UPDATE IN OFFICE MANAGEMENT

Clinical Perspectives of Statin-Induced Rhabdomyolysis

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ABSTRACT

Fear of muscle toxicity remains a major reason that patients with hyperlipidemia are undertreated. Recent evaluations of statin-induced rhabdomyolysis offer new insights on the clinical management of both muscle symptoms and hyperlipidemia after rhabdomyolysis. The incidence of statin-induced rhabdomyolysis is higher in practice than in controlled trials in which high-risk subjects are excluded. Accepted risks include age; renal, hepatic, and thyroid dysfunction; and hypertriglyceridemia. New findings suggest that exercise, Asian race, and perioperative status also may increase the risk of statin muscle toxicity. The proposed causes and the relationship of drug levels to statin rhabdomyolysis are briefly reviewed along with the problems with the pharmacokinetic theory. Data suggesting that patients with certain metabolic abnormalities are predisposed to statin rhabdomyolysis are presented. The evaluation and treatment of patients’ muscle symptoms and hyperlipidemia after statin rhabdomyolysis are presented. Patients whose symptoms are related to other disorders need to be identified. Lipid management of those whose symptoms are statin-related is reviewed including treatment suggestions. © 2006 Elsevier Inc. All rights reserved.

The use of 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors or statins in randomized trials has demonstrated 30% reductions in atherosclerotic end points without serious morbidity.1-3 Yet, statins are prescribed for less than half of the patients who should receive this therapy.4,5 Unfortunately, fear of rare but serious muscle toxicity remains a major impediment to the appropriate use of these drugs.

New evaluations have refined the description of statin-induced rhabdomyolysis.6,7 Findings from recent publications are supplemented by our published experience managing patients in a statin myopathy clinic. This review offers clinical insights on the management of patients’ muscle symptoms and hyperlipidemia after statin-induced rhabdomyolysis.

DEFINITIONS

Historically, the terminology used to describe muscle toxicity and rhabdomyolysis has been imprecise and sometimes inconsistent.8-10 The Clinical Advisory on Statins made a significant step toward standardization of the terms (Table 1).11 Rhabdomyolysis required muscle symptoms with marked creatine kinase elevation typically substantially greater than 10 times the upper limit of normal, with a creatinine elevation consistent with pigment nephropathy and usually with brown urine with myoglobinuria. Although this is an improvement over prior classifications, the requirement that creatine kinase exceed 10 times the upper limit of normal is arbitrary and excludes some cases of serious muscle toxicity. It is also unclear why the diagnosis of rhabdomyolysis, a muscle disorder, should require evidence of renal impairment. Subsequent expert definitions have not included this requirement, and this definition will certainly be revised further as statin-induced rhabdomyolysis is better understood.6

INCIDENCE

The incidence of statin-induced rhabdomyolysis is low in randomized, controlled trials in which high-risk patients were excluded.1,3 However, increased scrutiny shows a higher incidence of statin-induced rhabdomyolysis when statins are applied outside of clinical trials.6,7 Epidemiologic studies have shown that rhabdomyolysis was 12 times more frequent when statins were combined with fibrates, compared with statin monotherapy (Table 2). It has been observed that either myopathy12 or rhabdomyolysis8 was 6 times more common with...
fibrate monotherapy than when compared with statin monotherapy. The incidence of rhabdomyolysis also seems similar among atorvastatin, pravastatin, and simvastatin, although no study has been adequately powered to provide a definite comparison. Controversy persists, with some analyses suggesting that simvastatin and rosuvastatin may have higher rates of muscle toxicity.

**PRESENTATION**

Rhabdomyolysis apart from statin use presents with a muscle symptom only 50% of the time. Although statin-induced rhabdomyolysis may present with the onset of diffuse myalgias and weakness over several days, its presentation may also be variable (Table 3). Patients often present with a subacute progression of low back and proximal muscle pain over weeks. The most common presentation in the preclinical rosuvastatin studies was of a flu-like syndrome. A high index of suspicion is essential for any patient presenting with an elevated creatine kinase on statins because symptoms may be atypical. One survey of 81 patients with statin-induced rhabdomyolysis showed that fatigue (74%) was nearly as common as muscle pain (88%) in these patients. The average length of time on a statin dose before rhabdomyolysis is approximately 1 year, suggesting patients may tolerate a dose for a long time before a reaction develops. However, the average time between the addition of a fibrate to statin and subsequent onset of rhabdomyolysis is only 32 days.

**RISK FACTORS**

Clinical trials of statins have excluded patients who are older, who have renal or hepatic dysfunction, who have severe hypertriglyceridemia, and who are taking other medications that might predispose to muscle toxicity. Consequently, muscle toxicity occurs more commonly in clinical practice than is reported in these trials. Accepted risks for statin myopathy are summarized in Table 4. Other risks are less well accepted.

Exercise is an acknowledged risk for rhabdomyolysis in patients with metabolic muscle disease. Myopathy occurs in those who perform unaccustomed heavy exercise while on statins. Frank rhabdomyolysis is less common.

Studies performed in Singapore and Japan show 2-fold higher rosuvastatin drug levels in Asians, compared with whites, without any increase in muscle toxicity. Despite the lack of evidence for increased myotoxicity, rosuvastatin now is labeled for lower doses in Asians.

The data supporting the perioperative period as a risk factor for statin-induced rhabdomyolysis are incomplete. Case reports describe rhabdomyolysis after uncomplicated surgeries, but two of the three patients described had muscle symptoms before admission for surgery. Meanwhile, retrospective and prospective reviews suggest significant benefit to statin use perioperative to coronary bypass or vascular surgery. Other work has shown neither benefit nor harm. In the presence of this conflicting information, the current guidelines suggesting that statins be withheld perioperatively require reexamination.

**CLINICAL SIGNIFICANCE**

- Clinicians may be challenged by patients with muscle complaints and hyperlipidemia after statin-induced rhabdomyolysis.
- New findings concerning the cause of muscle toxicity and the risk factors for statin-induced rhabdomyolysis are outlined.
- An algorithm for the evaluation and treatment of muscle symptoms after statin-induced myotoxicity is suggested.
- The options for lipid-lowering therapy in patients with prior statin-induced muscle toxicity are reviewed.

| Table 1 Definitions of Muscle Toxicity and Rhabdomyolysis by Clinical Advisory on Statins |
|------------------------------------------|---------------------------------------------------------------|
| **Myopathy** | A general term referring to any disease of muscles; myopathies can be acquired or inherited and can occur at birth or later in life |
| **Myalgia** | Muscle ache or weakness without creatine kinase elevation |
| **Myositis** | Muscle symptoms with increased creatine kinase levels |
| **Rhabdomyolysis** | Muscle symptoms with marked creatine kinase elevation typically substantially greater than 10 times the upper limit of normal with a creatinine elevation consistent with pigment nephropathy and usually with brown urine with myoglobinuria |

<table>
<thead>
<tr>
<th>Table 2 Number of Patients on 1 year of Therapy to Cause Rhabdomyolysis and Incidence Rate per 1 Year of Therapy</th>
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<tbody>
<tr>
<td>The number of patients on 1 year of therapy to cause a single case of rhabdomyolysis</td>
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<tr>
<td>Statin monotherapy</td>
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<tr>
<td>Fibrate monotherapy</td>
</tr>
<tr>
<td>Cerivastatin monotherapy</td>
</tr>
<tr>
<td>Any statin (except cerivastatin) + fibrate</td>
</tr>
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<td>Cerivastatin + fibrate</td>
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the preponderance of data substantiate the benefits of continued statin therapy for reduced vascular events, statins should be continued through the perioperative period for all vascular procedures including coronary bypass. Statins should be discontinued for any patient with preoperative muscle symptoms or whose surgery may cause unusually prolonged tissue pressure or postoperative calorie depletion. Under these circumstances the metabolic risk probably exceeds the vascular stabilizing benefit of these agents.

Risk stratification based on these accepted risks has been touted as a means of accounting for most serious rhabdomyolysis cases. Yet, statin-induced rhabdomyolysis may develop even when accepted risks are avoided, and better definition of risk groups is needed.

**CAUSE**

The cause of statin-induced rhabdomyolysis remains obscure. Muscle toxicity has generally been attributed to deficiencies of synthetic products of the 3-hydroxy-3-methylglutaryl-CoA reductase pathway. The most common explanations invoke the deficiency of one of 3 main end products: cholesterol deficiency with secondary abnormal membrane behaviors, coenzyme Q10 deficiency causing abnormal mitochondrial respiratory function, or prenylated protein abnormalities causing imbalances in intracellular protein messaging (Figure 1).

Drug interactions can increase the risk of statin-induced rhabdomyolysis. This risk is partly pharmacokinetic because interference with both hepatic metabolism and gut wall transport increases statin bioavailability and serum concentrations. However, several incongruities in the kinetic data clearly indicate a role for pharmacodynamic effects as well.

The greatest incidence of statin-induced rhabdomyolysis with drug interactions occurs when other lipid-modifying therapies, particularly fibrates, are added to statins. This occurs with gemfibrozil despite kinetic interactions, which are less severe than with other commonly used cardiac agents and with fenofibrate despite the absence of any significant kinetic interaction. At similar doses, pravastatin achieves a higher peak serum concentration, compared with simvastatin and atorvastatin. Yet, it does not carry a higher risk of rhabdomyolysis; whereas rosuvastatin achieves lower serum concentration but does not carry a reduced risk.

Approximately 25% of individuals with recurrent rhabdomyolysis unrelated to lipid-lowering therapy have underlying metabolic muscle disorders. Several lines of evidence suggest that patients who have statin-induced rhabdomyolysis may have an underlying metabolic predisposition to this reaction. An unusually high number of patients with statin-induced rhabdomyolysis also have underlying metabolic muscle defects. Cultured myocytes from patients with statin-induced muscle reactions demonstrate abnormal fatty acid oxidation responses to statins compared with control muscle, further supporting a metabolic predisposition.

**TREATMENT OF ACUTE STATIN-INDUCED MUSCLE TOXICITY**

The supportive treatment of acute rhabdomyolysis from any cause includes hydration, alkalinization of the urine to minimize precipitation of myoglobin in the renal tubules, and withdrawal of the offending agent or condition. It is not yet clear whether metabolic supplements will be useful acutely for statin-induced rhabdomyolysis.

**EVALUATION AFTER STATIN-INDUCED RHABDOMYOLYSIS**

Because there is a high level of public concern regarding statin muscle toxicity, patients may incorrectly attribute muscular symptoms to a poststatinrhabdomyolysis myopathy. Nonetheless, many patients have persistent muscle pain, weakness, or chronic elevations of creatine kinase after an episode of statin-induced rhabdomyolysis. It is important to diagnose and treat these patients’ muscle symptoms before their hyperlipidemia can be addressed. The evaluation outlined below and in Figure 2 may be applied to any patient with suspected statin-

**Table 3 Presentation of Statin-induced Rhabdomyolysis**

<table>
<thead>
<tr>
<th>Signs and Symptoms of Statin-induced Rhabdomyolysis</th>
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<tbody>
<tr>
<td>Diffuse myalgias and weakness</td>
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<tr>
<td>Low back and proximal muscle pain and aching</td>
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<tr>
<td>Flu-like illness</td>
</tr>
<tr>
<td>Asymptomatic elevation of creatine kinase</td>
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**Table 4 Proposed Risk Factors for Statin-induced Rhabdomyolysis (Adapted from References 13, 15, 74)**

<table>
<thead>
<tr>
<th>Endogenous Risks</th>
<th>Exogenous Risks</th>
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<tbody>
<tr>
<td>Advanced age (&gt;80 y)</td>
<td>Alcohol consumption</td>
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<tr>
<td>Small body frame and frailty</td>
<td>Heavy exercise</td>
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<tr>
<td>Multisystem disease:</td>
<td>Surgery with severe metabolic demands</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Drugs affecting the CYP-450 system:</td>
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<tr>
<td>Hepatic dysfunction</td>
<td></td>
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<tr>
<td>Thyroid disorders, especially hypothyroidism</td>
<td></td>
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<tr>
<td>Hypertriglyceridemia</td>
<td></td>
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<tr>
<td>Metabolic muscle diseases:</td>
<td></td>
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<tr>
<td>Carnitine palmityl transferase II deficiency</td>
<td></td>
</tr>
<tr>
<td>McArdle disease</td>
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<tr>
<td>Myoadenylate deaminase deficiency</td>
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HIV = human immunodeficiency virus.
Figure 1  Synthetic products of the mevalonate pathway are represented with myotoxic observations numbered at various sites in the synthetic pathways. The red pathway pertains to cholesterol concentrations and membrane integrity. The blue pathway affects ubiquinone concentrations and mitochondrial respiration. Products from the green pathway affect cell signaling and apoptosis. From the pathway, products are listed above and are color-coded to reflect the model used in making the observation.50,100-117

Key to observations:  ■ cell culture ■ rodent models ■ human models

General Observations:
1. Blocked HMG-CoA reductase results in an increased Acyl-CoA/free CoA ratio in cells. This leads to a higher carnitine requirement and to a secondary carnitine deficiency. Muscle carnitine was reduced but carnitine palmitoyl transferase and carnitine acetyltransferase were unchanged.
   Rabbit model. Bhuiyan, 1998
2. Adding mevalonate back to the diet reduced statin toxicity arguing it’s not the statin per se but the metabolic effects of statin causing the toxicity.
   Rat Model Westwood, 2005
3. Supplemeting the growth medium with mevalonate abrogated toxicity in myocytes.
   FRTL5 Thyroid cells Biifuco, 1993
4. Rat Myocytes Flint, 1997
5. Adding mevalonate to the growth medium with statin only reduced 50% of the observed myocyte toxicity.
   Human Myocytes Sacher, 2005

Observations related to cholesterol concentration and membrane integrity:
6. The inhibition of cholesterol synthesis by blocking squalene synthase causes no myotoxicity
   Rat Myocytes Fintel, 1997
7. Rat and Human Myocytes Johnson, 2004
8. The replacement of cholesterol or squalene did not reverse the toxic effects of statins.
   Rat mesangial cells O'Donnell, 1993
   Mammalian osteocytes Kim, 1990
   Cell Model Soms, 1992
7. Myotoxicity was not related to cholesterol lowering effects of different statins.
   Rabbit Model Nakahara, 1998
8. Predispotion for fast twitch, glycolytic type 2 myocytes suggests the toxicity is more related to cholesterol concentration than to oxidative processes.
   Rat Model Wadzaw, 1993
   Rat Model Schaefer, 2004
   Rat Model Westwood, 2005

Observations related to ubiquinone and mitochondrial respiration:
9. Despite decreased ubiquinone concentrations and mitochondrial abnormalities, mitochondrial respiratory activity remained normal during toxicity.
   Rabbit Model Nakahara, 1998
   Ubiquinone concentration was decreased but did not correlate with creatine kinase. Mitochondrial function remained normal in toxic cells.
   Rat Model Schaefer, 2004
   Lovastatin exposed neuroblastoma cells have significantly reduced ubiquinone without any change in mitochondrial function.
   Neuroblastoma cells Malekis, 1985
   Ubiquinone supplementation did not reverse cellular toxicity
   FRTL5 Thyroid cells Biifuco, 1993
10. Ubiquinone supplementation reduced the severity of myotoxicity in humans exposed to massive statin doses.
    Human Model Thibault, 1996
    Kim, 2001
11. Muscle ubiquinone and mitochondrial enzyme activity were reduced in muscle of patients on simvastatin 8 weeks.
    Human Model Paiva, 2005

Observations related to cell signaling cascades and apoptosis:
11. Geranylgeranylated supplementation abolishes statin myotoxicity suggesting that myotoxicity is related to the post translational modification of regulatory proteins.
    Rat Myocytes Flint, 1997
    Statin exposure caused apoptosis in human skeletal muscle cells.
    Human Myocytes Sacher, 2005
12. Myocyte apoptosis correlated with reduced geranylgeranylation but not with ubiquinone concentrations.
    Human and Rat myocytes Johnson, 2004
    Human model Uraso, 2005
14. Apoptosis was increased in degenerative muscle fibers of a patient with statin-induced rhabdomyolysis.
    Human model Sakerieh, 2004
induced myotoxicity, as well as to the patients with statin-induced rhabdomyolysis we focused on here. As we have observed, the requirement of creatine kinase more than 10 times the upper limit of normal for rhabdomyolysis is arbitrary, and any patient with symptoms that may be attributed to a metabolic toxicity of their lipid-lowering therapy warrants evaluation.

**History**

A complete history should determine whether the indication for lipid-lowering therapy was for primary or secondary prevention. The nature and severity of muscle symptoms are important. Muscle pain that is increased by exercise or that resolves during a 2-week statin holiday is more likely to be related to statin myotoxicity. Dyspnea and fatigue associated with the muscle symptoms also increase the likelihood of statin-related muscle disorders. Incidental causes of elevated creatine kinase, such as recent exercise and injections, should be excluded. A complete medication history including duration and dosing of all lipid-lowering therapies and medications known to interfere with statin metabolism is essential. Excess alcohol and vitamin E supplements can

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**Figure 2** Evaluation algorithm of patients with persistent symptoms after statin-induced rhabdomyolysis. CK = creatine kinase, TSH = thyroid stimulating hormone, ANA = anti-nuclear antibody, ESR = sedimentation rate, RER = respiratory exchange ratio, VO2 max = maximal oxygen consumption, AT = anaerobic threshold.
cause myopathy and should be discontinued. A family history of fasting or exercise-induced muscle cramping or rhabdomyolysis is important.

Physical Examination

Signs of hypothyroidism or excessive alcohol consumption should be looked for. A careful neurologic examination and ankle-brachial indices help to tease out myopathy mimics such as claudication, myelopathy caused by spinal stenosis, peripheral neuropathy, amyotrophy, and lumbosacral radiculopathy. For example, atrophy, fasciculations, and weakness coupled with lower extremity hyperreflexia and extensor plantar responses would be most suggestive of a myelopathy. Alternatively, descending paresthesias into the lateral shin and dorsal foot associated with dorsiflexion weakness would be suggestive of an L5 radiculopathy. Finally, stocking-and-glove sensory hypoesthesia with intrinsic atrophy in the feet and distal weakness would be compatible with peripheral neuropathy.

Additionally, somatic pain inhibits forceful muscle contraction resembling weakness. Therefore, musculoskeletal testing will help sort out patients with rotator cuff tendinitis, tendinopathies, arthropathies, and myofascial pain syndromes. If testing will help sort out patients with rotator cuff tendinitis resembling weakness. Therefore, musculoskeletal intrinsic atrophy in the feet and distal weakness would be suggestive of an L5 radiculopathy.

Laboratory Evaluation

All patients undergo evaluation of creatine kinase, thyroid-stimulating hormone, and lipid panel. When specific rheumatologic disorders are suspected, sedimentation rate, C-reactive protein, anti-Jo antibody, and antinuclear antibody are tested.

Cardiopulmonary Testing

We have discovered that many patients who remain symptomatic after statin-induced rhabdomyolysis have evidence for decreased fasting fat oxidation and decreased aerobic indices on exercise. We therefore perform cardiopulmonary exercise testing with exhaled gas analysis after an overnight fast in all these subjects. Those with an abnormal fasting respiratory exchange ratio of greater than 0.80 are most likely to have measurable abnormalities at biopsy.

Biopsy

The incidence of underlying metabolic muscle disorders is approximately 25% in patients evaluated for symptoms after statin-induced rhabdomyolysis. Some patients in this group need to have alternate diagnoses excluded, such as inclusion body myositis or polymyositis. Consequently, we refer most patients with abnormal fasting respiratory exchange ratios or persistently elevated creatine kinase for percutaneous muscle biopsy. Muscle is sent for standard muscle stains, with additional cytochrome oxidase and succinic dehydrogenase stains and full electron microscopy.

TREATMENT OF CHRONIC MYOPATHY AFTER STATIN-INDUCED RHABDOMYOLYSIS

There are little well-controlled data to indicate therapy for patients with persistent muscle pain and weakness after statin-induced rhabdomyolysis. Because of the absence of well-controlled evaluations of therapy, patients and physicians have often tried supplements empirically before referral for evaluation.

Coenzyme Q10 supplementation has been considered for statin myotoxicity. Serum levels and mitochondrial concentrations of coenzyme Q10 increase after supplementation. Coenzyme Q10 supplementation has been shown to have clinical use in patients with primary and secondary enzyme deficiency states and in other mitochondrial disorders. Three case reports of patients with statin myopathy reported some resolution of symptoms with coenzyme Q10. In each of these trials, coenzyme Q10 did not reduce the incidence of muscle toxicity, but it significantly reduced its severity. One pilot trial has been completed suggesting possible benefit in patients with pain but not myositis on statins. These studies require confirmation.

Although coenzyme Q10 doses up to 1200 mg daily have been shown to be safe in trials of older patients with Parkinson disease, patients with statin-induced rhabdomyolysis should not be encouraged to initiate these supplements on their own because many marketed preparations contain little bioavailable coenzyme Q10. Because of the absence of large prospective studies, coenzyme Q10 supplementation for statin-associated myopathy remains an interesting idea without firm evidence to support its use.

LIPID-LOWERING THERAPY AFTER STATIN-INDUCED RHABDOMYOLYSIS

The Clinical Advisory on Statins recommended that patients with statin-induced rhabdomyolysis discontinue statins. However, further lipid-lowering treatment was not addressed. Current guidelines ignore the possibility that these patients may have a disorder of lipid metabolism that leaves them vulnerable to therapies that reduce or alter free fatty acid and triglyceride concentrations. Because there are few studies testing the safety of lipid-lowering therapy in patients with prior statin myotoxicity, the proper management of these patients’ lipids remains challenging.

Despite the lack of clear evidence that lipophilicity is related to myotoxicity, physicians often choose to treat the lipids of patients with statin-induced rhabdomyolysis by changing to a low dose of an alternate, less lipid-soluble statin. With acknowledgment of the controversy here, the best existing evidence suggests that hydrophilic statins (rosuvastatin and pravastatin) are as likely to cause muscle toxicity as lipophilic statins. One review described...
two patients with myopathy on simvastatin who redeveloped the syndrome shortly after being switched to pravastatin. Golomb and colleagues found that 55% of patients with muscle symptoms had a recurrence of symptoms when challenged with a smaller low-density lipoprotein (LDL)-lowering dose of another statin. When patients were rechallenged with an equal LDL-lowering dose, symptoms redeveloped in 95%. We do not believe it is safe to change to an alternate statin formulation after statin-induced rhabdomyolysis.

Ezetimibe has been considered when myotoxicity is a concern. Unfortunately, this drug has not been studied in patients with prior statin-induced muscle toxicity. A meta-analysis showed no reduction in muscle adverse events when ezetimibe was used to reduce statin dose. Myopathy with creatine kinase elevation has been attributed to ezetimibe when it was added to stable statin therapy. We have repeatedly found that the majority of statin-intolerant subjects are also intolerant of ezetimibe. We also reported a patient with prior normal creatine kinase statin-induced myopathy who became profoundly weak with an elevated creatine kinase level and biopsy-proven myopathy on ezetimibe monotherapy. Ezetimibe has precipitated rhabdomyolysis when used in a patient with McArdle disease. Pending definitive studies addressing its safety, ezetimibe should not be considered for statin-intolerant patients.

Both niacin and fibrates can cause rhabdomyolysis. The incidence of rhabdomyolysis or myopathy with fibrate monotherapy is 6 times that of statin monotherapy. Our own experience using both niacin and fibrates in patients with statin-associated muscle toxicity suggests that the majority of these patients redevelop muscle symptoms on either therapy. Much has been discussed about the relative safety of fenofibrate compared with gemfibrozil with respect to muscle toxicity. It remains unclear whether increased statin levels are the sine qua non of statin myotoxicity, and the largest review of statin-induced rhabdomyolysis failed to distinguish among gemfibrozil, bezafibrate, and fenofibrate in contributing to this toxicity. As more cases of fenofibrate-induced muscle reactions accrue, there is mounting support for more cautious use of this drug too.

Diet therapy becomes the cornerstone in managing the lipid profile of patients who are intolerant of lipid-lowering medications. We recommend a low-fat diet that conforms to the National Cholesterol Education Program Adult Treatment Panel III recommendations for all of these patients. The Portfolio Diet is offered to those who can comply with a vegan diet. In crossover clinical trials, the Portfolio Diet over a 4-week period reduced LDL levels comparable to 20 mg of lovastatin.

Because statin muscle toxicity may be related to impaired fat oxidation in patients whose symptoms persist after statins are withdrawn, we studied the response of these patients to bile acid sequestrants. Resins would be a logical choice for these subjects because they have minimal effect or even increase triglyceride and free fatty acid levels, while lowering LDL cholesterol 15% to 20%. There has never been a case of rhabdomyolysis attributed to resin monotherapy. This preliminary work showed that resins were effective and well tolerated in patients who are intolerant of multiple lipid-lowering therapies.

**SUMMARY AND FUTURE DIRECTIONS**

We have outlined a clinical approach to patients with statin-induced rhabdomyolysis that is based on the best available evidence from largely observational series. Clinicians should avoid lipid-lowering pharmacotherapy in any patient who has had statin myotoxicity while being treated for primary prevention. These patients are best managed with a dietary approach. We add resin therapy to this diet for any patient with a history of statin myotoxicity who needs secondary prevention after a vascular event or who is unable to reach target LDL with diet alone. Occasionally, patients with prior serious statin muscle reactions are placed on very low-dose statin in combination with both diet and resin therapy. These patients are monitored with quarterly creatine kinase levels and cautioned to stop statin at the onset of any flu-like syndrome. They also are cautioned to discontinue statin during any period of metabolic stress such as extended exercise, fasting, surgery, or viral illness.

Despite improved epidemiologic descriptions of statin-induced rhabdomyolysis, our understanding of the cause and treatment of this disorder remains limited. Because fear of muscle toxicity remains a major reason that patients with hyperlipidemia are undertreated, further work is needed to clarify this disorder. A biomarker that is specific for statin-induced muscle injury is needed. Whether the specific biomarker is an abnormal urine organic acid or a troponin specific for skeletal muscle, it would provide the diagnostic certainty necessary for more detailed investigations into the cause and therapy of statin-induced rhabdomyolysis.

Although pharmacokinetic causes of elevated statin activity clearly contribute to the risk of statin-induced rhabdomyolysis, there seem to be factors involved other than statin level and bioactivity. It seems that latent metabolic defects may render some previously asymptomatic patients vulnerable to the metabolic effects of statins. Studies of fatty acid oxidation and the protein signals for atrophy in myocytes cultured from myotoxic patients may provide further pathophysiologic clues. Further studies of the mechanisms of muscle catabolism and atrophy will be important to clarify this disorder.

Prospective studies of patients with statin-induced rhabdomyolysis are needed to assess their metabolic abnormalities and responses to various supplements. Mitochondrial adjuvants, as well as mevalonate supplementation, taken shortly after the onset of statin myotoxicity need to be tested. The safety of other lipid-lowering therapies in patients with statin-induced rhabdomyolysis must be confirmed before they can be offered for this challenging group of patients.
References


15. Omar MA, Wilson JP. FDA adverse event reports on statin-associ-


73. Sochman J, Podzimkova M. Not all statins are alike: induced rhabdomyolysis on changing from one statin to another. *Int J Cardiol.* 2005;99(1):145-146.


