Approach to the Patient Who Is Intolerant of Statin Therapy

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Myopathy occurs in approximately 10% of statin-treated patients and is most commonly manifested by myalgias with or without plasma creatine kinase (CK) elevations. Predisposition exists in patients treated with high doses of potent statins and those who are older, female, have a genetic predisposition, and when statins are coadministered with drugs that compete with or inhibit drug metabolism. In symptomatic patients, CK levels may assist in guiding management. If less than five times the upper limit of normal, the existing statin should be titrated to achieve cholesterol goals and the CK repeated when symptoms appear or worsen. In patients with moderate to severe symptoms and any patient with CK elevated to more than 5-fold the upper limit of normal, the statin should be stopped. Once asymptomatic and CK is reduced (if elevated previously), cholesterol goals can be approached by: 1) a different statin (e.g. fluvastatin or pravastatin), starting with a low dose and titrating up; 2) an alternate daily or weekly more potent statin (e.g. rosuvastatin or atorvastatin); or 3) the combination of the lowest tolerated statin with a cholesterol absorption inhibitor (ezetimibe) and/or bile acid sequestrant. Over-the-counter preparations, e.g. red yeast rice, containing natural statin-like agents, or plant sterols can also lower cholesterol. These, however, have limited efficacy to achieve targeted cholesterol levels for most patients. In patients without CK elevations and symptoms, progress can be followed clinically, but in patients who show CK elevations, CK should be monitored. At present, the superiority of one approach has not been demonstrated, and the need for clinical trials in well-characterized patients with statin intolerance cannot be dismissed. (J Clin Endocrinol Metab 95: 2015–2022, 2010)

The Case

A 49-yr-old woman with known hypertension and coronary heart disease (CHD) for 6 months is referred because of intolerance to statins. Untreated, her fasting cholesterol was 250 mg/dl; triglycerides, 200 mg/dl; high-density lipoprotein (HDL) cholesterol, 45 mg/dl; and low-density lipoprotein (LDL) cholesterol, 165 mg/dl. Two weeks after administration of 40 mg of simvastatin, she experienced moderately severe myalgias in her thighs and upper arms and some muscle weakness. A creatine kinase (CK) was elevated at 420 IU/liter. When symptoms re-
solved, she was prescribed 20 mg of atorvastatin but experienced a similar response within 10 d. Her CK was then 525 IU/liter. At presentation, she had been off atorvastatin for 1 month and was asymptomatic. Current medications were an angiotensin-converting enzyme inhibitor, aspirin, diltiazem, and beta-blocker. Other than a blood pressure of 138/88 mm Hg and bilateral arcus cornealis, her physical examination was normal.

**Background**

In the setting of a Lipid Clinic at an academic medical center, approximately 40% of my referrals are patients in whom statin therapy has been difficult if not “impossible.” Typically, almost all of these patients are referred for the evaluation of myalgias and muscle weakness, but a wide variety of complaints not related to the musculoskeletal system may also be present, e.g., elevation of liver enzymes, gastric upset, diarrhea, constipation, rash, headache, dizziness, mental confusion, forgetfulness, or erectile dysfunction. Because of the prevalence of musculoskeletal complaints that define statin intolerance, this Approach to the Patient will focus on patients who are intolerant because of myalgias and other forms of myopathy.

**Definitions**

Myalgia is generally defined as pain in a muscle or group of muscles. The Food and Drug Administration (FDA) has defined myopathy as a CK elevated at least 10-fold but has not specified a definition for myalgias or myositis. The FDA defines rhabdomyolysis as a greater than 50-fold increase in CK and evidence of organ damage, most often renal compromise. The National Lipid Association (NLA) has similar definitions, except that it qualifies myopathy by requiring the presence of myalgias; and according to the NLA, rhabdomyolysis also includes patients with a CK greater than 10,000 IU/liter (1). The American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute (ACC/AHA/NHLBI) Advisory defined myopathy as any disease of muscles, myalgia as muscle aching or weakness without CK elevation, myositis as muscle symptoms with increases in CK, and rhabdomyolysis as muscle symptoms with a greater than 10-fold increase in CK, with increases in serum creatinine (usually with brown urine and myoglobinuria) (2). Although these definitions from a variety of different organizations are not well substantiated clinically, they are consolidated in Table 1. In statin-treated patients, myalgias typically are reported in the proximal limbs and trunk, with less frequent associated muscular weakness, cramps, and/or stiffness (3–5). In general, patients with isolated and unilateral symptoms have an alternative explanation for their complaint.

**Frequency**

Of utmost urgency in statin-intolerant patients is rhabdomyolysis. This relates to the risk of acute renal failure if therapeutic steps including hydration are delayed. For statins other than cerivastatin, the incidence of rhabdomyolysis, defined using FDA criteria, in two cohort studies was 3.4 (1.6 to 6.5) per 100,000 person-years, an estimate supported by data from 20 randomized controlled trials (6). Typically, not all subjects with rhabdomyolysis show renal impairment clinically, especially if management can be instituted early. Of course, cerivastatin was ultimately removed from the marketplace because of an apparent 15- to 80-fold increased risk of rhabdomyolysis (7). In general, rhabdomyolysis is more common with higher statin doses (6, 8) and when fibrate therapy is coadministered (9).

A meta-analysis from 74,102 patients in 35 randomized clinical trials through December of 2005 compared statin monotherapy vs. placebo, with a follow-up period from 1 to 65 months. When patients treated with cerivastatin were excluded, there was no significant risk of myalgias, CK elevation, rhabdomyolysis, or discontinuation of the statin due to any adverse effect (10). Of note, there was a risk difference for statin-induced increases in transaminases per 1000 patients of 4.2 [95% confidence interval (CI), 1.5–6.9; P < 0.01]. A more historic meta-analysis of 83,858 patients treated with atorvastatin, fluvasatin, lovastatin, pravastatin, simvastatin, and only 114 with cerivastatin also revealed a low incidence of myositis (0.11%) or rhabdomyolysis (0.016%), with no significant increase in statin-treated compared with placebo-treated patients (11). Of note, many of these patients were also included in those trials reported by Kashani et al. (10).

Muscle complaints, however, are much more common in clinical practice than reported in clinical trials; and myalgias occur in 5–10% of statin-treated patients. The
initiated statin therapy and in both the group with diabetes were experienced in a greater percentage of patients who
were confined to bed or unable to work. Fluvastatin XL was associated with the lowest rate of muscular symptoms by 10.5% of patients, with a median time of onset of 1 month after initiation of statin therapy. Importantly, muscular pain prevented even moderate exertion during everyday activities in 38% of these patients, whereas 4% were confined to bed or unable to work. Fluvastatin XL was associated with the lowest rate of muscular symptoms (5.1%), and simvastatin the highest (18.2%).

In another study, 32,225 patients in a community-based practice were identified and classified into two cohorts: diabetes (n = 10,247) and absence of diabetes (n = 21,978) (13). Myalgias, myositis, and rhabdomyolysis were experienced in a greater percentage of patients who initiated statin therapy and in both the group with diabetes (7.9 vs. 5.5%; P < 0.001) and the group without diabetes (9.0 vs. 3.7%; P < 0.001). However, 95% of these events were myalgias or mild myositis (CK one to three times increased). The prevalence of severe myositis (CK four to 10 times increased) was 0.4 per 1000 person-years (95% CI, 0.2–0.7) and 0.8 per 1000 person-years (95% CI, 0.6–1.1) among statin initiators with or without diabetes, respectively. This compared with rates of 0.3 per 1000 person-years (95% CI, 0.1–0.5) and 0.2 per 1000 person-years (95% CI, 0.1–0.4) among non-statin users with or without diabetes, respectively. Finally, postmarketing surveillance data from the FDA Adverse Event Reporting System (AERS) report 0.3–2.2 cases of myopathy and 0.3–13.5 cases of rhabdomyolysis per 1 million statin prescriptions (14). Because these data are reported by volunteers, both underreporting and bias are major limitations.

A question that often arises is why the frequency of myopathy is so much higher in the clinic than in randomized controlled trials? One possibility is that persons with a prior history of muscle-related symptoms are excluded from participation in clinical trials. In addition, the presence of muscle symptoms or increases in CK during the run-in phase of trials may exclude these subjects from retention. Another reason is the presence of underlying conditions and/or drug therapy that would be considered to be exclusion criteria from participating in trials. These might include advanced age, female gender, multisystem disease, hypothyroidism, alcoholism, high quantities of grapefruit juice consumption, excessive physical activity, a history of elevated CK with or without other forms of clinical myopathy, or drugs that interfere or compete with statins for metabolism such as fibrates, cyclosporine, azole antifungals, macrolide antibiotics, calcium channel blockers, HIV protease inhibitors, or amiodarone (15).

### Pathopharmacology

Some of the statin-related toxicity may relate to the pharmacokinetic properties of the specific statin used. Many statin–drug interactions involve the CYP3A4 isoenzyme, a pathway important in the metabolism of approximately 50% of all currently available drugs. For statins that are metabolized by CYP3A4 (Table 2) and rosuvastatin that is an inhibitor of CYP3A4, interactions with CYP3A4 inhibitors such as azole antifungals, cimetidine, clarithromycin, cyclosporine, diltiazem, erythromycin, specific HIV protease inhibitors, and grapefruit juice may be seen more often (16). Genetic differences in drug-metabolizing enzymes may also relate to statin-induced myopathy susceptibility (17). For gemfibrozil, the parent

### Table 2. Clinical pharmacokinetics of HMG-CoA reductase inhibitors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Atorvastatin</th>
<th>Fluvastatin</th>
<th>Lovastatin</th>
<th>Pitavastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Simvastatin</th>
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<tbody>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>2–3</td>
<td>0.4–2.1</td>
<td>2–4</td>
<td>0.6–0.8</td>
<td>0.9–1.6</td>
<td>3</td>
<td>1.3–2.4</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/ml)</td>
<td>27–66</td>
<td>45–66</td>
<td>10–20</td>
<td>35–63</td>
<td>45–55</td>
<td>37</td>
<td>10–34</td>
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<tr>
<td>Bioavailability (%)</td>
<td>12</td>
<td>24</td>
<td>5</td>
<td>80</td>
<td>18</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Lipophilicity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>80–90</td>
<td>&gt;98</td>
<td>&gt;95</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A4</td>
<td>CYP2C9</td>
<td>CYP3A4</td>
<td>Limited</td>
<td>Sulfation</td>
<td>Limited</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Metabolites</td>
<td>Active</td>
<td>Inactive</td>
<td>Active</td>
<td>Active (minor)</td>
<td>Inactive</td>
<td>Active (minor)</td>
<td>Active</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>15</td>
<td>1.2</td>
<td>2.9</td>
<td>10–11</td>
<td>1.3–2.8</td>
<td>19</td>
<td>2–3</td>
</tr>
<tr>
<td>Urinary excretion (%)</td>
<td>2</td>
<td>6</td>
<td>10</td>
<td>NA</td>
<td>20</td>
<td>10</td>
<td>13</td>
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<tr>
<td>Fecal excretion (%)</td>
<td>70</td>
<td>90</td>
<td>83</td>
<td>90</td>
<td>71</td>
<td>90</td>
<td>58</td>
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</tbody>
</table>

Data are based on a 40-mg oral dose. Table is adapted from data in Refs. 55–61. HMG-CoA, 3-Hydroxy-3-methylglutaryl coenzyme A; NA, not available; T<sub>max</sub>, time after administration of a drug when the maximum plasma concentration is reached; C<sub>max</sub>, maximum plasma concentration of a drug; T<sub>1/2</sub>, time taken for the plasma concentration of a drug to be reduced by 50%.
drug and its glucuronide conjugate seem to competitively inhibit CYP2C8 (18), whereas in human hepatocytes, fenofibrate is an inducer of both CYP3A4 and CYP2C8 (19). These differences in fibrate metabolism may explain in part the apparent relative safety of fenofibrate or fenofibric acid vs. gemfibrozil in patients treated with specific statins (20).

A number of additional mechanisms have been suggested to explain the risk for statin-induced myopathy. Patients with known or undiscovered asymptomatic neuromuscular disorders have been described. Genetic disorders such as myophosphorylase deficiency, mitochondrial myopathy, acid maltase deficiency, McArdle’s disease, myotonic dystrophy, MELAS syndrome, polymyositis, or susceptibility to malignant hyperthermia have all been described to coexist in patients with statin-induced myopathy (21–23). Moreover, in 133 statin-intolerant patients vs. 158 statin-tolerant patients, two single nucleotide polymorphisms (SNPs) in coenzyme Q2 genotypes were associated with an approximate 2.5 times higher relative risk of statin-induced myopathy (24). Genetic polymorphisms in CYP2D2, 3A4, or SLCO1B1 that encode the organic anion-transporting polypeptide OATP1B1 have also been found to be associated with statin-intolerant patients. OATP1B1 contributes to statin uptake by the liver and was identified by genome-wide scanning in the SEARCH Collaborative Group to be associated with a 4.5-fold increased risk of myopathy in heterozygotes and 17-fold higher risk in homozygotes when coadministered with simvastatin (25, 26). In a small study of patients with atorvastatin-induced myopathy, however, differences in pharmacokinetics of atorvastatin were found in the absence of any difference in the frequency of SLCO1B1, MDR1, and CYP3A5 polymorphisms in healthy volunteers (27). In the SEARCH Study the SLCO1B1*5 genotype demonstrated a gene dosage effect ranging from 19% in those without the SNP, to 27% with one SNP, and to 50% when two SNPs were present (28). Female sex was also associated with statin-induced myopathy, and again the effect was more commonly observed in simvastatin-treated patients.

To determine the histopathology of the statin-induced injury, skeletal muscle biopsies were performed in 10 patients with statin-induced myopathy (29). The patients ranged in age between 50 and 76 yr, and five were treated with simvastatin, four with atorvastatin, and one with cerivastatin. In eight patients, there had been a recent statin dose escalation before symptoms ensued, and six were on other drugs that were metabolized by or inhibited the cytochrome 3A4 pathway of drug metabolism. All 10 patients had weakness, eight myalgias, and three myoglobinuria, and CK levels peaked to levels from 1100–160,000 IU/liter. All biopsies demonstrated necrotizing myopathy, with minimal inflammation in four. In all patients, signs and symptoms of myopathy normalized within a few months after statin withdrawal.

Several hypotheses for how statins damage muscle have been summarized recently (23, 30). Leading mechanisms include: 1) decreased sarcolemmal cholesterol; 2) mitochondrial dysfunction secondary to decreases in coenzyme Q; and 3) depletion of isoprenoids, cholesterol synthetic by-products that normally reduce rates of apoptosis. Additionally proposed toxic pathways are enhanced lipoprotein lipase-dependent triglyceride-rich lipoprotein particle uptake with cholesterol or phytosterol accumulation (31), and relative vitamin E deficiency (32).

It is important to note that when muscular symptoms are not severe, muscle biopsies examined by light microscopy only are often normal (33). Yet in 25 of 44 patients who were either taking statins and had symptoms or in whom statins had recently been discontinued because of symptoms, muscle injury on biopsy was seen, and also in one patient with no myopathy (34). Lipid stasis was seen in 30% of biopsies in another study (35). However, even in myotubes from statin-treated patients without symptoms, increases in fatty acid oxidation have been demonstrated (36). This finding seems somewhat contradicted by data that have demonstrated increases (not decreases) in respiratory quotient associated with statin intolerance (37, 38). In rats, simvastatin in vivo blunted Akt/FOXO signaling and activation of genes controlling atrophy and fuel use (39). Mitochondrial toxicity, disruption of calcium homeostasis, altered membrane fluidity, and ATPases have been reported in 11 patients with increased CK and myalgias on statins (40). In vitro contracture tests, demonstrating the same type of impaired calcium homeostasis as seen in malignant hyperthermia, were abnormal in seven of nine patients, and pH recovery after exercise was delayed (41). In this study, mitochondrial function was normal, whereas some studies have shown impaired mitochondrial activity even when CK is normal.

**Diagnostic and Therapeutic Strategies**

**Diagnosis**

As for every other endocrine/metabolic patient, the diagnostic approach begins with a good history and physical examination. Typical symptoms are myalgias (90%), muscle weakness (30%), and less frequently muscle cramps (42). Important information to gather relates to the timing, location, severity, and duration of symptoms. The inciting drug(s) with dose and the duration of therapy before the onset of symptoms should also be noted. Patients should be asked whether exercise is limited because
of symptoms and whether symptoms are precipitated by exertion. Because many patients may have been previously treated with several different statins, a careful history of which statins have been used and their dosage and duration of therapy before symptoms is necessary information. A careful review of all previous laboratory data including plasma CK, creatinine, transaminases, TSH, and inflammatory markers if present is important. A complete exam should consider related conditions such as hypothyroidism, rheumatological disorders, neuromuscular diseases, and depression. A recent study also noted that over 90% of vitamin D-deficient patients with myalgias on statins had resolution of their symptoms after 50,000 U/wk of vitamin D for 12 wk (43). Thus, measurements of CK, TSH, and vitamin D should be carried out if not recently done. The level of CK should be used to define the type of myopathy (Table 1).

**Therapy**

In all patients, the severity of symptoms should influence clinical decision making at the time of presentation (Fig. 1). Under routine clinical settings, a baseline CK is not necessary but is an option if the patient is at higher risk for statin-induced myopathy (1). And, in asymptomatic patients, the measurement of CK is not cost effective (44). However, if the patient is asymptomatic and a previously measured CK is elevated, a statin can be initiated or continued to assist in reaching LDL cholesterol and non-HDL cholesterol goals (45). When myalgias and other symptoms are moderate to severe, the statin should be stopped whether or not the CK is elevated. If the CK is more than 10 times normal and/or signs of renal impairment exist, hydration should be implemented promptly in an attempt to ensure preservation of baseline renal function, and CK should be repeated until normal or levels are stabilized. Because the mechanism of statin action variably results in lower levels of ubiquinone, the addition of 100–200 mg of coenzyme Q10 daily is generally regarded as safe, but evidence of benefit is still lacking (46). In minimally symptomatic patients wherein the CK is less than five times normal, the current statin could be continued or the dose titrated to achieve the cholesterol goals. If symptoms increase, the statin should either be stopped or the dose reduced, and CK should be remeasured.

In patients in whom the statin is discontinued or the dose is reduced to levels where LDL and non-HDL cholesterol levels are not achieved, I have listed five options that I have employed in my Lipid Clinic, four of which are documented in the literature. One choice is to avoid a statin altogether. Ezetimibe or a bile acid sequestrant (BAS), *i.e.* coleselam, cholestyramine, or colestipol, can be used instead. Expected LDL cholesterol lowering is 15–20% for ezetimibe and coleselam and up to 30% at maximum doses of cholestyramine or colestipol (47). Of course, higher doses of cholestyramine and colestipol are difficult to achieve because of side effects. BASs, however, can raise plasma triglycerides and should be used cautiously or not at all in patients with hypertriglyceridemia.

Another option is to use a low-dose, less potent statin such as 80 mg of fluvastatin XL nightly (48). A fourth and increasingly well-documented approach is to use a more potent statin such as rosvastatin at a low dose daily (49), every other day (50), or weekly (51). A final option is red yeast rice at doses ranging from 600–1800 mg twice a day (bid) (53, 54); however, at this time this approach cannot be recommended.

![FIG. 1. In asymptomatic patients, a CK should be measured only in patients at high risk of developing myopathy. If a value has already been obtained and is less than five times normal, the existing statin dose should be adjusted to achieve the LDL and non-HDL cholesterol goals. If symptoms ensue or worsen, a CK should be measured, and the statin stopped or the dosage reduced. In patients with more severe statin intolerance in whom the statin is discontinued or reduced in dose and levels of LDL and non-HDL cholesterol levels are not achieved, five options for an altered approach are presented. Ezetimibe or a BAS, *i.e.* coleselam, cholestyramine, or colestipol, can be used instead. BASs, however, can raise plasma triglycerides and should be used cautiously or not at all in patients with hypertriglyceridemia. Another option is to use a low-dose, low-potency statin nightly or every other night and gradually increase the dose if symptoms are absent or minimal. A third choice is to use a high-dose, less-potent statin such as 80 mg of fluvastatin XL nightly (48). A fourth and increasingly well-documented approach is to use a more potent statin such as rosvastatin at a low dose daily (49), every other day (50), or weekly (51). A final option is red yeast rice at doses ranging from 600–1800 mg twice a day (bid) (53, 54); however, at this time this approach cannot be recommended.](image-url)
more than three times normal or discontinued therapy because of adverse effects (49). In 51 statin-intolerant patients, 31 were able to tolerate every other day doses of rosuvastatin (average dose, 5.6 mg) with a 35% lowering of LDL cholesterol (50). However, only four of these patients had a previous history of elevated CK levels, and in none did CK rise on rosuvastatin. When given once weekly, 5–20 mg of rosuvastatin reduced LDL cholesterol by 29% in eight of 10 tolerant patients, whereas two experienced side effects and discontinued therapy (51). A final option is red yeast rice, an over-the-counter Chinese herb used for centuries for a variety of medicinal purposes. Red yeast rice contains naturally occurring lovastatin (monacolin K) and other monacolins that may also inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase and lower LDL cholesterol (52). In 79 hypercholesterolemic patients without a history of statin intolerance who were randomly assigned to a twice-daily 600 mg dose of red yeast rice or a placebo for 8 wk, LDL cholesterol decreased by 25% in the red yeast rice group (53). This amount (1200 mg) of red yeast rice is approximately 2 mg of lovastatin. In another study, 62 statin-intolerant patients were provided an aggressive lifestyle modification and randomized to receive 1800 mg twice a day of red yeast rice vs. placebo. A 22% differential decrease in LDL cholesterol was seen at 12 wk and 12% at 24 wk (54). Although there was no difference in the incidence of side effects between the red yeast rice and placebo groups, two of the 29 patients on red yeast rice discontinued treatment because of intolerable myalgias, despite normal levels of CK. Because the LDL cholesterol-reducing effect of 1200 mg was approximately the same as that from 3600 mg, uncertainties exist about the variation between lots of red yeast rice, and the FDA continues to be concerned about such differences. Another issue is the possibility that some red yeast rice products may contain toxic components (55) (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108962.htm). Overall, despite the data, red yeast rice cannot be recommended as an alternative to FDA-approved and -regulated statins at this time.

**Controversies/Areas of Uncertainty**

Figure 1 speaks for itself in declaring the existing controversy in how to approach patients with muscle-related statin intolerance. In terms of baseline levels of CK, how should high risk for statin-induced myopathy be identified? Yes, retrospective analysis of clinical trials and post-marketing surveillance data provide examples of relative risk, e.g. advanced age, being female, and specific drugs or drug classes, but this has yet to be well characterized, and clear recommendations related to therapeutic approaches have not been provided. How soon will we be ready to use pharmacogenomics to identify genetic risk for adverse effects when statins are prescribed, i.e. the propensity for neuromuscular disorders or altered drug metabolism? When myopathy ensues, what is the best next step for optimal lipid management once symptoms have receded, and why do statin-intolerant patients seem to respond to red yeast rice better than expected for the amount of statin in the supplement, and why is red yeast rice better tolerated when equivalent exposures to statins have previously resulted in myopathy?

**Returning to the Patient**

At this time, the CK should be repeated. This will help to discern whether or not the CK elevation while she was symptomatic could be attributable to statin intolerance. Although she appeared euthyroid on exam, a TSH should be checked to eliminate hypothyroidism as a cause of both the elevated LDL cholesterol and CK. Now what next? The CK was repeated and normal at 180 IU/liter. Based on National Cholesterol Education Program:Adult Treatment Panel III guidelines (45), her LDL cholesterol level should be less than 100 mg/dl with an option for less than 70 mg/dl. Although a combination of ezetimibe and colesevelam could lower LDL cholesterol by up to 40%, the benefit of ezetimibe in reducing CHD risk has not been demonstrated, and colesevelam is not cholestyramine, the BAS previously demonstrated to reduce CHD risk in the Coronary Primary Prevention Trial. If one of these two drugs is used, it might be implemented after another attempt at statin therapy. Here, we have four choices: 1) a low-dose, low-end statin, fluvastatin or pravastatin, given nightly or every other night; 2) a high dose of a less potent statin; 3) rosuvastatin 5 mg daily, every other day or once weekly; and 4) red yeast rice. In the absence of head-to-head trials and with the limited number of studies in dissimilar patients, the optimal choice is not clear. In general, I prefer fluvastatin or pravastatin at 20 mg every other night as the first step. A CK should be obtained at the same time as her next set of fasting lipids (and transaminases) in 4–6 wk, and earlier if symptoms of myopathy occur. I recommend that escalation in statin dose should occur no more often than every 2–4 wk as tolerated with continued surveillance of CK. Because maximum doses of fluvastatin or pravastatin will maximally reduce the LDL cholesterol by 30%, a second drug or alternative more potent statin will be necessary to achieve a LDL cholesterol level of less
than 100 mg/dl. At this point, genetic testing is premature; however, if statin dose escalation is unsuccessful because of symptoms and CK elevation, diltiazem should be discontinued and another antihypertensive prescribed.

**Conclusions**

Myopathy occurs in up to 10% of statin-treated patients and is most commonly manifested by myalgias with or without CK elevations. Predisposition exists in particular in the setting of high-dose potent statins, genetic predisposition, and when coadministered with drugs that compete with or inhibit the CYP3A4 pathway of drug metabolism. In patients with mild symptoms, the level of CK may assist in directing further statin therapy. In patients with moderate to severe symptoms, the statin should be stopped. Once asymptomatic, the LDL cholesterol goal can be accomplished by the use of nonstatin LDL-lowering drugs, gradually increasing doses of fluvastatin or pravastatin; high-dose fluvastatin; low-dose rosuvastatin given daily, every other day, or once weekly; or a combination of nonstatin LDL cholesterol-lowering drugs plus the highest tolerated dose of a statin. The use of red yeast rice is not encouraged at the present time.

**Acknowledgments**

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26. Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, Collins R 2002 Myopathy occurs in up to 10% of statin-treated patients and is most commonly manifested by myalgias with or without CK elevations. Predisposition exists in particular in the setting of high-dose potent statins, genetic predisposition, and when coadministered with drugs that compete with or inhibit the CYP3A4 pathway of drug metabolism. In patients with mild symptoms, the level of CK may assist in directing further statin therapy. In patients with moderate to severe symptoms, the statin should be stopped. Once asymptomatic, the LDL cholesterol goal can be accomplished by the use of nonstatin LDL-lowering drugs, gradually increasing doses of fluvastatin or pravastatin; high-dose fluvastatin; low-dose rosuvastatin given daily, every other day, or once weekly; or a combination of nonstatin LDL cholesterol-lowering drugs plus the highest tolerated dose of a statin. The use of red yeast rice is not encouraged at the present time.

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