

Statin-Associated Myopathy

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STATINS (3-HYDROXY-3-METHYL-glutaryl coenzyme A [HMG-CoA] reductase inhibitors) reduce cholesterol production by reducing the synthesis of mevalonate, a critical intermediary in the cholesterol pathway. The HMG-CoA reductase inhibitors are the most effective medications for managing elevated concentrations of low-density lipoprotein cholesterol (LDL-C). Furthermore, these drugs reduce cardiovascular events in coronary heart disease patients with moderate¹ and mild² LDL-C elevations and in previously healthy patients with high³ and normal⁴ baseline LDL-C values.

Statins are well tolerated by most patients but can produce a variety of muscle-related complaints or myopathies. The most serious risk of these drugs is myositis with rhabdomyolysis. This risk has been emphasized by the withdrawal of cerivastatin in August 2001 after the drug was associated with approximately 100 rhabdomyolysis-related deaths.⁵ Rhabdomyolysis was also a factor in the withdrawal of the antihypertensive drug mibefradil in June 1998⁶ and in the decision by Merck & Co to abandon the development of a 160-mg sustained-release simvastatin formulation in the mid-1990s.⁷

Clinically important rhabdomyolysis with statins is rare, with an overall reported incidence of fatal rhabdomyolysis of 0.15 deaths per 1 million prescriptions.⁸ The possibility of statin-related rhabdomyolysis is generally appreciated by the medical community, but these medications are more fre-

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are associated with skeletal muscle complaints, including clinically important myositis and rhabdomyolysis, mild serum creatine kinase (CK) elevations, myalgia with and without elevated CK levels, muscle weakness, muscle cramps, and persistent myalgia and CK elevations after statin withdrawal. We performed a literature review to provide a clinical summary of statin-associated myopathy and discuss possible mediating mechanisms. We also update the US Food and Drug Administration (FDA) reports on statin-associated rhabdomyolysis. Articles on statin myopathy were identified via a PubMed search through November 2002 and articles on statin clinical trials, case series, and review articles were identified via a PubMed search through January 2003. Adverse event reports of statin-associated rhabdomyolysis were also collected from the FDA MEDWATCH database. The literature review found that reports of muscle problems during statin clinical trials are extremely rare. The FDA MEDWATCH Reporting System lists 3339 cases of statin-associated rhabdomyolysis reported between January 1, 1990, and March 31, 2002. Cerivastatin was the most commonly implicated statin. Few data are available regarding the frequency of less-serious events such as muscle pain and weakness, which may affect 1% to 5% of patients. The risk of rhabdomyolysis and other adverse effects with statin use can be exacerbated by several factors, including compromised hepatic and renal function, hypothyroidism, diabetes, and concomitant medications. Medications such as the fibrate gemfibrozil alter statin metabolism and increase statin plasma concentration. How statins injure skeletal muscle is not clear, although recent evidence suggests that statins reduce the production of small regulatory proteins that are important for myocyte maintenance.

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quently associated with a variety of skeletal muscle complaints including myalgia with or without creatinine kinase (CK) elevations.

This review discusses the skeletal muscle complaints associated with statins as well as the incidence, possible causes, and approach to these skeletal muscle problems. It also presents recent US Food and Drug Administration (FDA) data on the occurrence of statin-associated rhabdomyolysis.

METHODS

Literature Review

English-language articles on statin myopathy were identified via a PubMed search through December 2002 and from reference citations in other articles. The PubMed search was performed using the terms *myopathy* or *rhabdomyolysis* and *statin*, or *HMG-CoA reductase inhibitor(s)* and *statin*, or *HMG-CoA reductase inhibitors* and *skeletal muscle*. Abstracts were reviewed by 1 of the authors (either P.D.T. or P.C.) and all articles addressing statin myopathy were examined in detail. Selected articles included clinical trials, reviews, case series, and clinical guidelines. Articles describing possible mechanisms were also examined and included if they had clinical relevance or provided novel information. No attempt was made to include every publication on the biochemistry of statin-associated myopathy. Articles on randomized controlled clinical trials using statins were also identified via a PubMed search through January 2003. This search was performed using the terms *statin* and *clinical trial(s)* or *statin* and *randomized clinical trials*. Abstracts were reviewed by 1 of the authors (P.C.), and all articles presenting the results of randomized controlled clinical trials using statins as the intervention and placebo or usual care as the control condition were included. The PubMed search results were checked for completeness against 2 recent summaries of cardiovascular clinical trials.^{9,10}

Search of FDA Database

Adverse event reports of statin-associated rhabdomyolysis were col-

lected from the Qscan FDA database using Qscan FDA software (QED Solutions, McLean, Va). All reports of rhabdomyolysis reported to the FDA MEDWATCH system in which a statin was listed as either a causative suspect or a concomitant medication from January 1, 1990, through March 31, 2002, were included in this analysis. The percentage of the reports of statin-associated rhabdomyolysis was calculated for each statin. The percentage of adverse events for each statin due to rhabdomyolysis was also calculated. Outcomes categories, including death, significant disability, hospitalization, and life-threatening reaction, were coded as defined by the FDA MEDWATCH system.

STATIN-RELATED MUSCLE COMPLAINTS

The literature on skeletal muscle complaints with statins is confusing, in part because of a lack of clear definitions. The recent American College of Cardiology/American Heart Association clinical advisory on the use and safety of statins¹¹ defined 4 syndromes: statin myopathy (any muscle complaints related to these drugs); myalgia (muscle complaints without serum CK elevations); myositis (muscle symptoms with CK elevations); and rhabdomyolysis (markedly elevated CK levels, usually >10 times the upper limit of normal [ULN], with an elevated creatinine level consistent with pigment-induced nephropathy).

These definitions have several limitations. They do not address increased CK levels in the absence of symptoms. Also, some degree of myositis with rhabdomyolysis or skeletal muscle breakdown exists whenever skeletal muscle CK levels exceed normal or pretreatment values. Clinically important myositis or rhabdomyolysis is defined in most studies as muscle pain with CK levels greater than 10 times the ULN.¹² This magnitude of CK elevation may be associated with myoglobinuria, but greater degrees of muscle damage and CK elevations are usually required to cause myoglobin pigment-induced renal dysfunction, and some patients ex-

perience great increases in CK levels without renal problems.¹³ The occurrence of renal failure with rhabdomyolysis is related to the magnitude of muscle injury, the patient's hydration status, and possibly other factors, such as concomitant medications or genetic predisposition; it is not related to the degree of muscle injury alone. An alternative approach separates statin-associated muscle problems into the following syndromes.

Clinically Important Myositis and Rhabdomyolysis

This is defined as muscle pain with CK levels greater than 10 times the ULN.¹² Skeletal muscle biopsies in patients with statin-associated myositis demonstrate polymyositis¹⁴ and myolysis.¹⁵ Clinically important rhabdomyolysis can be associated with azotemia as well as multiple metabolic abnormalities, including elevated potassium and phosphate levels due to their release from injured myocytes, as well as low calcium levels produced by calcium precipitation with phosphate.¹³ Death can result from hyperkalemia and cardiac arrhythmia, renal failure, and disseminated intravascular coagulation.

Mild CK Elevations

Statins more frequently produce CK elevations that do not exceed 10 times the ULN. Patients with mild CK elevations may not be symptomatic; CK elevations in asymptomatic patients are detected by routine testing or during the evaluation of other conditions. The incidence of CK elevations that do not exceed 10 times the ULN is not known because this information is rarely reported in clinical studies. Statin-induced CK elevations could be erroneously attributed to myocardial infarction, but the myocardial CK fraction is rarely elevated.^{16,17} Statins magnify the increase in CK levels that can occur following exercise,¹⁸ and there are multiple case reports¹⁹⁻²¹ of both mild and clinically significant CK elevations after vigorous exertion in patients taking statins.

Myalgia

Myalgia is defined as muscle pain and affects patients' quality of life and compliance with these medications. Myalgia is a common complaint and significant problem for patients taking statins.^{22,23} Review of 2 databases showed that myalgia contributed to 19% to 25%²² and 6% to 14%²³ of all adverse events associated with statin use. Myalgia was also noted in 45 (8.9%) of 508 patients with familial hypercholesterolemia treated for 2 years with simvastatin, 80 mg/d, and musculoskeletal complaints prompted 9 (1.8%) of these patients to discontinue treatment.²⁴ In contrast, myalgia was rarely reported in clinical trials and infrequently led to statin discontinuation in these studies. In the Medical Research Council/British Heart Foundation Heart Protection Study,²⁵ there was no difference in muscle pain or weakness between patients treated with simvastatin, 40 mg/d, or placebo for 5 years, nor were there differences in the number of patients who discontinued treatment for musculoskeletal complaints. Furthermore, labeling information from controlled studies shows rates of myalgia of 1% to 5%²⁶ (TABLE 1), which is not significantly different from placebo.

Consequently, there is no consensus that statins are responsible for these myalgic complaints, although many clinicians believe that statins can induce myalgia without CK elevations. Patients may respond to statin withdrawal, further implicating these medications. A recent report supports the concept of statin myopathy without CK elevations.²⁷ Four of 20 patients randomized in a double-blind crossover clinical trial developed muscle complaints during statin therapy that resolved during the placebo phase. Muscle biopsies in 3 of these patients demonstrated evidence of mitochondrial dysfunction, including increased lipid storage and ragged red muscle fibers. Symptoms occurred despite normal serum statin levels in the patients.

Muscle Weakness

Skeletal muscle weakness is frequent in association with clinically important

myositis and rhabdomyolysis but can also occur in patients with no or little CK elevation. The frequency of symptomatic weakness has not been reported, and the only study to examine muscle strength in patients treated with statins reported on only 4 subjects.²⁷ In that study, hip abduction strength decreased 47%, 10%, 30%, and 13% among the 4 patients when taking statins; hip flexion strength decreased 47%, 5%, 12%, and 11%.²⁷

Muscle Cramps

Muscle cramps are anecdotally related to statin use, although there are few data linking these drugs to this complaint²⁶ (Table 1).

Persistent Myalgia/CK Elevations After Statin Withdrawal

There are rare clinical anecdotes that patients complain of persistent muscle discomfort while taking statins, occasionally associated with CK elevations, both of which persist after withdrawal of the medication.²⁸ Such patients should be evaluated for other conditions, such as polymyalgia rheumatica and temporal arteritis, which may have been unmasked by statin therapy, as well as hypothyroidism, which can elevate CK concentrations.

INCIDENCE OF CLINICALLY IMPORTANT STATIN-INDUCED MUSCLE INJURY

Historically, rhabdomyolysis was most commonly produced by crushing injuries of the muscle and extreme exertion. Medications were an unusual cause of this syndrome prior to statin therapy. The FDA Adverse Event Reporting System database contains 601 cases of statin-associated rhabdomyolysis from November 1997 through March 2000.²⁹ The percentage of total cases associated with each drug were as follows: for simvastatin, 36%; cerivastatin, 32%; atorvastatin, 12%; pravastatin, 12%; lovastatin, 7%; and fluvastatin, 2%, demonstrating that rhabdomyolysis had been associated with each of the then-available statins.²⁹ We identified 3339 cases of statin-associated rhabdomyoly-

Table 1. Reported Rates of Statin-Associated Muscle Complaints in Controlled Studies*

Symptoms	Placebo	Statin
Lovastatin, 40 mg twice per day		
Sample size	1663	1649
Cramps, %	0.5	1.0
Myalgia, %	1.7	3.0
Pravastatin, dose not specified		
Sample size	411	900
Myalgia, %	1.0	2.7
Simvastatin, 20-40 mg/d		
Sample size	2223	2221
Myalgia, %	1.3	1.2
Fluvastatin, dose not specified		
Sample size	960	2326
Myalgia, %	4.5	5.0
Atorvastatin, 10 mg/d		
Sample size	270	863
Myalgia, %	1.1	3.2
Cerivastatin, dose not specified		
Sample size	702	2231
Myalgia, %	2.3	2.5

*Data are adapted from the *Physicians' Desk Reference*.²⁶

sis in our review of the Qscan FDA database from January 1, 1990, through March 31, 2002 (TABLE 2).

To ensure comparability with prior searches,²⁹ we repeated the search from November 1997 through March 2000 and identified 612 cases, suggesting that both search techniques provide comparable data. In our expanded search, cerivastatin (57%) was the most commonly implicated statin, followed by simvastatin (18%) and atorvastatin (12%). Approximately half of the cases occurred in patients 51 to 75 years old, with an additional 17% occurring in patients older than 75 years. The reactions were relatively severe, with a total of 64% of patients either requiring hospitalization or having a life-threatening reaction. Death occurred in 7.8% of patients. These data rely on voluntary physician reporting and do not use a uniform definition of rhabdomyolysis. The effect of these vagaries on the results is unknown, but these data provide some insight into the magnitude of the problem.

The incidence of fatal rhabdomyolysis through May 2001 has been esti-

Table 2. FDA Reports of Rhabdomyolysis, January 1, 1990–March 31, 2002

Drugs	No. of Reports	Reports of Rhabdomyolysis Due to Drug, %	Adverse Event Reports With Drug Due to Rhabdomyolysis, %	Age, %, y*				Outcomes, %*				
				<30	31-50	51-75	>75	Death	Disability	Hospitalization	Life	
											Threatening	Other
Cerivastatin	1899	56.9	27.7	0.3	5.5	48.4	19.9	7.2	3.4	56.7	8.2	17.3
Simvastatin	612	18.3	16.8	0.6	9.3	59.5	18.3	8.0	7.4	51.5	13.9	10.6
Atorvastatin	383	11.5	18.0	1.0	11.7	53.0	10.4	9.5	2.6	45.1	9.7	25.9
Pravastatin	243	7.3	15.7	0.4	8.2	48.6	14.4	7.9	5.9	58.5	10.1	11.8
Lovastatin	147	4.4	20.4	1.4	6.1	61.2	6.1	10.9	7.1	50.3	14.2	8.7
Fluvastatin	55	1.6	19.6	0	1.8	54.5	20.0	4.6	6.9	49.4	13.8	13.7
Total	3339	100		0.5	7.2	51.0	17.4	7.8	4.5	53.6	10.4	16.0

*Percentages for age distribution and outcomes do not sum to 100% because of unreported data.

mated using databases from the FDA and National Prescription Audit Plus (IMS Health, Fairfield, Conn) and is low at only 0.15 deaths per 1 million prescriptions.⁸ The estimated incidence rates (per 1 million prescriptions) for the various statins are as follows: lovastatin, 0.19; pravastatin, 0.04; simvastatin, 0.12; fluvastatin, 0; atorvastatin, 0.04; and cerivastatin, 3.16. The death rate for cerivastatin was 16 to 80 times greater than the other statins, but there were no apparent differences among the other agents.⁸ These incidence figures are also likely to underestimate the risk because they are also based on voluntary reporting by health care professionals and use as the denominator the number of prescriptions, not the number of individuals using the medication.

Clinical trial results support a low incidence of severe muscle problems with statin therapy (TABLE 3). A compilation of all randomized controlled statin trials identified by our search revealed that among 83 858 patients randomly assigned to receive either statin treatment or placebo, there were only 49 cases of myositis and 7 cases of rhabdomyolysis in the statin treatment groups vs 44 cases of myositis and 5 cases of rhabdomyolysis among placebo controls (Table 3). The Heart Protection Study randomized 20 536 patients to simvastatin, 40 mg/d, or placebo.²⁵ Creatine kinase levels were measured in patients with unexplained muscle complaints and in those using a nonstudy statin during the 3 first-year visits. Over the mean 5 years

of the study, 32.9% of the simvastatin and 33.2% of the placebo participants complained of unexplained muscle pain or weakness during at least 1 of the 3 first-year or subsequent biannual visits. Nevertheless, only 49 (0.48%) of 10 269 statin patients and 50 (0.49%) of 10 267 control patients discontinued treatment because of muscle symptoms. Rhabdomyolysis, defined as CK values greater than 40 times the ULN, occurred in 5 statin and 3 placebo participants, although 1 of the latter was taking a nonstudy statin. Study drug was stopped when CK levels were greater than 10 times the ULN but continued with lower CK levels and the CK value was remeasured approximately 1 week later. Persistent CK elevations of greater than 4 times the ULN occurred in 7 (0.07%) statin patients and 1 (0.01%) placebo patient ($P=.07$). These controlled study results document the low incidence of important muscle complaints with statin therapy. However, these results in volunteer study participants who were followed by lipid researchers may underestimate the incidence when statins are used in unselected populations followed with less precision.

The risk of rhabdomyolysis with statins increases with serum concentrations of the medications.⁵⁸ Factors affecting the volume of distribution, such as body size and sex, as well as factors reducing drug metabolism, such as renal and hepatic function, age, hypothyroidism, debilitation, and diabetes, alter the risk of rhabdomyolysis.⁵⁹ Concomitant medications also affect the

rhabdomyolysis risk, primarily by altering statin catabolism (BOX). Of the 601 cases of statin-induced rhabdomyolysis submitted to the FDA between November 1997 and March 2000, approximately 55% were associated with drugs affecting statin metabolism, including mibefradil (16%), fibrates (13%), cyclosporine (8%), macrolide antibiotics (7%), warfarin (5%), digoxin (4%), and azole antifungals (2%).²⁹ In our review of the Qscan FDA database from January 1, 1990, through March 31, 2002, approximately 58% of cases were associated with concomitant medications affecting statin metabolism, including mibefradil (2%), fibrates (38%), cyclosporine (4%), macrolide antibiotics (3%), warfarin (4%), digoxin (5%), and azole antifungals (1%).

Such drug interactions are generally attributed to effects on the cytochrome P-450 (CYP) 3A4 system.⁵⁸ Lovastatin, simvastatin, and atorvastatin are primarily metabolized by CYP 3A4,⁵⁸ with nearly complete metabolism for lovastatin and simvastatin on the first hepatic pass. Pravastatin has minimal metabolism by CYP 3A4 and is primarily cleared by the kidneys. Fluvastatin is metabolized by CYP 2C9 and cerivastatin is metabolized by both the CYP 3A4 and CYP 2C8 systems.⁵⁸ Medications that inhibit CYP 3A4, such as macrolide antibiotics, azole antifungals, and cyclosporine, increase serum concentrations of selected statins and risk of rhabdomyolysis. Individual variation is important because CYP 3A4 activity can vary 10-fold among patients,⁶⁰ and this large varia-

tion may result from genetic polymorphisms of these enzymes.⁶¹

Mechanisms other than CYP 3A4 inhibition also contribute to drug interactions with statins. There has been considerable marketing emphasis placed on the lipophilicity vs hydrophilicity of the various statins. Passage across the cell membrane requires either a high de-

gree of lipid solubility or active transport. Transmembrane transport for statins is mediated by the organic anion transporter polypeptide 2.⁶² This protein is present on hepatic cells but absent on human myocytes.⁶² Passage into the muscle cell is therefore dependent on passive diffusion and may increase with the lipophilicity of the statin. Hy-

drophilic statins such as pravastatin are less likely to enter the muscle, theoretically reducing the risk of muscle injury. However, egress from cells also depends on statin solubility and can affect drug interactions. Hydrophilic agents require transport out of the cell via such proteins as the multidrug resistance protein 2 (MRP2), also known as the cana-

Table 3. Myopathy in Randomized Controlled Trials of Statin Therapy

Studies*	Type of Patients†	Duration, y	Statin Dosage, mg/d	No. of Patients		No. With Rhabdomyolysis		No. With Myositis‡		% With CK Elevation		% With Myalgia	
				Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
Lovastatin													
AFCAPS/ TexCAPS ⁴	No CAD	5.2 (Mean)	20-40	3304	3301	1	2	21	21	NR			NR
FATS ³⁰	CAD (men)	2.5	20 (×2)§	38	46	NR		NR		NR			NR
CCAIT ³¹	CAD	2	40-80	165	166	NR		NR		NR			NR
Post-CABG ³²	CAD	4.3 (Mean)	76 (Mean)§	628	628	0	0	NR		0.64	0.15		NR
Pravastatin													
CARE ^{2,37}	CAD	5 (Median)	40	2078	2081	0	0	0	4	0.57	0.33		NR
WOSCOPS ³	No CAD (men)	4.9 (Mean)	40	3302	3293	0	0	NR		0.09	0.03	3.5	3.7
PLAC-I ³³	CAD	3	40	206	202	0	0	0	0	NR			NR
PLAC-II ³⁴	CAD	3	10-40	75	76	NR		NR		NR			NR
REGRESS ^{35,36}	CAD	2	40	323	330	0	0	0	0	NR		0.3	0
PREDICT ³⁸	CAD	0.5	40	347	348	NR		NR		NR			NR
LIPID ³⁹	CAD	6.1 (Median)	40	4512	4502	0	0	8	10				NR
L-CAD ⁴⁰	CAD	2	NR§	70	56	NR		NR		NR			NR
GISSI-P ⁴¹	CAD	0.4 (Median)	20-40	2138	2133	0	0	NR		NR			NR
PRINCE ⁴²	No CAD	0.5	40	666	673	NR		NR		NR			NR
ALLHAT-LLT ⁴³	Both	4.8 (Median)	40	5170	5185	NR		NR		NR			NR
PROSPER ⁴⁴	Both, aged 70-82 y	3.2 (Mean)	40	2891	2913	0	0	0	0	NR		1.2	1
FAST ⁴⁵	No CAD	2	10	83	81	NR		NR		NR			NR
Simvastatin													
4S ¹	CAD	5.4 (Median)	10-40	2221	2223	1	0	6	1	NR			NR
CIS ⁴⁶	CAD	2.3 (Mean)	40	129	125	NR		NR		NR			NR
Wenke et al ⁴⁷	Heart transplantation	4	10 (Mean)	35	37	0	0	0	0	0	0		NR
Heart Protection Study ²⁵	Both	5 (Median)	40	10 269	10 267	5	3	11	6	0.19	0.13	32.9	33.2
Fluvastatin													
LCAS ⁴⁸	CAD	2.5	20 (×2)§	214	215	0	0	1	2	NR			NR
LISA ⁴⁹	CAD	1	40-80	187	178	0	0	0	0	0	0.56		NR
FLARE ⁵⁰	CAD	0.8	40	409	427	0	0	0	0	NR			NR
Holdaas et al ⁵¹	Renal transplantation	0.2	40	182	182	0	0	0	0	4.9	3.8		NR
Atorvastatin													
AVERT ^{52,53}	CAD	1.5	80	164	177	0	0	0	0	0	0	1.2	1.2
MIRACL ⁵⁴	CAD	0.3	80	1538	1548	0	0	0	0	NR			NR
GAIN ⁵⁵	CAD	1	33 (Mean)	65	66	0	0	0	0	NR			NR
GREACE ⁵⁶	CAD	3 (Median)	10-80	800	800	0	0	0	0	NR			NR
Cerivastatin													
ENCORE ⁵⁷	CAD	0.5	0.4	114	119	NR		2	0	0.61	0.58		NR
Total				42 323	41 535	7	5	49	44				

Abbreviations: CAD, coronary artery disease; CK, creatine kinase; NR, not reported.

*See references for explanations of study abbreviations.

†“Both” indicates both patients with and without CAD.

‡Myositis was defined by study investigators or as a CK elevation of greater than 10 times the upper limit of normal.

§Plus another medication.

Box. Concomitant Medications That Increase Risk of Statin-Associated Myopathy*

Fibric acid derivatives, especially gemfibrozil
 Niacin
 Cyclosporine
 Azole antifungals
 Macrolide antibiotics
 Human immunodeficiency virus protease inhibitors
 Nefazodone
 Verapamil and diltiazem
 Amiodarone
 Grapefruit juice, >1 qt/d

*Data are adapted from Pasternak et al.¹¹

licular multispecific organic anion transporter.⁶³ Pravastatin is not metabolized by CYP 3A4, but its serum levels increase with cyclosporine,⁶⁴ a CYP 3A4 inhibitor, possibly because cyclosporine also inhibits MRP2 activity⁶⁵ and may reduce hepatic excretion. Little is known about egress of statins from skeletal muscle, but MRP is detectable in muscle cells⁶⁶ and its inhibition by other agents may contribute to myopathy with the more water-soluble statins.

Gemfibrozil is known to increase the risk of rhabdomyolysis with statin therapy,^{59,67} but it does not inhibit the P-450 system and probably affects statin concentrations via the recently described glucuronidation pathway.⁶⁸ All statins except simvastatin and lovastatin are administered as their active hydroxy acid forms. Simvastatin and lovastatin are administered as the delta lactone and are converted to the active acid metabolite.⁶⁸ The active statin form has previously been thought to undergo metabolism primarily by the P-450 system. Recent *in vivo* evidence demonstrates that the active acid forms of simvastatin, atorvastatin, and cerivastatin can be metabolized to an unstable glucuronide that rapidly and spontaneously converts to the inactive statin lactone.⁶⁸ The glucuronidation pathway thus appears to provide an additional mechanism for eliminating active statin.

The glucuronidation process was not previously detected and, therefore, not considered a major pathway of statin clearance because of the instability of the glucuronide. Recent data indicate that gemfibrozil inhibits this glucuronidation of statins, thereby increasing the concentration of the active statin acid forms of simvastatin, atorvastatin, and cerivastatin.⁶⁹ This inhibition by gemfibrozil is most marked for cerivastatin, which is also the statin with the greatest risk of muscle injury alone or with gemfibrozil. In contrast, published⁷⁰ and preliminary⁷¹ data suggest that fenofibrate has little effect on the glucuronidation of cerivastatin, simvastatin, atorvastatin, and rosuvastatin, a statin not yet available for clinical use.

MECHANISMS OF STATIN-INDUCED MUSCLE INJURY

Little is known regarding how statins produce muscle injury, but several theories have been proposed based on the biosynthetic pathways inhibited by statins, as discussed elsewhere.⁷² One theory maintains that blocking cholesterol synthesis reduces the cholesterol content of skeletal muscle cell membranes, making them unstable. This concept is supported by observations of muscle injury with clofibrate^{73,74} and niacin.^{12,75} Blocking cholesterol synthesis with squalene synthase inhibitors, however, does not produce myotoxicity in *in vitro* models, suggesting that other compounds produced by HMG-CoA reductase activity are responsible.⁷⁶

Two other theories maintain that reduced levels of isoprenoids, such as ubiquinone, or regulatory proteins are responsible for the muscle injury. Statins and HMG-CoA reductase inhibition block production of farnesyl pyrophosphate⁷⁶ (FIGURE), an intermediary for the production of ubiquinone that is required for the activation of small guanosine triphosphate (GTP)-binding regulatory proteins. Ubiquinone, or coenzyme Q10, is a steroid isoprenoid that participates in electron transport during oxidative phosphorylation in mam-

malian mitochondria. Ubiquinone is fat soluble, and approximately 50% of the body's ubiquinone is thought to be obtained through fat ingestion, whereas 50% is derived from endogenous synthesis.⁷⁷ Serum ubiquinone levels decrease with statin treatment. For example, hypercholesterolemic patients treated with a low-fat diet plus 20 mg/d of simvastatin, pravastatin, or placebo experienced reductions in serum ubiquinone levels of 54%, 50%, and 17%, respectively.⁷⁷ Levels of LDL-C decreased 29%, 21%, and 11% with simvastatin, pravastatin, and placebo treatment, respectively,⁷⁷ and this probably accounts for some of the decrease in ubiquinone since ubiquinone is transported in the LDL particle. In contrast with serum ubiquinone concentrations, intramuscular levels of ubiquinone are not reduced by statin treatment.⁷⁸⁻⁸⁰ Such observations make it unlikely that decreases in ubiquinone metabolism cause muscle complaints with statin therapy, but tissue levels were not determined in symptomatic patients.

There is other evidence that supports a role for ubiquinone depletion in producing statin myopathy. The ratio of lactate to pyruvate is higher in statin-treated patients, suggesting a shift toward anaerobic metabolism and possible mitochondrial dysfunction.⁸¹ Mitochondrial dysfunction has recently been demonstrated by biopsy studies of individuals with muscle complaints without CK elevations, but intramuscular ubiquinone levels were not reported.²⁷ Ubiquinone deficiency has been documented in some forms of congenital mitochondrial encephalopathy, which responded to quinone therapy,⁸² and there is at least 1 case report of the mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome induced by statin treatment that responded to ubiquinone replacement.⁸³ Finally, there are 2 US patents, 1 of which is registered by a Nobel Prize-winning lipid expert, for using ubiquinone to manage statin-induced myopathy.^{84,85}

More recent work, however, suggests that a reduction in small GTP-

binding proteins participates in the myotoxicity of statins. Both pravastatin and lovastatin reduce protein synthesis in neonatal rat myocytes.⁷⁶ This effect is reversed by adding farnesol and geranylgeraniol to the cultures, whereas reducing cholesterol levels with squalene synthase inhibitors produces only minimal cytotoxicity. Such results suggest that depletion of the mevalonate metabolites (farnesol and geranylgeraniol), not cholesterol, participates in statin-induced myotoxicity.

Farnesyl and geranylgeranyl pyrophosphate activate certain regulatory proteins via prenylation, the addition of a specific carbon structure to a protein.⁸⁶ Important regulatory proteins that are activated by prenylation are small GTP-binding proteins, such as Ras, Rac, and Rho, which promote cell maintenance and growth and attenuate apoptosis.⁸⁷⁻⁸⁹ Blocking production of farnesyl pyrophosphate would prevent the prenylation of the small GTP-binding regulatory proteins, thus inhibiting their action. Apoptosis, or programmed cell death, is a critical mechanism designed to assist in the remodeling and maintenance of tissue structure. When inappropriately activated, however, apoptosis can produce pathological conditions.

Atorvastatin, lovastatin, and simvastatin produce a dose-dependent increase in apoptosis in vascular smooth muscle cells (VSMCs).⁹⁰ This effect is reversed by mevalonate, farnesyl pyrophosphate, and geranylgeranyl pyrophosphate, but not by ubiquinone or squalene. Pretreatment of VSMCs treated with statins sensitizes the myocytes to apoptotic agents, an effect that is also prevented by treatment with mevalonate or geranylgeranyl pyrophosphate.⁹¹ These results document that statins enhance apoptosis, at least in VSMCs.

Apoptosis produced by statins could reduce the enlargement of atherosclerotic plaques by reducing VSMC proliferation, but apoptosis in skeletal muscle cells with HMG-CoA reductase inhibitors could produce the muscle damage observed with statins. Simvastatin but not squalene epoxy-

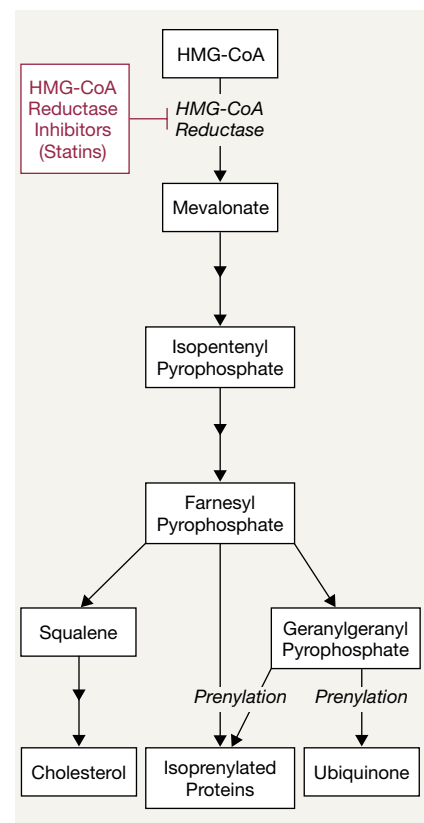
dase inhibitors reduced actin fiber formation in L6 myoblasts and produced apoptotic cell death in differentiated L6 muscle fibers.⁹² Nevertheless, additional work is required to demonstrate whether reduced production of GTP-binding proteins and an increase in apoptosis produces the myotoxicity of statin therapy.

That statin-induced skeletal muscle injury involves inhibition of pathways that activate GTP may explain why exercise appears to unmask the negative effects of statins on muscle in some patients. Exercise has been shown to activate signaling pathways, particularly the mitogen-activated protein kinase pathways that are important in the skeletal muscle cellular response to exercise stress.^{93,94} These pathways are regulated by the GTP-binding proteins. Thus, statins may impair the muscle's ability to appropriately respond and recover from physical exertion, resulting in skeletal muscle damage.

MANAGEMENT OF STATIN-RELATED MUSCLE COMPLAINTS

Expert consensus guidelines for the management of statin-related muscle complaints have been presented.¹¹ Prevention is the best approach to managing statin-related myopathy. This includes using the lowest statin dose required to achieve therapeutic goals and avoiding, when possible, concomitant therapy with drugs known to increase the risk of myopathy.¹¹ Patients should be instructed on the importance of discontinuing the medication and promptly reporting unexpected muscle pain or weakness or discoloration of urine. Many patients who presented with rhabdomyolysis and renal failure ignored such early signs of myopathy. Health care professionals should also not ignore such complaints, especially if accompanied by increased CK levels. Consideration should be given to discontinuation of statins before events that may exacerbate muscle injury, such as surgical procedures,⁹⁵ or prodigious amounts of physical exertion, like marathon running.¹⁸

Figure. Products of the Mevalonate Pathway Possibly Affected by HMG-CoA Reductase Inhibitors (Statins)



3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) prevent the conversion of HMG-CoA to mevalonate.⁴⁹

Much has been made of the risk of myopathy among the statins based on their water solubility or potency in reducing LDL-C. There is no clinical or epidemiological evidence that permits differentiation among the statins as to their myotoxicity potential.¹¹ For example, the estimated incidence of fatal rhabdomyolysis in the FDA database is low at 0.04 cases per 1 million prescriptions for both pravastatin and atorvastatin,⁸ despite that pravastatin is the most hydrophilic and atorvastatin is the most powerful of the available statins. This suggests that factors other than hydrophilicity or potency in reducing LDL-C affect the myopathic process.

There is no absolute contraindication to combining a statin with an agent known to increase the risk of myopa-

thy if the benefits of combined therapy are likely to outweigh the risks.¹¹ Such combination therapy with a statin and a fibrate or niacin is often required in patients with high serum levels of both LDL-C and triglycerides. Similarly, transplant recipients and patients with HIV infection frequently develop hyperlipidemia from immunosuppressive⁹⁶ or antiviral therapy,⁹⁷ respectively. These patients may require statin therapy and even therapy with a statin and a fibrate or niacin, despite the fact that cyclosporine and protease inhibitors increase the risk of rhabdomyolysis.¹¹ In such cases, the patient must understand the risks of the therapy and be willing to promptly report any untoward reactions. We generally select atorvastatin or pravastatin for such combined therapy because these agents appear to have a low incidence of rhabdomyolysis,^{8,29} although the available data do not permit firm conclusions.⁸ Also, Merck & Co has recently altered its labeling to state that simvastatin doses should not exceed 10 mg/d when combined with cyclosporine, fibrates, or more than 1 g/d of niacin, or 20 mg/d with concomitant verapamil or amiodarone therapy.⁹⁸

Ezetimibe is a recently approved inhibitor of intestinal cholesterol absorption that can be used in combination with statins without increasing the risk of myopathy. Ezetimibe produces an average additional 14% reduction in LDL-C when combined with simvastatin in various doses.⁹⁹

Management of rare cases of frank rhabdomyolysis requires stopping the drug and initiating appropriate medical maneuvers to support the patient during this crisis. There are reports of restarting a lower dose of the offending statin or switching to a different statin after an episode of rhabdomyolysis,⁵⁸ although this should be avoided if at all possible and strong consideration given to using other lipid-lowering agents.

Routine measurement of CK levels in asymptomatic patients before or during statin treatment is not required,¹¹ although some experts recommend base-

line CK measurement to facilitate evaluation of subsequent muscle complaints,¹¹ and many physicians do monitor CK levels. There is also no need to discontinue statin therapy in asymptomatic patients whose CK levels are elevated but not more than 10 times the ULN.¹¹ These patients should be warned to stop the drug promptly and to contact their physician if they do become symptomatic or notice dark discoloration of their urine. Thyroid function should be evaluated to exclude hypothyroidism as a contributing factor.^{11,23} Even though we do not routinely monitor CK levels, we do initiate CK monitoring in asymptomatic patients if the CK is somehow detected to be more than 5 times the ULN. We also reevaluate the individual's benefits of statin therapy and are more likely to continue these medications in patients with established vascular disease or an estimated cardiovascular risk equivalent to that of patients with established disease.¹⁰⁰ We also stop the statin treatment if CK is elevated to more than 10 times the ULN, although some experts recommend only "strong consideration" to stopping the medication in this instance in asymptomatic patients.¹¹

Patients complaining of myalgias without elevated CK levels can continue the medication if their symptoms are tolerable.¹¹ If the symptoms are not tolerable or are progressive, the offending agent should be stopped. We advise waiting until the patient is totally asymptomatic and then trying another statin, since some patients will not have a recurrence of their complaints with a different drug. However, many patients do redevelop muscle complaints, often considerably earlier with the second drug, suggesting that the statins have depleted some metabolite in skeletal muscle. Additional different statins can be tried,²³ but this is often not well tolerated, and some other class of lipid-lowering medication, such as bile sequestrant resins, niacin, or ezetimibe, should be used instead of a statin.

CONCLUSION

Statins are the most effective therapeutic agents for reducing LDL-C and have

been documented to reduce the incidence of cardiac events in diverse patient groups. The major clinical complication to their use is a variety of muscle complaints ranging from myalgia to rhabdomyolysis. The incidence of fatal rhabdomyolysis with these agents is low, but the frequency of less-severe muscle complaints is not well defined. Impaired hepatic and renal function, hypothyroidism, diabetes, and certain concomitant medications increase the risk of clinically important myositis. The mechanism of statin-induced myopathy has not been determined but may relate to reduced levels of small proteins involved in myocyte maintenance. Prevention and early recognition of statin myopathy is critical to preventing serious sequelae.

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