Narrative Review: Statin-Related Myopathy

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Statin-related myopathy is a clinically important cause of statin intolerance and discontinuation. The spectrum of statin-related myopathy ranges from common but clinically benign myalgia to rare but life-threatening rhabdomyolysis. Observational studies suggest that myalgia can occur in up to 10% of persons prescribed statins, whereas rhabdomyolysis continues to be rare. The mechanisms of statin-related myopathy are unclear. Options for managing statin myopathy include statin switching, particularly to fluvastatin or low-dose rosuvastatin; nondaily dosing regimens; nonstatin alternatives, such as ezetimibe and bile acid–binding resins; and coenzyme Q10 supplementation. Few of these strategies have high-quality evidence supporting them. Because statin-related myopathy will probably become more common with greater numbers of persons starting high-dose statin therapy and the increasing stringency of low-density lipoprotein cholesterol level targets, research to better identify patients at risk for statin myopathy and to evaluate management strategies for statin-related myopathy is warranted.

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The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, have revolutionized the management of cardiovascular disease. In properly selected patients, statins decrease cardiovascular disease morbidity and mortality by about 25%. Thus, tens of millions of patients worldwide now receive statins for hypercholesterolemia, with more than 13 million patients in the United States alone (1). However, more than 40% of patients eligible for statin use are not currently receiving statins (1). Although 1 barrier to statin use has been affordability (1), another has been intolerance from myopathy.

The spectrum of statin-related myopathy ranges from common but clinically benign myalgia to rare but life-threatening rhabdomyolysis. Statin-related myopathy may be more prevalent in daily clinical practice than in controlled, clinical trials, however, because patients who are prone to this complication are often excluded from such trials. We reviewed the pathophysiology, epidemiology, clinical features, and management of statin-related myopathy because even a small percentage of tens of millions of patients is a large number, and statin myopathy can adversely affect both quality of life and adherence to this potentially life-saving treatment.

Methods

We identified data by searching MEDLINE from inception to October 2008 and from references cited in relevant articles. Search terms included *myalgia* or *myopathy* or *rhabdomyolysis*, *statin*, *rosuvastatin*, *fluvastatin*, *ezetimibe*, *pravastatin*, *simvastatin*, *cerivastatin*, *lovastatin*, *atorvastatin*, *coenzyme Q10*, and *pathophysiology*. Limits specified English-language papers with tag terms *title/abstract.* Emphasis was placed on methodologically sound articles, particularly reports of randomized, controlled trials (RCTs) and human translational pathology and physiology studies.

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Definition

No consensus on the definition of statin myopathy exists. The American College of Cardiology (ACC), American Heart Association (AHA), National Heart, Lung and Blood Institute (NHLBI), U.S. Food and Drug Administration (FDA), and National Lipid Association (NLA) have each proposed definitions for statin-associated muscle effects (**Table 1**) (2–4).

Pathophysiology

The precise mechanisms underlying statin myopathy are incompletely understood. Proposed mechanisms for statin-related myopathy include decreased cholesterol content of skeletal myocyte membranes inducing instability, depletion of isoprenoids (farnesyl pyrophosphate and geranyl pyrophosphate) or coenzyme Q10 (**Figure**), and mitochondrial dysfunction.

Decreased cholesterol synthesis with membrane destabilization is unlikely to be an important mechanism because in experimental models, nonstatin lipid-lowering agents, most importantly fibrates, induce myopathy through distinct nonoverlapping pathways (5–7). Furthermore, decreasing cholesterol synthesis by inhibiting squalene synthase does not result in myopathy (8).

Coenzyme Q10 depletion might contribute to statin myopathy because in mitochondria, coenzyme Q10 participates in the electron transport chain, prevents oxidative stress, and regenerates active antioxidant vitamins C and E (9). However, changes in both plasma and intramuscular coenzyme Q10 levels with statin therapy are inconsistent (10–17). Coenzyme Q10 is primarily transported on low-density lipoprotein (LDL) particles (18), and adjustment

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for reduced LDL cholesterol inconsistently accounts for reduced plasma coenzyme Q10 (15, 17, 19, 20). Intramuscular coenzyme Q10 correlates imperfectly with pathologic changes (10, 15, 21). Also, isoprenoid depletion might play a role in statin myopathy because pathology is reversed by mevalonate or geranylgeraniol (7), myopathy is absent with squalene synthase inhibition (8), and reduction of isoprenoids leads to apoptosis in vitro (22–24).

Muscle biopsies show myopathic changes in only some patients who received statins and are not consistently related to symptoms or creatine kinase elevations (25, 26). Electromyographic findings were also inconsistently associated with biopsy findings (26). Even asymptomatic patients who received statins have ultrastructural myocellular changes (27). Further investigations are needed to define the pathogenesis of statin myopathy.

Key Summary Points

Statin-related myopathy comprises myalgias, myositis, and rhabdomyolysis. Myalgias can affect up to 10% of persons prescribed statins, whereas rhabdomyolysis is rare.

The mechanisms responsible for statin-related myopathy are unclear but may include decreased levels of coenzyme Q10, decreased bioavailability of isoprenoids, or mitochondrial dysfunction.

Risk factors for myopathy include history of myopathy while receiving another lipid-lowering agent, family history of statin-related myopathy, high-dose statin therapy, increased age, female sex, and use of medications metabolized through cytochrome P450 3A4.

Assessment of statin-related myopathy includes a search for other causes of creatine kinase elevation and myopathy.

Management of statin-related myopathy can include switching agents or use of fluvastatin, low-dose rosuvastatin, nondaily dosing, and ezetimibe or bile acid–binding resins.

EPIDEMIOLOGY

In RCTs, statin myopathy incidence is about 1.5% to 5.0% (28, 29). However, it is difficult to directly compare the incidence of statin myopathy in clinical trials with real-world clinical practice given the inconsistent definitions (**Table 1**). A meta-analysis of 21 double-blind RCTs (n = 48 138) revealed a nonsignificant difference in myalgia incidence among participants who received statins or placebo (relative risk, 0.99 [95% CI, 0.96 to 1.03]) (30). However, participants who received atorvastatin (5.1%) had more cases of myalgia than those who received placebo (1.6%) (relative difference per 1000 patients, 31.9 [CI, 2.1 to 61.6]; P = 0.04). An analysis of 30 RCTs (n = 83 858) revealed 49 versus 44 cases of myositis and 7 versus 5 cases of rhabdomyolysis among patients who received statins versus placebo, respectively (31). Thus, in clinical trials, the incidence of statin myopathy is low. However, this might be related to the systematic exclusion of persons who have a history of statin-related intolerance or develop biochemical abnormalities during the unblinded, run-in phase before randomization. Some trials defined muscle-related effects by elevated plasma creatine kinase levels only. In addition, persons who have had previous statin intolerance would probably not enroll in clinical trials, whereas motivated enrolled patients might minimize reporting of mild statin-related myalgias.

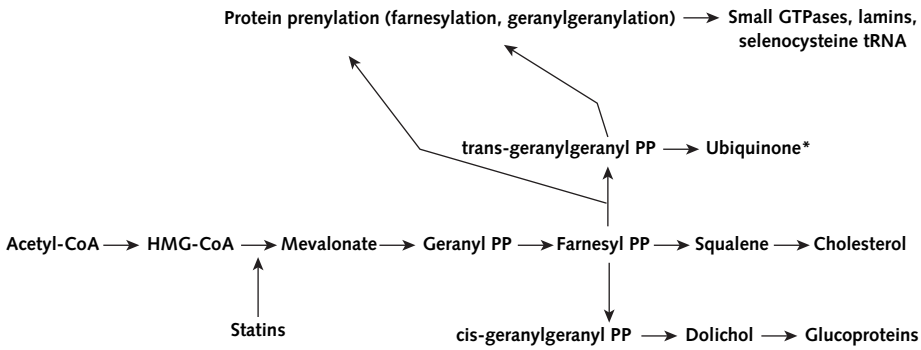
Postmarketing surveillance through the FDA Adverse Event Reporting System (AERS) has documented low reporting rates of statin-related myopathy, myositis, and rhabdomyolysis. From 1998 to 2000, reporting rates for all statins except cerivastatin were 0.38, 0.43, and 1.07 cases per 1 million prescriptions, respectively. From 2002 to 2004, these rates increased to 0.74, 0.57, and 3.56 cases per 1 million prescriptions, respectively, probably because of heightened awareness after the withdrawal of cerivastatin in 2001 (32). From 2002 to 2004, the FDA AERS rates

Table 1. **Proposed Definitions for Statin-Related Myopathy**

Clinical Entity	ACC/AHA/NHLBI (2)	NLA (4)	FDA (3)
Myopathy	General term referring to any disease of muscles	Symptoms of myalgia (muscle pain or soreness), weakness, or cramps, plus creatine kinase >10 × ULN	Creatine kinase ≥10 × ULN
Myalgia	Muscle ache or weakness without creatine kinase elevation	NA	NA
Myositis	Muscle symptoms with creatine kinase elevation	NA	NA
Rhabdomyolysis	Muscle symptoms with significant creatine kinase elevation (typically >10 × ULN), and creatinine elevation (usually with brown urine and urinary myoglobin)	Creatine kinase >10 000 IU/L or creatine kinase >10 × ULN plus an elevation in serum creatinine or medical intervention with intravenous hydration	Creatine kinase >50 × ULN and evidence of organ damage, such as renal compromise

ACC/AHA/NHLBI = American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute; FDA = U.S. Food and Drug Administration; NA = not available; NLA = National Lipid Association; ULN = upper limit of normal.

Figure. **Synthesis of isoprenoids through the cholesterol biosynthetic pathway.**



Acetyl-CoA = acetyl coenzyme A; GTP = guanine transfer protein; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; PP = pyrophosphate; tRNA = transfer ribonucleic acid.
* Ubiquinone can then enter the electron transport chain.

for myopathy were lowest for fluvastatin (0.43 cases per 1 million prescriptions) and highest for rosuvastatin (2.23 cases); for myositis, rates were lowest for atorvastatin (0.27 cases) and highest for rosuvastatin (2.37 cases); and for rhabdomyolysis, rates were lowest for pravastatin (1.63 cases) and highest for rosuvastatin (13.54 cases) (32). The high AERS rates for rosuvastatin, which is the only statin launched after cerivastatin's withdrawal, were attributed to a biased "new drug" reporting effect and to widespread lay media coverage in 2004 (32). Of importance, the proportionate AERS rate for rosuvastatin was about the same as, or was lower than, that for all statins (32). Limitations of FDA-derived data on statin myopathy include reliance on voluntary reporting and diagnostic criteria for myopathy or rhabdomyolysis, which required much higher creatine kinase elevations than the ACC/AHA/NHLBI clinical advisory (**Table 1**) and perhaps caused underestimation of myopathy incidence.

Several observational studies have documented a 5% to 10% incidence of statin-associated myalgia (33, 34). One observational study of 32 225 patients reported that 5.8% and 6.7% of diabetic and nondiabetic patients, respectively, had statin-related myalgia (34). The development of statin myopathy seems to be related to dose. The large, observational PRIMO (Prediction of Muscular Risk in Observational Conditions) study (33) of 7924 French patients exposed to high-dose statins found that 10.5% had muscle-related symptoms over 12 months. A meta-analysis of 4 RCTs (n = 27 545) comparing intensive and low- to moderate-dose statin therapy showed that intensive therapy was associated with a higher risk for creatine kinase levels greater than 10 times the upper limit of normal with or without myalgia (odds ratio [OR], 9.97 [CI, 1.28 to 77.9]; P = 0.028) (35). In contrast, a recent meta-analysis of 7 RCTs (n = 29 395) comparing intensive- versus low- to moderate-dose statin therapy showed no increase in risk for myopathy with intensive therapy (OR, 1.91 [CI, 0.11 to 32.1]) (36), although myopathic events were inconsistently reported in the constituent trials—an issue that has historically plagued documentation of statin myopathy.

Although no trials have directly compared the incidence of statin myopathy by agent, differences across members of the statin class have been suggested. In the PRIMO study (33), the proportion of patients with muscle-related symptoms differed when patients took fluvastatin (5.1%), pravastatin (10.9%), atorvastatin (14.9%), and simvastatin (18.2%). The 2001 AERS rates of fatal rhabdomyolysis varied by agent (1 reported case per 5.2 million prescriptions for lovastatin, 23.4 million prescriptions for atorvastatin, 27.1 million prescriptions for pravastatin, and 8.3 million for simvastatin). These low rates starkly contrast with the rate of 1 reported case of fatal rhabdomyolysis per about 316 000 prescriptions for cerivastatin. No case of fatal rhabdomyolysis has been reported yet with fluvastatin (37). Thus, although rates of myalgia are higher in clinical practice than in clinical trials and the AERS, the rates of rhabdomyolysis are still reassuringly low (about 0.1 to 0.2 case per 1000 person-years) and are similar to those reported in clinical trials (38).

Clinical Features and Risk Factors

Among the PRIMO study participants who developed myopathy, major sites of pain were the thighs, calves, or both, although about 25% of affected patients had generalized myalgia (33). Myalgia was described as heaviness, stiffness, or cramping sometimes associated with weakness during exertion (33). Often, the pain was intermittent and of variable duration. Twenty-five percent of affected patients reported tendon-associated pain, mostly involving several tendons. Twenty percent of affected patients had similar symptoms before statin therapy. Although 4% of affected patients had symptoms sufficiently severe to warrant confinement to bed or cessation of employment, 38% had symptoms

that prevented moderate exertion during daily activity, demonstrating a potential wider effect of statin-related myopathy on quality of life (33).

The temporal relation between statin therapy and the onset or resolution of myopathy is not fully defined. A retrospective study of 45 patients with statin myopathy at a tertiary center revealed a mean therapy duration of 6.3 months before symptom onset and a mean duration of 2.3 months for symptom resolution after discontinuation of statin therapy (39). Meanwhile, patients in PRIMO developed muscle symptoms after a median of 1 month after initiation of statin therapy, ranging up to 12 months after initiation (33). A commonly reported symptom trigger was unusually heavy physical exertion (33). Predictors for developing myopathy included a history of muscle pain during previous lipid-lowering treatment (OR, 10.12 [CI, 8.23 to 12.45]; $P < 0.001$), unexplained muscle cramps (OR, 4.14 [CI, 3.46 to 4.95]; $P < 0.001$), previous creatine kinase elevation (OR, 2.04 [CI, 1.55 to 2.68]; $P < 0.001$), family history of muscle symptoms (OR, 1.93 [CI, 1.10 to 3.34]; $P = 0.022$), family history of muscle symptoms while receiving lipid-lowering therapy (OR, 1.89 [CI, 1.12 to 3.17]; $P = 0.017$), or hypothyroidism (OR, 1.71 [CI, 1.10 to 2.65]; $P = 0.017$). Of interest, statin treatment of more than 3 months (OR, 0.28 [CI, 0.21 to 0.37]; $P < 0.001$) and antidepressant use (OR, 0.51 [CI, 0.35 to 0.74]; $P = 0.0004$) were associated with reduced myopathy risk (33).

The ACC/AHA/NHLBI clinical advisory proposes that statin-related myopathy risk is higher among patients with complex medical conditions or patients who take several medications, in addition to those with other potential risk factors (**Table 2**) (2). For example, thin elderly women may represent a demographic category with increased risk for creatine kinase elevations greater than 10 times the upper limit of normal with statin therapy because 5% to 7% of women who received cerivastatin, 0.4 to 0.8 mg/d, had these creatine kinase elevations (40). Also, only 6 of 22 professional athletes with familial hypercholesterolemia who received statins could tolerate 1 of several statins attempted, indicating that intense physical activity might be a risk factor (41). During hospitalization for major surgery, the ACC/AHA/NHLBI advise short-term cessation of statin therapy to minimize myopathy risk during the perioperative period (2).

Two additional, well-documented, treatment-related risk factors for myopathy are statin dosage and drug–drug interactions. On the basis of clinical trial databases, myopathy incidence increased with increasing simvastatin dose and was 0.02% at 20 mg/d, 0.08% at 40 mg/d, and 0.53% at 80 mg/d (42). Furthermore, a meta-analysis of 4 RCTs of intensive- versus low-dose statin therapy revealed a markedly increased risk (OR, 9.97 [CI, 1.28 to 77.92]; $P = 0.028$) for creatine kinase elevations greater than 10 times the upper limit of normal with intensive therapy (35).

Table 2. **Risk Factors for Statin-Related Myopathy**

Patient-related
Advanced age
Female sex
Small body frame and frailty
Multisystem disease (particularly involvement of liver, kidney, or both)
Hypothyroidism
Alcoholism
Grapefruit juice consumption (>1 qt/d)
Major surgery or perioperative period
Excessive physical activity
History of myopathy while receiving another lipid-lowering therapy
History of creatine kinase elevation
Unexplained cramps
Family history of myopathy
Family history of myopathy while receiving lipid-lowering therapy
Treatment-related
High-dose statin therapy
Interactions with concomitant drugs
Fibrates
Cyclosporine
Antifungals
Macrolide antibiotics
HIV protease inhibitors
Nefazodone
Amiodarone
Verapamil

Because simvastatin, lovastatin, and atorvastatin are primarily metabolized through the cytochrome P450 3A4 (CYP3A4) isoenzyme (43), inhibitors of CYP3A4 could theoretically increase serum statin levels and exposure to susceptible tissues. Drugs known to interact with statins include protease inhibitors, cyclosporine, amiodarone, and fibrates (44, 45). Protease inhibitors are potent CYP3A4 inhibitors and thus can increase up to 30 times the plasma concentrations of certain statins (45, 46). Consequently, both simvastatin and lovastatin should be avoided in patients receiving protease inhibitors (42, 45, 47). Cyclosporine is a potent inhibitor of not only CYP3A4 but also several membrane transporters, and it increases the pharmacokinetic area under the curve of statins by 2- to 25-fold, with many reported cases of rhabdomyolysis (44). Statin dosages in patients receiving cyclosporine have therefore been limited to 5 mg/d for rosuvastatin, 10 mg/d for simvastatin and atorvastatin, and 20 mg/d for lovastatin (42, 47–49).

Some patients with mixed dyslipidemias require the addition of a fibrate to statin therapy. However, gemfibrozil administration is associated with about a 2-fold increase in plasma levels of several statins (50–52). The AERS rate of rhabdomyolysis for the fenofibrate plus statin (other than cerivastatin) combination was about 15 times lower than that for gemfibrozil plus statin (0.58 vs. 8.6 cases per 1 million prescriptions) (53). Thus, fenofibrate can be cautiously coadministered with statins.

Amiodarone dramatically increased plasma levels of simvastatin but not pravastatin (54) and was associated with an RR of about 10 for myopathy when combined

with simvastatin, 80 mg/d (55). Consequently, dosages of simvastatin and lovastatin should not exceed 20 mg/d and 40 mg/d, respectively, in patients receiving amiodarone (47, 56).

Of importance, pravastatin is not metabolized by the P450 system and instead undergoes renal metabolism (43), although fluvastatin and rosuvastatin are primarily metabolized by CYP2C9 (43). These 3 statins may have a lower myopathy risk, especially in the context of polypharmacy.

Genetic Contributions to Statin Myopathy

Common DNA polymorphisms in genes encoding cytochrome P450 enzymes, intestinal P-glycoproteins, and organic anion-transporting polypeptide are inconsistently associated with statin myopathy (55, 57–61). DNA polymorphisms of genes involved in metabolism of coenzyme Q10 and serotonin pain receptors were also inconsistently associated with statin myopathy (62, 63). Recently, a common DNA polymorphism in the *SLCO1B1* gene encoding organic anion-transporting polypeptide was strongly associated with simvastatin-associated myopathy (55), but this association was not seen in patients with atorvastatin-associated myopathy (59). Finally, among 110 patients with statin myopathy, about 10% had heterozygous mutations in 1 of several genes that normally cause rare myopathy syndromes (64), suggesting that genetic susceptibility to statin myopathy may comprise a complex mixture of rare DNA variants and common DNA polymorphisms.

Management

The ACC/AHA/NHLBI and NLA have issued guidelines for managing statin-related myopathy, but they developed their guidelines using different processes. The 2002 clinical advisory statement by the ACC/AHA/NHLBI summarized information on statin use and safety compiled by the FDA, clinical trials, and the Adult Treatment Panel III of the National Cholesterol Education Program. In contrast, the 2006 NLA recommendations were based on review and independent research of New Drug Application information; AERS data; cohort and clinical trial results; analysis of administrative claims databases; and assessment of 4 expert panels focused on statin safety with regard to liver, muscle, renal, and neurologic systems (2, 4). These 2 guidelines share similarities but diverge in many respects. For instance, the NLA recommendations do not advise measuring creatine kinase levels at baseline in all patients but rather only in those at high risk for myopathy, such as elderly patients, patients receiving concomitant medications, or patients with renal or hepatic dysfunction (4). Meanwhile, the ACC/AHA/NHLBI advise measuring creatine kinase levels at baseline for all patients before initiation of statin therapy because asymptomatic creatine kinase elevations are common and could affect later clinical decisions (2).

If a patient develops myopathy symptoms while receiving therapy, ACC/AHA/NHLBI and NLA recommend determining serum creatine kinase levels and comparing them with baseline creatine kinase levels, if available, in addition to searching for other causes (**Table 3** [65–67]), regardless of creatine kinase elevation. The ACC/AHA/NHLBI also advise measuring serum thyroid-stimulating hormone levels because hypothyroidism can present with myopathy or creatine kinase elevations (2).

For a symptomatic increase in serum creatine kinase levels greater than 10 times the upper limit of normal or greater than 10 000 IU/L, the ACC/AHA/NHLBI advise immediate suspension of statin therapy (2). In contrast, the NLA recommends that statin therapy be discontinued in patients who develop intolerable muscle symptoms, regardless of creatine kinase elevations or in patients with rhabdomyolysis, as defined by the FDA (4). More commonly, patients with muscle symptoms have creatine kinase levels 3 to 10 times the upper limit of normal. In such instances, if symptoms are tolerable, the NLA recommends no change in therapy, even when creatine kinase levels are normal, with symptoms as the barometer for deciding whether to continue or stop therapy (4). In contrast, the ACC/AHA/NHLBI advise weekly monitoring of both creatine kinase levels and symptoms, either until symptoms or serum creatine kinase levels significantly worsen or until there is no longer a medical concern (2). If serial creatine kinase measurements increase progressively or symptoms worsen, statin therapy may be temporarily suspended or the dose decreased with monitoring for improvement of the clinical situation (2).

Of importance, neither guideline recommends routine creatine kinase measurements in asymptomatic patients who are receiving statin therapy because markedly elevated creatine kinase levels tend to be rare and, in the absence of symptoms, are often due to causes other than statin therapy (2, 4). However, ACC/AHA/NHLBI advise that if creatine kinase levels increase to greater than 10 times the upper limit of normal in an asymptomatic patient, discontinuation of statin therapy should be strongly considered, although how such levels would be ascertained without symptoms is not clear. Reinitiation, preferably with a lower dose of statin, is advocated only after creatine kinase levels have returned to normal (2). Meanwhile, among patients with asymptomatic creatine kinase elevations of 3 to 10 times the upper limit of normal, the ACC/AHA/NHLBI advise careful monitoring of symptoms and perhaps more frequent creatine kinase determinations.

From our own experience, documenting pretreatment myopathy symptoms by gauging the patient's pain level on a scale from 1 to 10, accurately defining the location and type of pain, and determining baseline serum creatine kinase levels are helpful to delineate the cause of symptoms when a patient experiences incremental myopathy while receiving a statin. For asymptomatic patients with creatine

kinase elevations less than 5 times the upper limit of normal while receiving therapy, we continue to titrate statin dose to achieve LDL cholesterol level targets while closely monitoring the patient for symptoms or further serum creatine kinase increases every 3 to 6 months. For symptomatic patients either with or without creatine kinase elevations greater than 5 times the upper limit of normal, or asymptomatic patients with isolated creatine kinase elevations greater than 5 times the upper limit of normal but with no other cause identified, we either discontinue current statin therapy or decrease the current statin dose and then monitor them to ensure complete resolution. Once symptoms or creatine kinase levels return to baseline, a trial of a different statin may be considered, because about 40% of patients will tolerate another statin without incident (39). Of importance, some alternate therapeutic strategies for myopathy may exist, including use of a statin associated with less risk for myopathy, such as fluvastatin (68) or rosuvastatin (69); altered dosing regimens using atorvastatin (70–72) or rosuvastatin (73–75); addition of a nonstatin, such as ezetimibe (68, 76, 77) or bile acid–binding resin (77); and possibly use of coenzyme Q10 (78, 79) (**Table 4**).

Switching the Statin

As mentioned, head-to-head comparisons in the PRIMO study showed that patients receiving fluvastatin had fewer myopathy symptoms than did those receiving lovastatin, simvastatin, or atorvastatin (33). Also, no case of fatal rhabdomyolysis has ever been reported with fluvastatin (37). A randomized, double-blind, double-placebo trial recently evaluated the safety and efficacy of 12 weeks of treatment using extended-release fluvastatin, 80 mg/d, alone; ezetimibe, 10 mg/d, alone; or the combination among 199 patients with symptomatic myopathy after receiving other statins (68). Recurrent muscle symptoms occurred in 24% of patients receiving ezetimibe at a median of 3.1 weeks, 17% of patients receiving extended-release fluvastatin at 1.4 weeks, and 14% of patients receiving the combination therapy at 2.1 weeks. Of interest, the rate of discontinuation due to recurring myopathy was low across all 3 treatment groups: 8% for ezetimibe alone, 4% for extended-release fluvastatin, and 3% for the combination. No cases of creatine kinase elevations greater than 10 times the upper limit of normal occurred. Extended-release fluvastatin, ezetimibe, and the combination lowered LDL cholesterol levels by 33%, 16%, and 46%, respectively. A total of 84%, 59% and 29% of patients receiving the combination therapy, extended-release fluvastatin alone, and ezetimibe alone, respectively, reached their target LDL cholesterol level ($P < 0.001$) (68). Thus, in patients with previous statin intolerance, fluvastatin alone or with ezetimibe was well tolerated and efficacious.

Furthermore, because high statin dose and drug–drug interactions are risk factors for statin myopathy, rosuvastatin may be considered because it comparably decreases LDL cholesterol levels at approximately 50% of the dose of atorvastatin (80) and is metabolized by CYP2C9, which has a theoretical benefit in patients receiving several medications (43). In a prospective, open-label pilot study of 61 patients with previous statin intolerance (69), patients received rosuvastatin, 5 or 10 mg/d, and had a mean decrease in LDL cholesterol level from baseline of 18% or 24%, respectively. Only 1 patient discontinued treatment because of myalgia, and none had creatine kinase elevation, suggesting that low doses of rosuvastatin were safe and efficacious in patients with a history of statin intolerance (69).

Table 3. **Differential Diagnosis of Myopathy or Creatine Kinase Elevations Not Due to Lipid-Lowering Therapy***

Muscle symptoms
Physical exertion (particularly in unaccustomed individuals)
Viral illness
Vitamin D deficiency
Hypo- or hyperthyroidism
The Cushing syndrome or adrenal insufficiency
Hypoparathyroidism
Fibromyalgia
Polymyalgia rheumatica
Polymyositis
Systemic lupus erythematosus
Tendon or joint disorder
Trauma
Seizures or severe chills
Peripheral arterial disease†
Medications
Glucocorticoids
Antipsychotics
Antiretroviral drugs
Illicit drugs (cocaine or amphetamines)
Creatine kinase elevations
Physical exertion
Hypothyroidism
Metabolic or inflammatory myopathies
Alcoholism
Neuropathy or radiculopathy
Ethnicity (black Americans may have elevated baseline creatine kinase levels)
Idiopathic hyperCKemia‡
Seizure or severe chills
Trauma
Medications
Illicit drugs (cocaine or amphetamines)
Antipsychotics

* Based on information from references 2, 4, 43, 65–67.
† For patients who present with cramping in their calves or thighs.
‡ Refers to elevated creatine kinase level without another cause identified.

Nondaily Dosing of Statins

Atorvastatin and rosuvastatin have relatively long plasma half-lives—15 and 20 hours, respectively (43)—which renders them potentially suitable for nondaily dosing regimens to lower LDL cholesterol levels while possibly reducing adverse effects. Alternate-day atorvastatin has been studied in hypercholesterolemic patients (70–72). A double-blind, placebo-controlled trial of 35 patients receiving atorvastatin, 10 mg/d, versus alternate-day atorvastatin,

Table 4. **Possible Management Strategies for Patients Intolerant of Statins**

Management Strategy	Evidence for Strategy						
	Study, Year (Reference)	Design	Investigated Treatment	Patients, *n*	Duration	LDL-C Reduction	Tolerability*
Fluvastatin XL (80 mg/d)	Stein et al, 2008 (68)	RCT (double-blind, double-dummy)	Fluvastatin XL (80 mg/d) vs. ezetimibe (10 mg/d) vs. combination	69 (fluvastatin XL); 66 (ezetimibe); 64 (fluvastatin XL plus ezetimibe)	12 wk	33% (fluvastatin XL); 16% (ezetimibe); 46% (fluvastatin XL plus ezetimibe)	4% (fluvastatin XL); 8% (ezetimibe); 3% (fluvastatin XL plus ezetimibe)
Low-dose rosuvastatin (5 or 10 mg/d)	Glueck et al, 2006 (69)	Prospective, open-label	Rosuvastatin (5 or 10 mg/d)	61	5 mg (16 wk); 10 mg (44 wk)	18% (5 mg); 24% (10 mg)	2%
Rosuvastatin (every 2 d)	Backes et al, 2008 (73)	Retrospective	Rosuvastatin (mean dose, 5.6 mg)	51	4.6 mo	34.5%	20%
	Hegele RA, 2009†	Retrospective	Rosuvastatin (mean dose, 7.9 mg)	7	6.0 mo	33.6%	0%
Rosuvastatin (3 times weekly)	Mackie et al, 2007 (75)	Case report	Rosuvastatin (2.5 or 5 mg)	2		20% (2.5 mg); 38% (5 mg)	0%
	Hegele RA, 2009†	Retrospective	Rosuvastatin (5 or 10 mg)	6	4.7 mo	27.5%	0%
Rosuvastatin (twice weekly)	Hegele RA, 2009†	Retrospective	Rosuvastatin (5 mg)	1	4 mo	13.2%	0%
Rosuvastatin (once weekly)	Backes et al, 2007 (74)	Case report	Rosuvastatin (5–20 mg)	8	4 mo	29%	10 patients initially received regimen, but 2 discontinued therapy; whether myopathy was cause of discontinuation is not entirely clear
Ezetimibe, alone or with a bile acid–binding resin	Gazi et al, 2007 (76)	Retrospective	Ezetimibe (10 mg/d)‡; ezetimibe (10 mg/d)§	25; 12	2–3 mo; 2–3 mo	26%; 20%	0%; 17%
	Stein et al, 2008 (68)	RCT (double-blind, double-dummy)	Fluvastatin XL (80 mg/d) vs. ezetimibe (10 mg/d) vs. combination	69 (fluvastatin XL); 66 (ezetimibe); 64 (fluvastatin XL plus ezetimibe)	12 wk	33% (fluvastatin XL); 16% (ezetimibe); 46% (fluvastatin XL plus ezetimibe)	4% (fluvastatin XL); 8% (ezetimibe); 3% (fluvastatin XL plus ezetimibe)
	Rivers et al, 2007 (77)	Retrospective	Ezetimibe (10 mg/d) and colesevelam (3.75 g/d)	16	≥3 mo	42.2%	0%
CoQ10	Caso et al, 2007 (78)	RCT (double-blind)	CoQ10 (100 mg/d) vs. vitamin E (400 IU/d)	32	30 d	–	40% reduction in pain severity and interference with activities in CoQ10 group only
	Young et al, 2007 (79)	RCT (double-blind)	CoQ10 (200 mg/d) vs. placebo	44	12 wk	–	No significant difference in myalgia or statin tolerance between the 2 groups

CoQ10 = coenzyme Q10; LDL-C = low-density lipoprotein cholesterol; RCT = randomized, controlled trial; XL = extended-release.
* Tolerability defined as percentage of patients who discontinued therapy because of recurrent myopathic symptoms.
† Unpublished observations.
‡ Monotherapy in patients intolerant of statins.
§ Add-on therapy in patients intolerant of high-dose statin therapy.

10 mg, showed LDL cholesterol reductions of 38% and 35%, respectively, with no development of myopathy (70). However, no study has yet reported alternate-day atorvastatin in patients with statin intolerance.

In contrast, nondaily dosing of rosuvastatin has been evaluated in patients with previous statin intolerance (73–75). Among 51 patients with previous statin intolerance who received rosuvastatin, 5 or 10 mg (mean, 5.6 mg/d), on alternate days for a mean of 4.6 months, the mean LDL cholesterol reduction was 34.5%, and 80% of patients had no recurrence of myalgia while receiving treatment (73). Two patients with statin intolerance tolerated rosuvastatin, 2.5 mg or 5 mg 3 times weekly, and had LDL cholesterol reductions of 20% and 38% (75). Once-weekly rosuvasta-

tin, 5 to 20 mg, resulted in statin tolerance and a mean LDL cholesterol reduction of 29% among 8 patients with previous statin intolerance (74). Retrospective analysis of 14 of our own patients who received nondaily dosing regimens for rosuvastatin showed mean LDL cholesterol reductions of 33.6% in 7 patients receiving a mean dose of rosuvastatin, 7.9 mg every other day; 27.5% in 6 patients receiving rosuvastatin, 5 or 10 mg 3 times weekly; and 13.2% in 1 patient receiving rosuvastatin, 5 mg twice weekly (unpublished observations). Thus, nondaily rosuvastatin seems tolerable and may help lower LDL cholesterol levels in patients with statin intolerance, although cardiovascular disease risk reduction needs to be evaluated.

Ezetimibe and Bile Acid–Binding Resins

Ezetimibe decreases LDL cholesterol levels by targeting the NPC1L1 transporter and inhibiting intestinal cholesterol absorption (81), whereas bile acid–binding resins, such as colestipol, cholestyramine, and colesevelam, interrupt enterohepatic recycling of bile acids in the terminal ileum. Ezetimibe monotherapy is associated with LDL cholesterol decreases of about 18% (82, 83); bile acid–binding resins are associated with decreases of 15% to 26% (84). The addition of ezetimibe to existing statin therapy causes LDL cholesterol reductions similar to those achieved with higher doses of statin alone (85). However, ezetimibe still lacks evidence for cardiovascular disease end point reduction. Nonetheless, in patients with statin intolerance who have not attained their target LDL cholesterol level, addition of ezetimibe may be worthwhile. In a retrospective, 3-month study evaluating the effect of ezetimibe in patients with statin intolerance (group 1; $n = 25$) and in patients intolerant of high-dose statins (group 2; $n = 10$), ezetimibe reduced LDL cholesterol levels by 26% and 20%, respectively, although target LDL cholesterol levels less than 70 mg/dL (<1.80 mmol/L) in very-high-risk patients were rarely attained (76). Another retrospective study of 16 patients intolerant of statins with diabetes or the metabolic syndrome who received ezetimibe plus the bile acid–binding resin colesevelam showed LDL cholesterol reductions of 42%; there were no associated myalgias or discontinuation of therapy, and 50% of high-risk patients achieved their LDL cholesterol target (77). Thus, ezetimibe also demonstrates LDL cholesterol–lowering efficacy and safety in patients intolerant of statins, although cardiovascular disease outcome data are pending.

Coenzyme Q10 Supplementation

Because coenzyme Q10 depletion may contribute to statin myopathy, oral coenzyme Q10 supplementation has been evaluated (78, 79). Caso and coworkers (78) randomly assigned 32 persons with statin myopathy to either coenzyme Q10, 100 mg/d, or vitamin E, 400 IU/d, while maintaining current statin therapy. Pain was assessed through the Brief Pain Inventory (86), which provided measures of pain severity and interference in daily activities. After 30 days, both pain severity and interference decreased by about 40% in the coenzyme Q10 group only, suggesting that coenzyme Q10 improved myopathy symptoms in patients receiving statin therapy (78). Meanwhile, Young and colleagues (79) randomly assigned 44 patients intolerant of statins to either coenzyme Q10, 200 mg/d, or placebo for 12 weeks. Patients discontinued lipid-lowering therapies (except ezetimibe) and instead started simvastatin, 10 mg/d, with a doubling dose of simvastatin every 4 weeks to a maximum of 40 mg/d, if tolerated. Pain was assessed by using a modified visual analogue scale (87). The trial found no significant difference in myalgia score; number of patients tolerating simvastatin therapy, 40 mg/d; or number of patients who continued to receive therapy (79). Because of a lack of firm evidence, a recent systematic review did not recommend routine use of coenzyme Q10 (9). However, supplementation still might be considered in some patients who do not benefit from other approaches because some patients may respond, if only through a placebo effect (9), and because coenzyme Q10 has no known detrimental effects.

Conclusion

Myalgia affects up to 10% of patients receiving statin treatment. Fortunately, statin-induced fatal rhabdomyolysis is extremely rare. However, statin myopathy will probably become an increasingly relevant problem in absolute terms because of the increasing number of patients receiving statin treatment and the stringency of recent LDL cholesterol targets. Increased access to health information from the Internet or other sources may increase patient fears of statin side effects, leading to nonadherence to statin therapy and sometimes self-medication with alternate therapies, such as red rice yeast, guggulipid, or garlic preparations. Although such therapies may have acceptable tolerability, consistent data do not yet support their efficacy. Consequently, identifying patients at risk for statin myopathy and using more established management strategies to maximize the ratio of efficacy to side effects are important. In patients with statin myopathy, therapy with fluvastatin or rosuvastatin, alternate dosing regimens, and ezetimibe or bile acid–binding resins have demonstrated reasonable tolerability and efficacy. Coenzyme Q10 supplementation is not currently recommended for routine use. Further studies are warranted for the development of alternate strategies in statin myopathy and of newer statins with lower potential for statin myopathy.

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