Statin-Related Muscle Toxicity
Derek M. Fine, MD

ABSTRACT

According to estimates, 102 million Americans have cholesterol problems, and millions more have serious elevations of low-density lipoproteins and triglycerides. With national guidelines that set aggressive treatment strategies for dyslipidemia, more and more patients are now taking statin medications to reduce their risks of coronary heart disease and other atherosclerotic vascular diseases. Although side effects of these drugs, particularly those involving muscle, are reported infrequently, the increase in numbers of patients using them raises the possibility that primary care physicians may be seeing more patients with such symptoms. This article reviews the major side effects of statin therapy and identifies factors that can contribute to patient risks.


Hyperlipidemia is widely recognized as one of the major risk factors for coronary heart disease (CHD). Whereas therapeutic lifestyle changes are the first-line modality for reducing low-density lipoprotein (LDL) cholesterol, many patients also require medication to achieve cholesterol level goals. Primary and secondary prevention studies have demonstrated that adequate reduction of LDL cholesterol concentrations with lipid-lowering drugs is an effective treatment strategy for reducing coronary morbidity and mortality.1-8

Like its predecessors, the third report of the National Cholesterol Education Program Adult Treatment Panel (ATP III) continues to identify elevated LDL cholesterol as the primary target of cholesterol-lowering therapy.9 This latest report identifies levels of LDL cholesterol below 100 mg/dL as optimal for some groups, increases the thresholds for high-density lipoprotein (HDL) cholesterol from 35 to 40 mg/dL, and decreases the triglyceride (TG) classification thresholds to acknowledge the risks associated with even moderate elevations in TG. Furthermore, the new guidelines incorporate a modified Framingham Risk Prediction Score for estimating 10-year CHD risk, which recommends that patients with a 10-year risk for CHD greater than 20% should be treated in the same way as patients with established CHD. Based upon ATP III's lower cutpoints for treatment, it is estimated that more than 102 million Americans have undesirable total cholesterol levels (values greater than 200 mg/dL), of whom 41.3 million exhibit profound elevations (greater than 240 mg/dL). These new data represent a substantial increase in the total number of Americans who can benefit from statin therapy.10

In addition to the numerous reports of the efficacy of statins in preventing CHD and cerebrovascular disease and slowing their progression, recent studies point to additional indications for statin therapy.11 Such indications may include reducing proteinuria and slowing the progression of renal insufficiency in those with kidney disease12 and reducing
atrial fibrillation in those with coronary artery disease. A recent percutaneous coronary intervention study reported a reduction in mortality rate in those treated with statins, particularly diabetics and those with multivessel disease. With the pervasiveness of hypercholesterolemia within the population and emerging indications for statin use, statins will continue to be the most widely prescribed therapy for the foreseeable future. However, those who may benefit most from statin therapy—patients with diabetes, CHD, and renal insufficiency who frequently take multiple medications—may also be those at greatest risk for drug–drug interactions, an important safety issue that is widely overlooked in clinical practice.

The rise in the number of patients taking statins has raised new concerns about drug interactions and other safety issues. These concerns gained national attention in recent years with the withdrawal of cerivastatin from the market because of myotoxicity. This review of the recent medical literature surrounding the safety of statin therapy will highlight the potential risks associated with statin use. This information is intended to help physicians formulate a risk–benefit profile for each patient to better inform clinical practice decisions.

Efficacy and Mechanism of Action

Metabolic studies suggest reduced synthesis of LDL cholesterol and enhanced catabolism of LDL as the principal mechanisms for the lipid-lowering effects of all statins. At the intracellular level, statins inhibit the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, interrupting the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. In the hepatocyte, statins result in a drop in intracellular cholesterol concentration, upregulation of LDL cholesterol receptors and, ultimately, in increased clearance of LDL cholesterol from the plasma. Whereas first-generation statin drugs were fermentation products derived from fungal metabolites, second-generation statins are synthetically manufactured and are structurally dissimilar to them.

Clinically, LDL cholesterol is reduced by 18% to 55% when statins are added to dietary therapy, and triglycerides are reduced by 7% to 30%. The impact of statins on HDL is more modest, with elevations ranging from 5% to 15%. Although clinical trials have consistently shown that statin therapy reduces the risk for CHD, these reductions are not attributable solely to regression of atherosclerosis. Benefits are likely achieved by additional mechanisms, such as plaque stabilization, reversal of endothelial dysfunction, and decreased thrombogenicity. Regardless of mechanism, benefits remain pervasive, with statins proven effective in lowering LDL cholesterol in a dose-dependent manner. Given that reports of efficacy vary from agent to agent (Figure), the choice of statin will depend on the number of cardiac risk factors a patient has and the therapeutic goals for the patient.

Adverse Effects of Statins

The most frequently reported side effects associated with statin use are hepatic dysfunction and muscle injury. The latter is of greatest significance and may result in mortality and significant morbidity. Serious but less frequently reported side effects associated with statins include headache, nausea, and sleep disturbances.

Hepatic Dysfunction

Approximately 1% to 2% of patients will experience an elevation in aminotransferases within the first 12 weeks of statin therapy. Progression to liver failure is extremely rare. The elevation typically occurs slowly, is benign, and can be identified early with screening. For those reasons, the Food and Drug Administration (FDA) recommends that patients undergo liver function testing to achieve a baseline measure prior to initiation of statin therapy, and then again at 12 weeks. Liver screening should be repeated each time the statin dose is increased, and thereafter periodically. Statins can generally be continued as long as the aminotransferase elevations are less than 3 times normal. The FDA recommends not withstanding, some clinical experts...
believe that monitoring is only necessary in patients with pre-existing liver disease, because of the low incidence of significant increases in liver enzymes that necessitate withdrawal of the medication. This is a matter for individual clinical judgment, but failure to monitor may be risky from both a medical and legal standpoint.

Muscle Toxicity

The toxic effects of statins on muscles have been widely reported. The primary mechanism of statin myotoxicity is thought to be attributable to intrinsic pharmacologic properties of statins that limit the synthesis of cholesterol and many of its intermediates. Although the pathophysiology of the myopathy is not clear, its occurrence does appear to be dose related. This side effect of statins warrants clinical caution for several reasons. Whereas hepatotoxicity is gradual and observable over time, myotoxicity can occur suddenly, weeks or even months after the drug has been initiated.

To varying degrees, each of the lipid-lowering agents available today can cause muscle complaints. All statins share a common site of action but differ in how they reach that destination, depending on whether they are hydrophilic or liposoluble. These distinctions may have implications for the actions of these drugs within the cholesterol biosynthesis pathway of skeletal muscle, accounting for variations in muscle side effects among the agents. For example, pravastatin and fluvasatatin are hydrophilic compounds and rely on a specific protein to propel them through the cell membrane. The remaining statins are liposoluble, capable of passing into the cell membrane without assistance from a transporter protein. Therefore, passage into the muscle cell may increase with the lipophilicity of the statin and, hence, increase its myotoxicity.

Types of Muscle Toxicity

The American College of Cardiology and the American Heart Association (ACC/AHA) clinical advisory on statins recently defined 3 syndromes: myalgias (muscle ache or weakness without creatine kinase [CK] elevation), myositis (muscle symptoms with increased CK levels), and rhabdomyolysis (muscle symptoms with marked elevation of CK; usually >10 times the upper limit of normal). The advisory defined myopathy as a general term referring to any disease of the muscles, encompassing the 3 syndromes and muscle disease with asymptomatic CK elevations.

Of these syndromes, myalgia is the most common muscle complaint among patients taking statins. Labeling information from controlled studies shows rates of myalgia of only 1% to 5%. This may be an underestimate because statistical reports of myopathy in clinical trials, frequently based on CK values, may not accurately demonstrate the prevalence of myalgias. A review of 2 large databases by Thompson and colleagues shows that myalgia contributed 6% to 25% of all adverse events associated with statin use.

Until recently, most experts believed that other than being a source of discomfort to the patient, myalgias were benign. However, a recent study indicates that as yet unknown percentage of these patients, most likely a minority, do in fact develop histopathologic changes. In this study, 4 patients who had normal CK levels were able to accurately predict whether they were taking a placebo or a statin based upon muscle symptoms. In fact, the investigators were able to demonstrate muscle weakness during drug treatment by using objective measures of muscle strength. Furthermore, muscle biopsies revealed an ill-defined mitochondrial myopathy. Upon discontinuation of the statin, the clinical and histopathological findings reversed. These observations were reported with the use of cerivastatin, pravastatin, simvastatin, atorvastatin, and lovastatin and were, therefore, not likely attributable to a drug class effect. The long-term significance of these findings remains unclear.

These findings do suggest that as clinicians, we should not be overly dependent on CK testing as an indicator of problems; symptom monitoring is

<table>
<thead>
<tr>
<th>Trial</th>
<th>Myositis Statin</th>
<th>Myositis Control</th>
<th>Rhabdomyolysis Statin</th>
<th>Rhabdomyolysis Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin Pooling Project (CARE, LIPID, W O SCO PS)</td>
<td>3</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N = 19,592</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFCAPS/TEXCAPS study</td>
<td>21</td>
<td>21</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>N = 6,605</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S simvastatin randomized trial</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>N = 6,605</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>30</td>
<td>29</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>N = 30,641</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CARE = Cholesterol and Recurrent Events trial; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease trial; WOSCO PS = West of Scotland Coronary Prevention Study; AFCAPS/TEXCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; 4S = Scandinavian Simvastatin Survival Study. Adapted with permission from Elsevier (The Lancet) 2001:358:1383.
a valuable clinical tool and may well be indicative of myopathy, even in the absence of elevated CK. In the face of such a presentation, changing the class of drug prescribed is recommended, because most myalgias are likely not due to a mitochondrial myopathy. If class switching fails to bring relief, a muscle biopsy may be of some use in confirming myopathy and documenting the necessity for discontinuing statin use in order to prevent progression and undue pain.

When muscle complaints are accompanied by CK elevation, a diagnosis of myositis or rhabdomyolysis is made. Clinically significant myositis and rhabdomyolysis occur at a rate of less than 0.5% with statins, which is relatively infrequent. In several large trials these rates did not differ significantly from those with placebo (Table 1); however, such trials with their strict entry criteria may not reflect the general population at risk. Though infrequent, because of the large number of patients taking statins and particularly those taking them with potentially interacting medications, the otherwise rare occurrence of rhabdomyolysis may be observed clinically by individual practitioners. It is important for clinicians to be mindful of this serious complication, because it can advance to severe rhabdomyolysis with myoglobinuric acute renal failure and death. Fortunately, progression of myotoxicity to the severe complication of rhabdomyolysis-induced renal failure is rarely reported (Table 2).

RISK FACTORS FOR STATIN MYOPATHY

CLINICAL FACTORS

Several clinical conditions appear to predispose patients to myopathy, including advanced age, small body frame, hypothyroidism, and renal insufficiency. In patients with renal failure, statins are not contraindicated; in fact, a growing consensus exists for the expanded use of these agents because of the high prevalence of cardiovascular disease in this patient population. Though these drugs are predominantly cleared by hepatic metabolism, variable levels of renal clearance have been described. For these reasons, with the exception of atorvastatin, most statins should be prescribed at lower starting doses in patients with severe renal impairment, based on manufacturer’s recommendations.

DRUG INTERACTIONS

The possibility of drug interactions with statins is frequently unrecognized in clinical practice. Although the large clinical trials indicate that there are few safety concerns associated with statin use alone, as soon as statins are combined with interacting agents, toxicity can increase dramatically. This is particularly important with the high rates of polypharmacy among patients taking statins. The majority of interactions that result in myotoxicity occur with medications metabolized by the cytochrome P-450 (CYP) 3A4 enzyme system and with fibrates, particularly gemfibrozil. The likelihood of interactions depends upon the type of statin used, as there are recognized differences in the metabolism of these drugs, which collectively contribute to a class effect.

CYP3A4 is the predominant isoform for metabolism of lovastatin, simvastatin, and atorvastatin. Cerivastatin is metabolized by both 2C8 and 3A4. Fluvastatin primarily uses the 2C9 isoform, and pravastatin is unique among the statins in that it is not metabolized by CYP. Given these differences in metabolism, drug-drug interactions are less frequently reported with fluvastatin or pravastatin, but these agents also appear to be less potent than other statins (Figure), which limits their use in some patients. Many medications are metabolized via the CYP3A4 enzyme system, increasing the likelihood of drug-drug interactions. Clinicians should be cautious, therefore, when prescribing statins in patients taking drugs such as macrolide antibiotics (erythromycin, clarithromycin), antifungal azoles, calcineurin inhibitors (cyclosporine, tacrolimus), protease inhibitors, non-dihydropyridine calcium channel blockers (diltiazem, verapamil), amiodarone, warfarin, and even oral contraceptives.

The interaction between statins and warfarin anticoagulants causes a small increase in the anticoagulant effect that may warrant a reduction in

Table 2. Reported Cases of Fatal Rhabdomyolysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date approved</th>
<th>Fatal cases</th>
<th>No. prescriptions</th>
<th>Reporting rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>Aug 1987</td>
<td>19</td>
<td>99.2 (millions)</td>
<td>0.19</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Oct 1991</td>
<td>3</td>
<td>81.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Dec 1991</td>
<td>14</td>
<td>116.1</td>
<td>0.12</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Dec 1993</td>
<td>0</td>
<td>37.4</td>
<td>0</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Dec 1996</td>
<td>6</td>
<td>140.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>Jun 1997</td>
<td>31</td>
<td>9.8</td>
<td>3.16</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>73</td>
<td>484.2</td>
<td>0.15</td>
</tr>
</tbody>
</table>


*a Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin
warfarin dosage. Although the reasons for the interaction are unclear, warfarin is metabolized via both CYP3A4 and CYP2C9 isoenzymes, and this pathophysiology may be implicated.26

The interaction of statins with cyclosporine, and by extrapolation the calcineurin inhibitor tacrolimus (FK506), is particularly important. A separate, head-to-head study of simvastatin and pravastatin36 use in heart transplant patients on cyclosporine therapy further points to the possibility of a statin class effect on drug interactions. Despite no significant differences in lipid levels or liver function in patients taking simvastatin (N = 45) versus those taking pravastatin (N = 42), rhabdomyolysis or myositis occurred only in patients taking simvastatin; in 13% in total. Based on this and other studies,31,36 pravastatin is the only FDA-approved drug for cholesterol treatment in patients who are also taking cyclosporine.

While clinical trial reports have found the incidence of myopathy to be 0.15% with use of lovastatin, the risk increased to 2%, 5%, and 28% in patients who were also taking niacin, niacin plus cyclosporine, or cyclosporine plus gemfibrozil, respectively.32 Myositis has also been reported with the combination of atorvastatin and cyclosporine.37

These findings not only have implications for nephrologists and cardiologists, but also for primary care physicians who are increasingly treating transplant patients who are surviving longer with the benefits of modern medicine. Primary care physicians are frequently required to treat transplant patients over the long term, adjusting their medications while treating other medical problems. Thus, therapeutic goals, clinical potency, and risks of myotoxicity must all be weighed in clinical decision making for these higher-risk patients.

**STATINS AND FIBRATES**

The possibility of increased myotoxicity with the use of statins in combination with fibric acid therapy is an additional important clinical consideration. With ATP III’s lowered cutpoint for triglycerides (from 200 to 150 mg/dL) and the elevation of the normal HDL cholesterol level (from 35 to 40 mg/dL), clinicians are more likely to use statins in combination with fibric acid derivatives and niacin to achieve these goals. Gemfibrozil interactions are well described,38,39 with increases in muscle toxicity of 1% to 5%.31,39-41 In a recent trial,42 the combination of simvastatin and gemfibrozil resulted in simvastatin acid concentrations that were almost 3-fold higher. A similar result was reported with lovastatin and gemfibrozil, but bezafibrate (marketed in Europe) had no effect on lovastatin concentrations, which suggests a difference in effect among fibric acid derivatives.43 This class effect is also suggested by reports that fenofibrate does not affect pravastatin concentrations.44 A reasonable approach in the use of combination therapy might be to lower the statin dose and add a fibrate that is not likely to increase statin plasma levels. The patient should also be observed closely for signs and symptoms of muscle toxicity.

**Recommendations for CK Monitoring**

According to the ACC/AHA clinical advisory22 and other sources,46 CK monitoring is not required in patients taking statins. Because the onset of myopathy is frequently abrupt, unlike hepatotoxicity, monitoring is not deemed beneficial. On the other hand, many experts and the ATP III guidelines recommend that a baseline CK reading be obtained prior to starting statin therapy, since asymptomatic CK elevations are sometimes present. Certainly, if myopathy exists prior to statin treat-
ment, clinicians should carefully consider the type and dose of statin, as well as the age of the patient and the possibility of drug-drug interactions that may increase statin concentrations. Clinicians should repeat CK monitoring when adding an interacting agent or increasing the dose of a statin. Some clinicians monitor CK levels every 6 months initially, and then annually. This is an individual decision that will vary depending on the patient's risk profile and the clinician's overall comfort with the therapy.

Perhaps even more important than CK monitoring is counseling the patient about symptoms of myopathy and when these symptoms warrant contacting the physician. Specifically, any new muscle weakness, aches, or pains experienced by the patient should prompt communication with a physician. Once these complaints are determined by the physician to be of significance, it is recommended that statins be discontinued immediately and CK levels checked.22–24 Statin treatment should be stopped if CK elevations are more than 10 times the upper limit of normal. In this instance it is also recommended that hypothyroidism be excluded as a contributing factor.22–24

CONCLUSION

Statins are generally safe with a favorable benefit-to-risk ratio. Because of the risk of significant drug-drug interactions that can increase the likelihood of serious complications, caution should be used when prescribing new medications to patients taking statins. Transplant patients may be at particular risk of statin interactions with calcineurin inhibitors, cyclosporine, and tacrolimus. There is likely a statin class effect, with pravastatin and fluvastatin potentially having the best safety profiles. Monitoring of CK levels is not recommended; however, physicians should monitor symptoms. It is important to inform patients about which symptoms they should report, even if the symptoms occur long after the statin medication was initiated. Early recognition of muscle toxicity can prevent the progression to the most serious complications of rhabdomyolysis and renal failure.

As long as vigilance is exercised, statins can be used safely and with great benefit to the patient. Toxicity can be minimized by using the lowest dose possible to achieve the desired lipid-lowering effect, while balancing the efficacy and potential toxicity of individual agents.

REFERENCES


