PEER REVIEWED LETTER

Metabolic Myopathies Discovered During Investigations of Statin Myopathy

Steven K. Baker, Georgirene D. Vladutiu, Wendy L. Peltier, Paul J. Isackson, Mark A. Tarnopolsky

Can. J. Neurol. Sci. 2008; 35: 94-97

The statins have emerged as the dominant class of drug for the treatment of hypercholesterolemia. These medications are generally well tolerated. However, myalgias, the most frequent side-effect, occur in up to 7% of patients.[1] Transaminitis and skeletal myotoxicity, with elevated serum creatine kinase (CK) levels (i.e., >10 times the upper limit of normal), occur with reported frequencies of 1% and 0.1%, respectively.[2] Various hypotheses have been proposed to explain the relationship between statin therapy and the spectrum of muscle dysfunction manifested by myalgia, myopathy, and rhabdomyolysis.

Statin-mediated inhibition of mevalonate metabolism impairs the synthesis of isoprenylated products–the most notable of which is ubiquinone. However, isoprenylation is responsible for the post-translational modification of up to 2% of cellular proteins.[3] Therefore, numerous metabolic pathways are potentially modified by statin-mediated hypoprenylation. Subclinical defects in one or more energy-deriving pathways may be unmasked upon exposure to the pleotropic effects of statins. Such pharmacogenomic synergism may underlie the development of "statin myopathy" in a subset of patients. In this regard, we describe four patients with mutations in the myophosphorylase (*PYGM*; MIM 232600), myoadenylate deaminase (*AMPD1*; MIM 102770), and carnitine palmitoyltransferase (*CPT2*; MIM 600650) genes whose diagnoses became apparent during the course of investigations for statin-induced myalgias and hyperCKemia.

Case Reports

Patient A, a 70-year-old Italian male, was found to have a high CK activity (416 U/L) on routine blood work approximately one year following initiation of cerivastatin. A repeat CK measured 1516 U/L and the statin was discontinued after which the CK dropped to 287 U/L five months later. Over the next eight months his CK remained elevated with the nadir of 488 U/L. He consistently reported proximal muscle aches with slight weakness on stair climbing and easy fatigability with moderate intensity activities. These symptoms were exaggerated during statin exposure and improved after discontinuation of the statin and coincident coenzyme Q10 supplementation (60 mg twice daily). Neurologic examination was normal. Specifically, there was no evidence of ptosis, ophthalmoparesis, dysphagia, or neck extensor weakness. Muscle stretch reflexes and sensation were intact. He manifested mild hip flexor weakness. Nerve conduction studies and electromyography (EMG) were normal. Ergometry and forearm ischemic testing were not performed. Periodic acid Schiff reaction demonstrated increased glycogen. Muscle histochemistry revealed absent staining for myophosphorylase activity. Neither ragged-red nor cytochrome oxidase negative fibers were observed. Oil red O staining revealed normal intramyocellar lipid content. Routine adenosine triphosphatase staining did not reveal type I fiber atrophy. Rare mitochondrial paracrystalline inclusions were evident with electron microscopy. Glycogen granule accumulation was noted in the subsarcolemmal and intermyofibrillary compartments. Mutation analysis demonstrated homozygosity for the R50X mutation in exon 1 of the *PGYM* gene at chromosome 11q13 confirming a diagnosis of McArdle disease and carrier status for the Q12X mutation in exon 2 of the *AMPD1* gene on chromosome 1p21-13 was found [4].

Patient B, a 53-year-old athletic man with a history of essential hypertension and familial hypercholesterolemia, reported exercise intolerance, exertional cramps, and fatigue three months after initiating atorvastatin therapy (20 mg). The initial CK was elevated at 2,990 U/L and subsequently declined to normal several weeks after discontinuation. Symptoms persisted and he experienced mild CK elevations in response to day-surgery and *E. Coli* gastroenteritis.

There was no family history of neuromuscular disease and his physical examination was normal. Screening blood work revealed normal values for the following: erythrocyte sedimentation rate, complete blood count, electrolytes, lactate, pyruvate, homocysteine, anti-nuclear antibody, and carnitine levels (free, esterified, and total). Electrophysiologic studies demonstrated normal sensory and motor nerve function. Subtle small brief early recruiting motor unit action potentials were observed in proximal muscles on needle electromyography. Biopsy of the right vastus lateralis revealed mild variability in fiber size and rare ring fibers. There was dense uptake of

From the Department of Medicine (SKB), Department of Pediatrics (MAT), Neuromuscular Disease Clinic, McMaster University, McMaster University Medical Center, Hamilton, Ontario, Canada; Departments of Pediatrics, Neurology, and Pathology (GDV, PJI), School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, New York; Department of Neurology (WLP), Medical College of Wisconsin, Milwaukee, Wisconsin, USA.

Received January 24, 2007. Final Revisions Submitted October 16, 2007.
Reprint requests to: S. K. Baker, Department of Medicine (Physical Medicine & Neurology, Rm 2H22), McMaster University, Hamilton, Ontario, L8N 3Z5, Canada.

oxidative enzymes in the subsarcolemmal space of several fibers. Electron microscopy demonstrated marked mitochondrial proliferation and numerous paracrystalline inclusions. Biochemical analyses of intramuscular carnitine, myoadenylate deaminase, carnitine palmitoyltransferase (CPT) II, myophosphorylase, and mitochondrial oxidative enzymes were normal. Mutation analysis demonstrated heterozygosity for the R50X mutation in exon 1 of the *PYGM* gene at chromosome 11q13. Carrier status for McArdle disease was confirmed in leukocyte-derived DNA [4].

Patient C, a 58-year-old male, was noted to have asymptomatic hyperCKemia (1,045 U/L) on routine surveillance two months after starting atorvastatin (20 mg). His baseline CK was 266 U/L (N < 220 U/L). The atorvastatin was discontinued and his CK renormalized. Ezetimibe was trialed with no adverse effects. After approximately ten months of therapy his CK was found to be significantly elevated at 4,448 U/L. His CK normalized to 225 U/L within three weeks while remaining on ezetimibe. Similar monophasic rises were noted on two further occasions (i.e., 991 → 289 U/L and 1512 → 251 U/L). These fluctuations corresponded to sporadic exercise training.

Neurologic examination did not demonstrate ptosis, ophthalmoparesis, dyphagia, nor sensorimotor deficit. Muscle stretch reflexes, balance, and coordination were normal. Exercise intolerance was not documented on clinical history and therefore exercise testing was not performed. Nerve conduction studies were normal. Needle EMG in selected lower extremity muscles was unremarkable. A needle biopsy of *m. vastus lateralis* revealed normal fiber size/shape variability associated with mild nuclear internalization. There was no inflammatory infiltrate or vasculitis. Adenosine triphosphatase staining revealed normal type 1 and 2 fibers without grouping or type atrophy. Histochemical staining for myophosphorylase activity was normally reactive whereas myoadenylate deaminase was non-reactive. Staining for cytochrome oxidase, succinate dehydrogenase, Gomori trichrome, periodic acid Schiff, and Oil Red O revealed normal staining patterns. Electron microscopy showed normal sarcoplasmic Z-band architecture. There was no subsarcolemmal, intermyofibrillary nor vacuolar glycogen accumulation. In light of the staining abnormality, screening for potential subclinical molecular defects, in the three most common genes responsible for metabolic myopathies, was undertaken.[4] Homozygous mutations in the common cosegregating tandem mutations, Q12X and P48L, were identified in *AMPD1* confirming myoadenylate deaminase deficiency.

Patient D, a 65-year-old male, was placed on pravastatin (40 mg) after 3-vessel coronary artery bypass grafting. Within six months he developed lower extremity cramping, myalgia, and fatigue. The finding of moderate CK elevation prompted a switch to simvastatin (20 mg) without symptom resolution. Although initially normal (212 U/L) his CK rose to 980 U/L after an additional six month interval. A trial of rosuvastatin (20 mg) perpetuated his myalgias and cramping even with alternate day dosing. His CK remained elevated at 598 U/L. Finally, ezetimibe (10 mg) replaced rosuvastatin, the CK normalized to 138 U/L, and his symptoms improved.

Neurologic examination was within normal limits showing no evidence of craniobulbar, peripheral nerve or muscle dysfunction. A limited needle EMG showed occasional fibrillations and positive sharp waves in the left tibialis anterior. A needle biopsy of m. vastus lateralis revealed no abnormalities. Direct sequencing of the *CPT2* gene demonstrated a single defective allele harboring an F352C mutation.

Discussion

Statin myopathies are a heterogeneous group of disorders ranging from trivial myalgias to rhabdomyolysis. Multiple mechanisms presumably account for this phenotypic diversity. While clues to the pathogenesis of statin myopathy have recently emerged with the reports of polymorphisms in a variety of genes including CYP2D6,[5] OAT3,[6] COQ2,[7] and serotonin receptors (3B and 7)[8] our knowledge gap remains substantial. Calcium dysregulation has been implicated in myotoxicity as statins (1) increase cytoplasmic and sarcoplasmic reticulum (SR) calcium levels,[9] (2) regulate SR-calcium-adenosine triphosphatase expression,[10] and (3) induce calcium-dependent mitochondrial permeability transition pore formation.[11] Eccentric exercise upregulates components of the ubiquitin-proteosome pathway in statin-exposed muscle but this mechanism fails to explain symptoms in sedentary patients. G-protein hypoprenylation may be an important mechanism of statin toxicity as both farensylated Ras[12] and geranylgeranylated Rab[13] have been implicated in the development of myopathy.

It has been previously suggested that latent mitochondrial dysfunction renders muscle more vulnerable to the coenzyme Q10 (ubiquinone) depleting potential of statin therapy.[14] This notion is supported by reports of statins triggering a mitochondrial, encephalomyopathy, lactic acidosis stroke-like epidsodes (MELAS) syndrome in two patients[15,16] and lactic acidosis in another.[17] There is biochemical rationale for statin-mediated cellular energy dysfunction as inhibition of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase in the cholesterol biosynthetic pathway lowers mevalonate and its distal isoprenoid metabolites including ubiquinone. The redox activity of ubiquinone's quinoid moiety is critically dependent on the ten isoprenoid tail units, which confers mobility within the hydrophobic inner mitochondrial membrane enabling electron shuttling in the respiratory chain. Indeed, cases A and B manifested paracrystalline inclusions which represent the crystallized form of dimeric mitochondrial creatine kinase under conditions of oxidative stress. However, this often cited mechanism may be overly simplistic given the report of ezetimibe-induced rhabdomyolysis in a sedentary patient with McArdle disease.[18] Ezetimibe inhibits the intestinal cholesterol transporter Niemann-Pick C1-Like 1 protein and has no known effect on isoprenoid synthesis.[19]

In contrast to a previous report of complete reversal of a statin myopathy after coenzyme Q10 therapy,[20] patient A had a noticeable but incomplete response and continued to manifest hyperCKemia secondary to genetically confirmed McArdle disease. The finding of statin myopathies in patients harboring single mutant alleles in genes encoding either myophosphorylase and CPT II suggests that sub-clinical inborn errors of metabolism may be permissive in the development of myotoxic reactions. Similarly, a more benign metabolic defect of muscle–myoadenylate deaminase deficiency may be susceptible to statins only in the homozygous state.[4] We have recently found

Table: Neuromuscular disorders disclosed by statin exposure

Disease	Age/Gender	Statin	Dose (mg)	Duration	Symptoms	CK (U/L)	Ref
MHS	44 male	atorvastatin cerivastatin	NA	24 mo	C, F	523	31
	49 male	atorvastatin	NA	14 mo	C, F	390	31
	51 female	atorvastatin	10	6 mo	R, M	1132	32
GSD5	69 male	simvastatin	10	>4 yrs	F, M, W, R	400-40000	33
	62 male	simvastatin	20	~2 yrs	F, R	320-4400	33
	70 male	cerivastatin	0.3	1.5 yrs	W	700-1500	4
	54 male	atorvastatin	NA	>3 yrs	C, M	>2200	[4]
GSD2	34 male	simvastatin	NA	<1 mo	C, AP	1500	35
MADA	60 male	lovastatin	NA	NA	M, W, C	1100	4
	72 male	atorvastatin	NA	NA	M, W, R	>2200	4
	58 male	atorvastatin	NA	NA	M, R	~2200	4
	49 male	lovastatin	NA	NA	F, R	~2200	4
	46 male	lovastatin	NA	NA	F, R	~2200	4
	68 female	cerivastatin	NA	NA	M, W, R	>2200	4
	66 male	gemfibrozil	NA	NA	C, M, W	>2200	[4]
CPTII	51 male	cerivastatin	NA	NA	M, C, F, S	>2200	4
PM	69 male	pravastatin	10	2 wks	M, A, W	943	36
	75 male	simvastatin	20	4 mo	M, W, D, R	6010	37
DM	44 male	atorvastatin	10	1 yr	D, W, Ra	>2000	38
	68 male	pravastatin	40	~3 mo	D, W, Ra	2354	39
MG	67 female	atorvastatin	NA	3 mo	P, W, Di	normal	40
RMD	54 male	simvastatin	20	2 mo	Rp, M, P	158	41
DM1	48 male	pravastatin	20	3 mo	M, S, F	1130	34
MM	51 male	atorvastatin	40	18 mo	R, M, W, F	>45000	34
	63 female	simvastatin	20	8 mo	R, W, P, Di	20000	15
SBMA	58 male	pravastatin	40	<1 mo	W, C, Fs	850-1050	34

Disease: MHS, malignant hyperthermia susceptibility; GSD5, McArdle disease; GSD2, acid maltase deficiency; MADA, myoadenylate deaminase deficiency; CPTII, carnitine palmitoyltransferase deficiency; PM, polymyositis; DM, dermatomyositis; MG, myasthenia gravis; RMD, rippling muscle disease; DM1, myotonic dystrophy type 1; MM, mitochondrial myopathy; SBMA, Kennedy disease. Symptoms: A, arthralgias; AP, abdominal pain; C, cramps; CK, creatine kinase; D, dysarthria; Di, diplopia; F, fatigue; Fs, fasciculations; M, myalgia; NA, not available; P, ptosis; R, rhabdomyolysis; Ra, rash; Rp, rippling; S, stiffness; W, weakness.

that mutant alleles for McArdle disease (incidence: ~1/110,000[21]) and CPTII deficiency (incidence: ~1/291,000[4]) were respectively 20- and 11-fold more likely in statin intolerant patients than expected in the general population.[4]

The current case series permits speculation regarding the theory that inborn derangements of intermediary metabolism (i.e., glycolysis, β-oxidation, or purine nucleotide cycle) may render skeletal muscle more vulnerable to statin-mediated diminution of intramuscular coenzyme Q_{10} levels and metabolic activity. This "multiple pathway synergy" hypothesis is reinforced by the reports of combined partial deficiencies of CPT II and mitochondrial complex I causing hyperCKemia[22] and valproic acid unmasking a MELAS syndrome (i.e., fatty acid oxidation + oxidative phosphorylation).[23] A report of statin therapy producing symptomatic exacerbation in a patient with CPT II deficiency provides further support of multiple pathway interdependence.[24] Preliminary evidence of statin-mediated reductions in L-carnitine suggests that a pharmacogenomic disruption of a single pathway may be pathogenic.[4,25,26] Furthermore, statins impair mitochondrial respiration and reduce rates of β-oxidation and levels of intracellular long-chain fatty acids.[27,28] These effects may be mediated through activation of peroxisome proliferator-activated receptors (PPAR) α and γ.[28] The fibrates also activate PPARα and augment fatty acid metabolism. The combined influence on the PPAR system by statins and fibrates may offer a potential mechanism to explain their additive myotoxicity. Interestingly, fibrates have recently been shown to reduce mitochondrial complex I activity by approximately 20% offering another level of interaction between these two drug classes.[29] Thus the multiple pathway synergy model serves as a mechanism for both drug-drug and drug-gene interactions.

These cases reflect an emerging complexity in the diagnosis of statin myopathy and highlight the need for baseline CK

https://doi.org/10.1017/S0317167100007630 Published online by Cambridge University Press

measurement even though biopsy-proven myopathy can develop in the absence of CK perturbations.[30] The pleotropic metabolic effects of statins may be reflected in the broad spectrum of clinically and genetically diverse neuromuscular disorders that may be potentially unmasked upon statin exposure (Table). It is important to obtain a thorough neuromuscular history to determine if statin therapy may have unmasked a metabolic myopathy. However, searching for carriers of recessive inborn errors of metabolism, in statin intolerant patients, cannot be widely endorsed at this point and further work is needed to clarify a rational work-up of these patients.

References

1. Ucar M, Mjorndal T, Dahlqvist R. HMG-CoA reductase inhibitors and myotoxicity. Drug Saf. 2000; 22:441-57.
2. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. Circulation. 2000; 101:207-13.
3. Epstein WW, Lever D, Leining LM, Bruenger E, Rilling HC. Quantitation of prenylcysteines by a selective cleavage reaction. Proc Natl Acad Sci U S A. 1991; 88:9668-70.
4. Vladutiu GD, Simmons Z, Isackson PJ, Tarnopolsky M, Peltier WL, Barboi AC, et al. Genetic risk factors associated with lipid-lowering drug-induced myopathies. Muscle Nerve. 2006; 34:153-62.
5. Frudakis TN, Thomas MJ, Ginjupalli SN, Handelin B, Gabriel R, Gomez HJ. CYP2D6*4 polymorphism is associated with statin-induced muscle effects. Pharmacogenet Genomics. 2007; 17:695-707.
6. Takeda M, Noshiro R, Onozato ML, Tojo A, Hasannejad H, Huang XL, et al. Evidence for a role of human organic anion transporters in the muscular side effects of HMG-CoA reductase inhibitors. Eur J Pharmacol. 2004; 483:133-8.
7. Oh J, Ban MR, Miskie BA, Pollex RL, Hegele RA. Genetic determinants of statin intolerance. Lipids Health Dis. 2007; 6:7.
8. Ruano G, Thompson PD, Windemuth A, Seip RL, Dande A, Sorokin A, et al. Physiogenomic association of statin-related myalgia to serotonin receptors. Muscle Nerve. 2007; 36:329-35.
9. Sirvent P, Mercier J, Vassort G, Lacampagne A. Simvastatin triggers mitochondria-induced Ca2+ signaling alteration in skeletal muscle. Biochem Biophys Res Commun. 2005; 329:1067-75.
10. Kang L, Fang Q, Hu SJ. Regulation of phospholamban and sarcoplasmic reticulum Ca2+-ATPase by atorvastatin: implication for cardiac hypertrophy. Arch Pharm Res. 2007; 30:596-602.
11. Velho JA, Okanobo H, Degasperi GR, Matsumoto MY, Alberici LC, Cosso RG, et al. Statins induce calcium-dependent mitochondrial permeability transition. Toxicology. 2006; 219:124-32.
12. Matzno S, Yasuda S, Juman S, Yamamoto Y, Nagareya-Ishida N, Tazuya-Murayama K, et al. Statin-induced apoptosis linked with membrane farnesylated Ras small G protein depletion, rather than geranylated Rho protein. J Pharm Pharmacol. 2005; 57:1475-84.
13. Sakamoto K, Honda T, Yokoya S, Waguri S, Kimura J. Rab-small GTPases are involved in fluvastatin and pravastatin-induced vacuolation in rat skeletal myofibers. FASEB J. 2007; 21(14):4087-94.
14. Baker SK, Tarnopolsky MA. Statin myopathies: pathophysiologic and clinical perspectives. Clin Invest Med. 2001; 24:258-72.
15. Chariot P, Abadia R, Agnus D, Danan C, Charpentier C, Gherardi RK. Simvastatin-induced rhabdomyolysis followed by a MELAS syndrome. Am J Med. 1993; 94:109-10.
16. Thomas JE, Lee N, Thompson PD. Statins provoking MELAS Syndrome. A case report. Eur Neurol. 2007; 57:232-5.
17. Goli AK, Goli SA, Byrd RP, Jr., Roy TM. Simvastatin-induced lactic acidosis: a rare adverse reaction? Clin Pharmacol Ther. 2002; 72:461-4.
18. Perez-Calvo J, Civeira-Murillo F, Cabello A. Worsening myopathy associated with ezetimibe in a patient with McArdle disease. Qjm. 2005; 98:461-2.
19. Garcia-Calvo M, Lisnock J, Bull HG, Hawes BE, Burnett DA, Braun MP, et al. The target of ezetimibe is Niemann-Pick C1-Like 1 (NPC1L1). Proc Natl Acad Sci U S A. 2005; 102:8132-7.
20. Walravens PA, Greene C, Frerman FE. Lovastatin, isoprenes, and myopathy. Lancet. 1989; 2:1097-8.
21. Haller RG. Treatment of McArdle disease. Arch Neurol. 2000; 57:923-4.
22. Tsao CY, Mendell JR. Combined partial deficiencies of carnitine palmitoyltransferase II and mitochondrial complex I presenting as increased serum creatine kinase level. J Child Neurol. 2002; 17:304-6.
23. Lam CW, Lau CH, Williams JC, Chan YW, Wong LJ. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) triggered by valproate therapy. Eur J Pediatr. 1997; 156:562-4.
24. Delgado-Lopez F, Bautista-Lorite J, Villamil-Fernandez F. Worsening for using statin in carnitine palmityol transferase deficiency myopathy. Rev Neurol. 2004; 38:1095.
25. Arduini A, Peschechera A, Giannessi F, Carminati P. Improvement of statin-associated myotoxicity by L-carnitine. J Thromb Haemost. 2004; 2:2270-1.
26. Bhuiyan J, Seccombe DW. The effects of 3-hydroxy-3-methylglutaryl-CoA reductase inhibition on tissue levels of carnitine and carnitine acyltransferase activity in the rabbit. Lipids. 1996; 31:867-70.
27. Kaufmann P, Torok M, Zahno A, Waldhauser KM, Brecht K, Krahenbuhl S. Toxicity of statins on rat skeletal muscle mitochondria. Cell Mol Life Sci. 2006; 63(19-20):2415-25.
28. Yano M, Matsumura T, Senokuchi T, Ishii N, Murata Y, Taketa K, et al. Statins activate peroxisome proliferator-activated receptor gamma through extracellular signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase-dependent cyclooxygenase-2 expression in macrophages. Circ Res. 2007; 100:1442-51.
29. Scatena R, Bottoni P, Martorana GE, Vincenzoni F, Botta G, Pastore P, et al. Mitochondria, ciglitazone and liver: a neglected interaction in biochemical pharmacology. Eur J Pharmacol. 2007; 567:50-8.
30. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, et al. Statin-associated myopathy with normal creatine kinase levels. Ann Intern Med. 2002; 137:581-5.
31. Krivosic-Horber R, Depret T, Wagner JM, Maurage CA. Malignant hyperthermia susceptibility revealed by increased serum creatine kinase concentrations during statin treatment. Eur J Anaesthesiol. 2004; 21:572-4.
32. Guis S, Bendahan D, Kozak-Ribbens G, Figarella-Branger D, Mattei JP, Pellissier JF, et al. Rhabdomyolysis and myalgia associated with anticholesterolemic treatment as potential signs of malignant hyperthermia susceptibility. Arthritis Rheum. 2003; 49:237-8.
33. Livingstone C, Al Riyami S, Wilkins P, Ferns GA. McArdle's disease diagnosed following statin-induced myositis. Ann Clin Biochem. 2004; 41:338-40.
34. Tsivgoulis G, Spengos K, Karandreas N, Panas M, Kladi A, Manta P. Presymptomatic neuromuscular disorders disclosed following statin treatment. Arch Intern Med. 2006; 166:1519-24.
35. Voermans NC, Lammens M, Wevers RA, Hermus AR, van Engelen BG. Statin-disclosed acid maltase deficiency. J Intern Med. 2005; 258:196-7.
36. Takagi A, Shiio Y. Pravastatin-associated polymyositis, a case report. Rinsho Shinkeigaku. 2004; 44:25-7.
37. Riesco-Eizaguirre G, Arpa-Gutierrez FJ, Gutierrez M, Toribio E. Severe polymyositis with simvastatin use. Rev Neurol. 2003; 37:934-6.
38. Noel B, Cerottini JP, Panizzon RG. Atorvastatin-induced dermatomyositis. Am J Med. 2001; 110:670-1.
39. Vasconcelos OM, Campbell WW. Dermatomyositis-like syndrome and HMG-CoA reductase inhibitor (statin) intake. Muscle Nerve. 2004; 30:803-7.
40. Parmar B, Francis PJ, Ragge NK. Statins, fibrates, and ocular myasthenia. Lancet. 2002; 360:717.
41. Baker SK, Tarnopolsky MA. Sporadic rippling muscle disease unmasked by simvastatin. Muscle Nerve. 2006; 34:478-81.