moderada de uso frecuente hoy en día. Existen evidencias recientes que sugieren que el riesgo de toxicidad muscular severa con la simvastatina puede ser mayor que la reportada con otras estatinas, particularmente cuando se usa en combinación con otros inhibidores de las isoenzimas del citocromo P-450. Sin embargo, la carencia de estudios clínicos directos evaluando el riesgo de miotoxicidad entre las estatinas administradas en dosis equivalentes no permite hacer conclusiones definitivas. Fuentes de información examinando los efectos adversos con la administración de dosis bajas o medianas de la simvastatina sugieren que la miotoxicidad con este agente es infrecuente y similar a la descrita con otras estatinas. A la inversa, hallazgos obtenidos de otros estudios clínicos en los cuales se emplearon dosis diarias máximas (80 mg) o variadas de la simvastatina, sugieren un posible incremento en la tasa de miotoxicidad con la dosis de 80 mg comparada con la reportada con dosis más baja y con dosis máximas de otras estatinas.

CONCLUSIONES: En total, la tasa de incidencia de miotoxicidad con las estatinas es baja, especialmente cuando se usan en dosis bajas o medianas. Sin embargo, estudios recientes usando la simvastatina a dosis de 80 mg diarias sugieren una incidencia mayor de miotoxicidad comparada con la descrita con dosis máximas de otras estatinas. Los profesionales de la salud deberían estar al conocimiento de estos posibles riesgos e individualizar la terapia del paciente para limitar el desarrollo de esta toxicidad.

Traducido por Encarnación C Suárez

La Simvastatina Causa-t-elle Plus de Myotoxicité que les Autres Statines?
JM Backes, PA Howard, JF Ruisinger, y PM Moriarty

RÉSUMÉ

OBJECTIF: Passer en revue la littérature relative aux statines et à la myotoxicité et évaluer ces données pour déterminer si les taux d’incidence sont plus élevés avec la simvastatine.


SELECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Tous les articles de langue anglaise discutant la myotoxicité liée aux statines et les interactions médicamenteuses y rapportant ont été examinés.

SYNTHÈSE DES DONNÉES: La simvastatine est une statine modérément puissante communément prescrite. Des résultats récents suggèrent que le risque de toxicité musculaire sévère avec la simvastatine est plus important qu’avec les autres statines, en particulier en combinaison avec les inhibiteurs d’isoenzyme du cytochrome P-450. Toutefois, le manque d’essais comparatifs directs quantifiant le risque de myotoxicité parmi les statines à doses équivalentes écarte toute conclusion définitive. Les sources de données examinant des dosages de simvastatine faibles à modérées suggèrent que la myotoxicité due à cet agent est peu fréquente et similaire à celle des autres statines. À l’inverse, des essais cliniques utilisant la dose maximale (80 mg) ainsi qu’une base de données cliniques avec des doses variables suggèrent un accroissement possible des taux de myotoxicité avec une dose de 80 mg de simvastatine en comparaison de doses plus faibles et un taux d’incidence plus élevé relativement aux doses maximum des autres statines.

CONCLUSIONES: Dans l’ensemble, les taux de myotoxicité sévère sont faibles avec toutes les statines, spécialement aux doses faibles à modérées. Cependant, de récents essais utilisant la simvastatine à la dose quotidienne de 80 mg suggèrent une incidence de myotoxicité supérieure à celle des doses maximum approuvées pour les autres statines. Les thérapeutes doivent être conscients de ces risques potentiels et individualiser la thérapie pour limiter la myotoxicité.

Traduit par Guy Berthon