Published in final edited form as:

Muscle Nerve. 2008 September ; 38(3): 1101–1107. doi:10.1002/mus.21074.

STATINS MAY AGGRAVATE MYASTHENIA GRAVIS

SHIN J. OH, MD, ROHIT DHALL, MD, ANGELA YOUNG, MD, MARLA B. MORGAN, MD, LIANG LU, MD, and GWENDOLYN C. CLAUSSEN, MD

Department of Neurology, University of Alabama at Birmingham, Veterans Affairs Medical Center, Birmingham, Alabama 35294, USA

Abstract

Statin-induced myopathy is well-known, but the effect of cholesterol-lowering agents on myasthenia gravis (MG) has not been studied in detail. We investigated statin use and its effects on MG among patients with this disease. Statin information was systemically obtained from 170 patients being treated at the Neuromuscular Disease Clinic at the University of Alabama at Birmingham. When a new myalgic syndrome or worsening of MG developed within 4 months after statin treatment, no other likely cause was found, and clinical improvement occurred either with or without discontinuation of the statin, we considered these symptoms to be statin-induced. Fifty-four patients (31%) were on statins. The statin group had proportionally more males, and older patients compared with the non-statin group. A myalgic syndrome was noted in 7 (13%) patients, but it resolved without any sequelae after withdrawal of the statin. MG worsening occurred in 6 (11%) patients without regard to type of MG or brand of statin. MG worsening occurred independently of myalgic syndrome and involved predominantly oculobulbar symptoms within 1-16 weeks of statin treatment. In 4 patients, additional treatment was needed to reverse MG worsening. Statins are safe in the majority of MG patients, but their use must be accompanied by close observation for possible MG worsening.

Keywords

drug side effect; HMG coenzyme A reductase inhibitor; myasthenia gravis; myotoxicity; statin

Statins [3-hydroxy-3-methylglutaryl (HMG) coenzyme A reductase inhibitors] are known to reduce serum low-density lipoprotein (LDL) by inhibiting HMG coenzyme A reductase. In recent years, they have been used widely in the treatment of hypercholesterolemia. Their side effects on muscle are well known and range from myalgia and muscle cramp to elevation of creatine kinase (CK), myopathy, and rhabdomyolysis.^{13,17} It is also known that statins may unmask underlying neuromuscular diseases.^{1,16,19} There have been a few case reports of worsening of myasthenia gravis (MG) in patients treated with statins.^{3,9,12} However, their effect on MG has not been studied systematically. We investigated the use of statins and their effects on MG among our patients.

METHODS

The diagnosis of MG was made when fluctuating clinical weakness was present and at least one of four laboratory tests [acetylcholine receptor antibody (AChR-ab), muscle-specific protein tyrosine kinase antibody (MuSK-ab), repetitive nerve stimulation (RNS) test, or single-fiber electromyography (SFEMG)] was abnormal.⁸

To assess the adverse muscular side effects of statins in MG, we added “MG worsening” to the ACC/AHA/NHLBI classification in statin-induced muscular adverse events.¹⁰ The ACC/AHA/NHLBI classification includes the myalgic syndrome (muscle aches with normal CK), myositis (muscle symptoms with elevated CK), and rhabdomyolysis (muscle symptoms with CK >10 times the upper limit of normal and creatinine elevation).¹⁰ MG worsening is defined as worsening or relapse of any MG symptoms. Because we did not have any patients with myositis or rhabdomyolysis in our study, we used only two adverse side effects in our classification: myalgic syndrome or worsening of MG.

When new myalgic syndrome or worsening of MG developed clearly within 4 months following statin treatment, no other possible cause was found, and clinical improvement occurred either with or without modification of treatment after discontinuation of the statin, we considered these symptoms to be statin-induced.

Beginning in 2005, when the senior author (S.J.O.) suspected a close association between statin use and worsening of MG, the clinicians at the University of Alabama at Birmingham (UAB) Neuromuscular Disease Clinic began to ask patients about their use of statins during clinic visits and recorded this information in the patient charts. In order to obtain information on statin-induced myalgic syndrome or worsening of MG, we reviewed the clinic charts of all MG patients seen at the UAB Neuromuscular Disease Clinic for a 2.5-year period between January 1, 2005, and June 30, 2007. Any MG patient whose medical records did not include a specific reference to statin use was contacted via telephone or mail by one of the investigators to obtain this information, which was confirmed on a subsequent clinic visit.

When statin use was confirmed, the patients were asked to provide the name of the statin drug, its possible side effects, and any worsening of their MG. Statin-induced myalgic syndrome was determined with information provided by patients. On the other hand, MG worsening was determined by objective findings documented in the chart. This information was recorded in a study database and analyzed. This study was approved by the institutional review board at the UAB.

RESULTS

One hundred eighty-five MG patients were seen at the UAB Neuromuscular Disease Clinic between January 2005 and June 30, 2007. Statin information was available for 170 of the 185 patients. Statin information was obtained from the medical charts in 76 patients, by telephone in 80, and by mail in 14.

Among 170 patients, 50% ($n = 85$) were men (Table 1). The mean age of patients was 58.7 years, and the mean age at onset of MG was 48.7 years. Thus, the mean duration of disease was 9.1 years. Ocular MG was present in 15% of cases. AChR-ab was positive in 69% of patients. MuSK-ab was positive in 9 patients. A repetitive nerve stimulation (RNS) test was positive in 71% of 159 tested patients, and single-fiber electromyography (SFEMG) was positive in 90% of 136 tested patients.

Fifty-four (31%) patients were on statins. Clinical and laboratory features were compared between those on statins and those who were not (Table 1). Between the two groups, there were no significant differences between parameters except for age and gender. Mean age at the time of study and onset in the statin group was 9–11 years older than in the non-statin group. This difference was significant. All patients on statins were >40 years of age, whereas 22% of patients in the non-statin group were <40 years of age. There were more male patients in the statin group and more females in the non-statin group, even in patients >40 years of age.

Among 54 patients on statins, the myalgic syndrome was noted in 7 (13%) and MG worsening in 6 (11%) other patients (Tables 2 and 3). None had myopathy or rhabdomyolysis.

Among the 7 patients with the myalgic syndrome, 6 had a positive AChR-ab (Table 2). Three patients had used atorvastatin previously; 3 were on simvastatin; 2 were on rosuvastatin; and 1 each were on pravastatin, fluvastatin, and cerivastatin. Myalgia was observed in 3 patients and muscle cramping in 4. All myalgic symptoms resolved within 2 months of statin withdrawal, without any change of management. Among 7 patients, 4 tried alternative brands of statin for hypercholesterolemia—simvastatin in 2 and atorvastatin in 2—without induction of any myalgic symptoms. In 1 patient, reduction of atorvastatin dose from 40 mg/day to 10 mg/day led to resolution of myalgic symptoms.

MG worsening was observed in 6 patients (Table 3) and occurred in all types of MG. We observed MG worsening in 6 patients over 4 years from 2002 to 2006. Three patients had previously undergone thymectomy. All statin brands were associated with MG worsening, although simvastatin was responsible in 3 patients. In 2 patients, MG worsening occurred with challenge of another statin: atorvastatin in 1 and fluvastatin and pravastatin in the other. In 3 patients, MG worsening occurred within 1-2 weeks of statin initiation and, in 3 other patients, within 6-16 weeks. In 3 patients, MG worsening occurred 0.5-4 months after beginning statin treatment following a long-standing remission: a 5-year pharmacological remission and 2-year stable remission in 1 case; an 8-year pharmacological remission in another; and a 7-year pharmacological remission in the third case. MG worsening occurred independent of the myalgic syndrome in all patients except for 1 ocular MG patient who had myalgia together with worsening of diplopia. Three patients had AChR-ab, 1 had MuSK-ab, and 2 had no AChR-ab and MuSKab. This indicates that MG worsening was possible in all types of MG. One patient with ocular MG had aggravation of diplopia. Five patients experienced bulbar symptoms, and 1 patient reported limb weakness. In 2 patients, MG worsening resolved within 1 month without any change in treatment of MG. In 4 other patients, additional treatment was required to treat MG worsening. Two patients required hospitalization. Two had intravenous immunoglobulin (IVIg), and 1 with MG crisis required percutaneous endoscopic gastrostomy placement, tracheostomy, plasma exchange, and IVIg. One patient needed an increased dose of azathioprine and additional steroid treatment as an outpatient. In 3 patients, an alternative statin was tried: atorvastatin in 2 and pravastatin in 1. One patient took a reduced dose of atorvastatin despite a minor worsening of dysarthria. CK was checked in 4 cases, and was normal. AChR-ab was checked in 3 patients who needed treatment modification. AChR-ab continued to be negative in 1 MuSK MG patient. Two others experienced titers of 32- and 19-fold higher, respectively, compared with the last one recorded prior to worsening of MG.

DISCUSSION

In this study we have presented a general survey of statin-induced muscular adverse events and MG worsening in MG patients treated with statins. A further aim was to establish general guidelines for statin use in MG patients. We did not find any case of statin-induced myositis or rhabdomyolysis in this investigation. Because symptoms of statin-induced myositis or rhabdomyolysis mimic MG worsening, most likely such patients would have come to our medical attention. Thus, it is unlikely that we missed any such cases.

Arbitrarily, we chose 4 months as a reasonable period of statin treatment for statin-induced muscular adverse effects. The longest period of statin treatment associated with MG worsening in our series was 4 months, and more confounding factors exist with a longer period. The reported period of statin treatment ranged from 1 week to 3 months for MG worsening and from 5 months to 60 months for statin-induced autoimmune diseases.^{3,5-7,9,11,12,14,18}

Our study showed that about one third of MG patients are on a statin. Compared with the nonstatin group, more males and older MG patients are on a statin. Because statins are used mostly in older patients with cardiovascular disease, the older MG patients in our statin group reflect the general trend in statin treatment. The larger number of females in the non-statin group was partly due to female predominance among the young MG patients. Of the 26 patients <40 years of age, 77% were female. However, there was a significant difference by gender for 91 patients >40 years of age, suggesting that statins are used more frequently by male MG patients.

Among patients taking statins, the myalgic syndrome was present in 13% of cases. This rate of adverse events is at the mid-point between the 1%-7% incidence of dose-dependent myotoxic effects, based on the definition used in one study, and 19%-25% in a Swedish study.^{13,17} The myalgic syndrome was not a major concern, because all symptoms resolved without any sequelae upon withdrawal of statin. The majority of patients were able to switch to another statin or reduce their dose without any adverse muscular effect.

The most serious adverse effect of statin-induced myotoxicity is MG worsening, which occurred in 11% of MG patients on a statin. MG worsening is extremely rare, as we observed it in only 6 patients over a 4-year period. MG worsening occurred with all brands of statin and in all types of MG. In half the cases, MG worsening was obvious within 1-2 weeks after beginning statin treatment, and in the other half it was delayed, averaging 6-16 weeks. The most common symptom in MG worsening was oculobulbar weakness. Our study also showed that MG worsening reversed after withdrawal of the statin in half of the patients, but it required additional treatment for MG over a period of many months in the other half.

Statin use is also known to be associated with polymyositis, dermatomyositis-like syndrome, lupuslike syndromes, angioedema, vasculitis, polymyalgia rheumatica, hypereosinophilic syndrome, and mitochondrial myopathy.^{14,18} It is unclear whether these syndromes are induced or unmasked by statins. However, there have been reports of a case each for rippling myopathy, myotonic dystrophy, Kennedy disease, McArdle disease, and acid maltase deficiency, which were clearly unmasked by statins.^{1,16,19} In the case of rippling myopathy, transient seropositive generalized MG was documented 1 year after onset of the rippling myopathy.¹

There have been 6 cases of MG worsening associated with statin use reported in the literature (Table 4).^{3,9,12} In 2000, MG worsening was reported in a probable seronegative case with a 2-year history of MG.⁹ In this patient, ptosis, diplopia, and proximal weakness became worse with 3 months treatment of atorvastatin and subsequently with fluvastatin, simvastatin, and benzaifibrate. MG worsening resolved within 6 weeks after withdrawal of statins. Although some questioned the MG diagnosis in this case in the absence of any convincing objective test, most likely this case was seronegative MG.⁴ Since then, 5 additional cases of MG worsening have been reported. MG worsening has been reported with all brands of statins. The diagnosis of MG was confirmed in 4 patients by AChR-ab test and by SFEMG in 1 case. One patient developed worsening of existing MG symptoms, as was noted in 3 of our cases. One had a relapse of MG symptoms after a long-term stable remission, as was noted in 3 of our cases. In 4 cases, statins unmasked MG symptoms. In our series, we have not seen any case of MG unmasked by a statin. MG worsening or unmasking was noted within 1-2 weeks of statin treatment in the remaining 5 previously reported cases. In 2 cases, all MG symptoms resolved 6-8 weeks after withdrawal of statins, but in 2 cases additional steroid was needed to control MG symptoms. Thus, the reported experience of MG worsening in the literature is comparable with ours except that we did not have a case of unmasked MG.

One case of “MG plus syndrome” induced by a statin has been reported.⁷ The patient developed diplopia, blurred vision, and paresthesia during 2.5 months of treatment with atorvastatin. Abnormal neurological findings were hyperflexia, ataxia, ptosis, and ophthalmoparesis. Edrophonium and RNS tests were normal as was a spinal fluid test. However, the AChR-ab test was positive. All these symptoms resolved within 10 weeks after withdrawal of the statin.

There are two strong pieces of evidence that support statins being responsible for MG worsening. The first is unmasking of MG by statin treatment, and the second is worsening of MG by rechallenge with other statins. From the literature, there have been 4 cases of MG being unmasked by statin.^{3,12} All 4 patients experienced oculobulbar symptoms as the initial manifestations of MG within 2 weeks of statin treatment, and complete resolution of symptoms occurred 2 months after statin withdrawal in 1 case. In the other 3 cases, persistent MG symptoms required pyridostigmine in 2 cases and prednisone in another, even 12 months after withdrawal of statin. After rechallenge with other statins, MG worsening was documented in 2 of our cases and in 3 cases in the literature.^{3,9,12}

The precise mechanisms of direct myotoxicity are not clear, although two explanations have been proposed: mitochondrial dysfunction caused by reducing endogenous coenzyme Q10,² and muscle membrane dysfunction due to deficiency of the chloride channel or interruption of glycoprotein synthesis.^{5,15} It is possible that statin myotoxicity is responsible for MG worsening, especially in cases with a shorter resolution time, as noted in the myalgic syndrome. This is not the only mechanism, because MG worsening does not occur in the setting of the myalgic syndrome. Because statins are not known to have any effect at the neuromuscular junction,²⁰ MG worsening is not likely due to worsening neuromuscular transmission. We favor an immunomodulatory mechanism by modulation of disease activity through the statins’ effects on the immune system. Three pieces of evidence support this view. Statins are known to induce many autoimmune diseases, as discussed previously.^{14,18} Statins also have immunomodulatory properties, including loss of immune tolerance and production of pathogenic autoantibodies.⁶ AChR-ab titer increase in our 2 cases favors this theory. In 3 previous cases, the AChR-ab titer decreased when MG symptoms resolved.^{7,12} In 1 case, AChR-ab became negative 1 year after onset of unmasked MG by a statin.¹² In another case, AChR-ab became negative 10 weeks after recovery.⁷ Purvin et al. further suggested that the statins induced de novo formation of antibodies directed at the neuromuscular junction, citing penicillamine-induced MG.¹² This suggestion is untenable, because MG worsening occurred even in seronegative cases, and not all cases showed spontaneous improvement with withdrawal of the statin as noted in penicillamine-induced MG.¹¹

Our study has shown that an adverse effect of statins occurred in 24% of MG patients on statins, indicating that, in 76% of cases, statins appeared to be safe. Potential worsening of MG is seen in a much smaller number of patients and may require other therapeutic interventions. Thus, we conclude that statins are safe in the majority of MG patients, but close observation for possible MG worsening is recommended for those taking statins. We recommend the addition of statins to the list of drugs that may exacerbate MG.²¹ Given the findings from this retrospective study, we suggest that a definitive prospective study be undertaken to clarify the role of statins in MG and MG worsening.

Abbreviations

AChR-ab, acetylcholine receptor antibody; CK, creatine kinase; IVIg, intravenous immunoglobulin; HMG, 3-hydroxy-3-methylglutaryl; LDL, low-density lipoprotein; MG, myasthenia gravis; MuSK-ab, muscle-specific protein tyrosine kinase antibody; RNS, repetitive nerve stimulation; SFEMG, single-fiber electromyography.

REFERENCES

1. Baker SK, Tarnopolsky MA. Sporadic rippling muscle disease unmasked by simvastatin. *Muscle Nerve* 2006;34:478–481. [PubMed: 16688722]
2. Bliznakov EG, Wilkins DJ. Biochemical and clinical consequences of inhibiting coenzyme Q biosynthesis by lipid-lowering HMG-Co A reductase inhibitors (statins): a critical overview. *Adv Ther* 1998;15:218–228.
3. Cartwright MS, Jeffery DR, Nuss GR, Donofrio P. Statin-associated exacerbation of myasthenia gravis. *Neurology* 2004;63:2188. [PubMed: 15596782]
4. Engel WK. Reversal ocular myasthenia gravis or mitochondrial myopathy from statins. *Lancet* 2003;361:85–86. [PubMed: 12517506]
5. Golman JA, Fishman AB, Lee JE, Johnson RJ. The role of cholesterol lowering agents in drug induced rhabdomyolysis and polymyositis. *Arthritis Rheum* 1989;32:358–359. [PubMed: 2930608]
6. Jimenez-Alonso J, Maimez L, Sabio JM, Hidalgo C, Leon L. Atorvastatin-induced reversible positive antinuclear antibodies. *Am J Med* 2002;112:329–330. [PubMed: 11893380]
7. Negvesky GJ, Kolsky MP, Laureno R, Yau TH. Reversible atorvastatin-associated external ophthalmoplegia, anti-acetylcholine receptor antibodies, and ataxia. *Arch Ophthalmol* 2000;118:427–428. [PubMed: 10721974]
8. Oh SJ, Kim DE, Kuruoglu R, Bradley RJ, Dwyer D. Diagnostic sensitivity of laboratory tests in myasthenia gravis. *Muscle Nerve* 1992;15:720–724. [PubMed: 1324429]
9. Parmar B, Francis P, Ragge NK. Statins, fibrates, and ocular myasthenia. *Lancet* 2002;360:717. [PubMed: 12241896]
10. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JJ, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Circulation* 2002;106:1024–1028. [PubMed: 12186811]
11. Penn AS, Low BW, Jaffe IA, Luo L, Jacques JJ. Drug-induced autoimmune myasthenia gravis. *Ann NY Acad Sci* 1998;841:433–449. [PubMed: 9668273]
12. Purvin V, Kawasaki A, Kyle H, Smith KH, Kesler A. Statin-associated myasthenia gravis: report of 4 cases and review of the literature. *Medicine* 2006;85:82–85. [PubMed: 16609346]
13. Rosenson RS. Current overview of statin-induced myopathy. *Am J Med* 2004;116:408–416. [PubMed: 15006590]
14. Rudski L, Rabinovitch MA, Danoff D. Systemic immune reactions to HMG-CoA reductase inhibitors. Report of 4 cases and review of the literature. *Medicine* 1998;77:378–383. [PubMed: 9854600]
15. Sonoda Y, Gotow T, Kuriyama M, Nakahara K, Arimura K, Osame M. Electrical myotonia of rabbit skeletal muscles by HMG-CoA reductase inhibitors. *Muscle Nerve* 1994;17:891–894. [PubMed: 8041396]
16. Tsivgoulis G, Spengos K, Karandreas N, Panas M, Kladi A, Manta P. Presymptomatic neuromuscular disorders disclosed following statin treatment. *Arch Intern Med* 2006;166:1519–1524. [PubMed: 16864763]
17. Ucar M, Mjorndal T, Dahlqvist R. HMG-CoA reductase inhibitors and myotoxicity. *Drug Safety* 2000;22:441–457. [PubMed: 10877038]
18. Vasconcelos OM, Campbell WW. Dermatomyositis-like syndrome and HMG-CoA reductase inhibitor (statin) intake. *Muscle Nerve* 2004;30:803–807. [PubMed: 15389654]
19. Voermans NC, Lammens M, Wevers RA, Hermus AR, van Engelen BG. Statin-disclosed acid maltase deficiency. *J Intern Med* 2005;258:196–197. [PubMed: 16018797]
20. Wierzbicki AS, Poston R, Ferro A. The lipid and non-lipid effects of statins. *Pharmacol Ther* 2003;99:95–112. [PubMed: 12804701]
21. Wittbrodt ET. Drugs and myasthenia gravis. An update. *Intern Med* 1997;157:399–408.

Table 1
Demographic, clinical, and laboratory features in the statin and no-statin groups

	Total	Statin group	No-statin group	P-value
No. of cases	170	54	116	
Mean age $\pm$ SD (yr)	58.7 $\pm$ 15.9	64.7 $\pm$ 10.5 [*]	55.9 $\pm$ 17.2	0.0007
<40; $\geq$ 40 yr	25:145	0:54 [†]	25:91	0.003
MG onset age (yr)	48.7 $\pm$ 18.5	56.4 $\pm$ 14.5 [‡]	45.1 $\pm$ 19.1	0.0002
Duration of MG (yr)	10.0 $\pm$ 9.5	8.3 $\pm$ 9.9	10.7 $\pm$ 9.2	
Gender (M:F)	85:85	36:18 [§]	49:67 (43:48) [#]	0.003 (0.02)
Race (white:black)	142:28	49:5	93:23	
Ocular-generalized	26:144	10:44	16:100	
AChR antibody (+)	118 (69%)	39 (72%)	79 (68%)	
MuSK antibody (+)	9	1	8	
RNS test	113/159 (71%)	31/48 (65%)	82/111 (74%)	
SFEMG	122/136 (90%)	37/40 (93%)	85/96 (89%)	
Thymoma	24	6	18	

Except for age and duration of disease, all entries represent number of cases.

^{*} $P = 0.0007$

[†] $P = 0.003$

[‡] $P = 0.0002$

[§] $P = 0.003$

[#] Represents number >40 years.

Table 2

Clinical features in myalgic syndrome

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age/gender	69/F	65/M	75/M	79/M	55/M	76/F	61/F
Age at onset	68	48	70	65	49	75	58
AChR antibody	Positive	Positive	Positive	Negative	Positive	Positive	Negative
Abnormal test	RNS	RNS, SFEMG	RNS, SFEMG	SFEMG	RNS, SFEMG	SFEMG	SFEMG
Thymectomy	No	Yes	Yes	No	Yes	No	Yes
Statin	Atorvastatin	Simvastatin, rosuvastatin, atorvastatin (40 mg)	Rosuvastatin	Simvastatin*	Atorvastatin	Pravastatin	Cerivastatin, simvastatin, fluvastatin
Adverse effect	Cramp	Myalgia	Cramp	Myalgia + MG worsening	Cramp	Cramp	Worsening of existing myalgia
Period of statin treatment	1 month	2 weeks	1 month	6 weeks	1 months	2 months	2 months
Treatment	Stop atorvastatin	Stop simvastatin, rosuvastatin	Stop rosuvastatin	Stop simvastatin	Stop atorvastatin	Stop pravastatin	Stop statins all
Resolution of symptoms	1 week	1 week	2 weeks	1 week	1 week	2 weeks	2-3 weeks
Other statins tried	Simvastatin	Atorvastatin (10 mg)	Atorvastatin	None	Simvastatin	None	None

Clinical and laboratory features in MG worsening

Table 3

	Case 1 (2005)	Case 2 (2006)	Case 3 (2004)	Case 4 (2005)	Case 5 (2002)	Case 6 (2006)
Age/gender	41/male	58/male	59/male	51/female	67/male	59/male
Age at onset	37	46	46	34	43	45
AChR-ab	Negative	Positive	Positive	Negative; MuSK-ab positive	Negative	Positive
Abnormal test	SFEMG	RNS, SFEMG	RNS, SFEMG	RNS, SFEMG	RNS, SFEMG	
Thymectomy	No	Yes for thymoma	No	Yes	No	Yes
MG status at time of MG worsening	I	Ia, stable	Ia, stable	CR for 2 year PR for 5 years	PR, MM2 for 7 years	PR, MM1 for 8 years
Medications at time of MG worsening	None	Prednisone, azathioprine, pyridostimine	Pyridostimine plasma exchange × 2 per year	None	Pyridostigmine	Azathioprine
Statin	Simvastatin	Rosuvastatin, atorvastatin (40 mg)	Simvastatin, fluvastatin, pravastatin	Rosuvastatin	Simvastatin	Lovastatin
Period of statin treatment	6 weeks	2 weeks	1 week	2 months	2 weeks	4 months
Symptoms worsened	Diplopia	Dysarthria, dysphagia	Dysphagia, dyspnea, more fatigue	Relapse: dysphagia, dysarthria crisis at 8 months	Relapse: limb weakness, dysarthria, chewing difficulty	Relapse: dysarthria, dysphagia, dyspnea
Change of treatment	None	IVIg, increased azathioprine	None	Hospitalized plasma exchange, IVIg, steroid, cyclophosphamidePEG, tracheostomy	IVIg, azathioprine added	Increased azathioprine, prednisone added
AChR-ab at the time of MG worsening		Increase × 32		Negative		Increase × 19
Resolution to pre-worsening state	1 week	22 months	1 month	16 months	2 months	2 months
Other statin tried	None	Atorvastatin (20 mg), slightlyworse	None	None	Pravastatin	Atorvastatin (20 mg)

PEG, percutaneous enteric-gastrostomy.

* MGFA classification: Ia, mild generalized MG; CR, complete remission; PR, pharmacological remission; MM1, minimal manifestation with immunosuppressor; MM2, minimal manifestation with anticholinesterase.

Table 4

Clinical and laboratory features of 6 reported cases with MG worsening

Study	Age/gender	Statin	MG class	Interval to onset	Tensilon test	AChR-ab	Tests	Worsening symptom	Resolution
Parmar et al. (2002)	67/F	Atorvastatin, 3 others*	IIa, 2 yr	3 mo		-		Oculo-limb	6 wk
Cartwright et al. (2004)	55/M	Atorvastatin, 3 others*	IIb, new	1 wk	+	+	RNS: decrement	Dysarthria	1 wk; with pyridostigmine
Purvin et al. (2006)	55/M	Rosuvastatin	IIb, new	1 wk	+	+	SFEMG: abnormal	Oculobulbar	4.5 mo with steroid, AChR-ab negative at 1 year
	70/M	Rosuvastatin	IIb, new	1 wk		+		Oculobulbar	7 mo with pyridostigmine, AChR-ab positive
	71/M	Simvastatin, pravastatin*	IIb, new	2 wk		-	SFEMG: abnormal	Oculobulbar	2 mo
	56/F	Pravastatin	IIa, (I,CR, 25 yr	1 wk	+	+	RNS: decrement	Neck-limb	Improved with steroid

F, female; M, male; I, ocular; IIa, mild; A, generalized; B, bulbar; CR, complete remission.

* Challenge of statin worsened MG symptoms.