Statins and Myotoxic Effects Associated With Anti-3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Autoantibodies

An Observational Study in Japan

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Abstract: Statins have a variety of myotoxic effects and can trigger the development of inflammatory myopathies or myasthenia gravis (MG) mediated by immunomodulatory properties. Autoantibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCAR) have been identified in patients with statin-associated myopathy. The purpose of the present study is to develop an enzyme-linked immunosorbent assay (ELISA) of anti-HMGCAR antibodies and to elucidate the clinical significance of anti-HMGCAR antibodies in Japanese patients with inflammatory myopathies or MG.

We enrolled 75 patients with inflammatory myopathies, who were all negative for anti-signal recognition particle and anti-aminocyl transfer RNA synthetase antibodies. They were referred to Keio University and National Center of Neurology and Psychiatry between October 2010 and September 2012. We also studied 251 patients with MG who were followed at the MG Clinic at Keio University Hospital. Anti-HMGCAR antibodies were detected by ELISA. We investigated demographic, clinical, radiological, and histological findings associated with anti-HMGCAR antibodies.

We established the anti-HMGCAR ELISA with the recombinant protein. Protein immunoprecipitation detected autoantigens corresponding to HMGCAR. Immunohistochemistry using muscle biopsy specimens revealed regenerating muscle fibers clearly stained by polyclonal anti-HMGCAR antibodies and patients’ serum. Anti-HMGCAR autoantibodies were specifically detected in 8 patients with necrotizing myopathy. The seropositivity rate in the necrotizing myopathy patients was significantly higher than those in the patients with other histological diagnoses of inflammatory myopathies (31% vs 2%, P = 0.001). Statins were administered in only 3 of the 8 anti-HMGCAR-positive patients. Myopathy associated with anti-HMGCAR antibodies showed mild limb weakness and favorable response to immunotherapy. All 8 patients exhibited increased signal intensities on short T1 inversion recovery of muscle MRI. Of the 251 patients with MG, 23 were administered statins at the onset of MG. One late-onset MG patient experienced MG worsening after 4-wk treatment with atorvastatin. However, anti-HMGCAR antibodies were not detected in the 251 MG patients except for one early-onset MG patient with no history of statin therapy.

Anti-HMGCAR antibodies are relevant clinical marker of necrotizing myopathy with or without statin exposure, but they are not associated with the onset or deterioration of MG.

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INTRODUCTION

Statins lower cholesterol levels by specifically inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCAR), a key enzyme in the cholesterol biosynthesis pathway. Statins are associated with ≥1 myotoxic effects including myalgia,
elevation of creatine kinase and transaminases, and weakness. Muscle problems occurred in 10% to 25% of patients treated with statins in clinical practice and in approximately 13% of participants of published clinical trials. Statins have immunomodulatory properties, and they may unmask or worsen certain neuromuscular disorders including myasthenia gravis (MG), myotonic dystrophy, McArdle disease, and mitochondrial myopathy. The most severe problem is the development of inflammatory myopathy requiring immunosuppressive therapy; this is now known to be mediated by anti-HMGCR antibodies. Anti-HMGCR antibodies were first found as 200- and 100-kDa proteins using protein immunoprecipitation. In 2011, the 100-kDa autoantigen was identified as HMGCR by RNA immunoprecipitation assay. The 75 patients’ mean age and anti-aminoacyl transfer RNA synthetase antibodies using protein immunoprecipitation. The patients’ mean age at diagnosis of idiopathic inflammatory myopathies was 50 years (range 20–82), and the sex ratio (M:F) was 30:45.

METHODS

Patients

We examined 75 adult patients with inflammatory myopathies, who were referred to Keio University or National Center of Neurology and Psychiatry between October 2010 and September 2012. We included patients with the definite diagnosis of idiopathic inflammatory myopathies by a comprehensive histological examination. In addition, the patients were all negative for anti-signal recognition particle (SRP) and anti-aminacyl transfer RNA synthetase antibodies using RNA immunoprecipitation assay. The 75 patients’ mean age at the examination was 61 ± 15 years (range 20–82), and the sex ratio (M:F) was 30:45.

Histological diagnoses were based on the established criteria. Briefly, sporadic inclusion body myositis was diagnosed by the identification of rimmed vacuoles without necrotic fibers invaded by mononuclear cells or increased major histocompatibility complex (MHC) class I expression. Polymyositis was diagnosed based on exclusively endomysial inflammation cell infiltrate surrounding or invading non-necrotic muscle fibers, accompanied by ubiquitous MHC class I expression. Dermatomyositis was diagnosed by clinical criteria including a rash typical of dermatomyositis and the identification of perifascicular atrophy. Necrotizing myopathy was diagnosed based on the observation of necrotic fibers with diffuse distribution without or with minimal inflammatory cell infiltration.

We also studied 251 patients with MG, who were followed at the MG Clinic at Keio University Hospital. The diagnosis of MG was based on clinical, electrophysiologic, and immunologic criteria. The clinical classification and quantitative MG score were graded based on the recommendation issued by the Task Force of the Medical Advisory Board of the Myasthenia Gravis Foundation of America. Disease subtypes were divided into early-onset, late-onset, and thymoma-associated MG. As disease controls and normal controls, we used serum samples from 25 patients with Duchenne muscular dystrophy and 30 healthy volunteers.

Clinical information was retrospectively obtained for all patients by reviewing their clinical charts. All clinical samples and information were collected after the patients and controls gave their written informed consent as approved by the Institutional Review Boards of both the National Center of Neurology and Psychiatry and Keio University. All analyses were performed using statistical analysis software (IBM/SPSS version 20).

Anti-HMGCR ELISA

Our anti-HMGCR ELISA was developed based on the original method with some modifications. First, 96-well polystyrene plates (Smilon multiwell plate H type; Sumitomo Bake) were coated with C-terminal recombinant HMGCR protein (Sigma, St. Louis, MO) at 0.1 μg/mL diluted in phosphate buffered. The remaining blocking sites were blocked with 3% bovine serum albumin. The wells were incubated with serum samples diluted at 1:400 and subsequently with peroxidase-conjugated anti-human IgG (Jackson Immuno Research, Westgrove, PA) diluted 1:100000. The antibody binding was visualized by incubation with tetramethylbenzidine (1 mg/mL) in phosphate-citrate buffer. The reaction was stopped by 1 mol/L sulfuric acid. The optical density at 450 nm (OD450) was read with an automatic plate reader (Biorad, Hercules, CA). Samples were tested in duplicate. The antibody index was calculated from the OD450 of the samples divided by the OD450 of the reference serum (patient 1 in Table 1). The cut-off value was set as the mean + 5 SD of 30 healthy control sera.

Protein Immunoprecipitation Assay

Autoantigens were analyzed by protein immunoprecipitation assay using 35S-labeled RD cellular extracts. RD cells (5 × 10⁶ per sample) were cultured in methionine-free DMEM (Sigma) containing 3% heat-inactivated fetal bovine serum in the presence of 20 μCi/mL 35S-methionine for 14 h. The 35S-labeled cells were suspended in an ice-cold buffer containing 500 mMol/L NaCl, 0.1% Nonidet P-40, 10 mMol/L Tris-HCl, and a cocktail of protease inhibitors (Complete; Roche, Indianapolis, IN), and sonicated intermittently on ice for a total of 90 s. The supernatant containing 35S-labeled soluble proteins originating from the nuclei, cytoplasm, and cellular membrane was recovered by centrifugation (13,000 g for 15 min) and used as the antigen source. Two milligrams of protein A-Sepharose CL-4B (Pharmacia Biotech, Little Chalfont) was incubated with 10 μL of a human serum sample. The immunoglobulins that were bound to protein A-Sepharose beads were then incubated with the 35S-labeled cellular extracts for 2 h. The immunoprecipitated
material was resolved by electrophoresis on SDS-7.5% polyacrylamide gels, which were subsequently treated with 0.5 mol/L sodium salicylate to enhance the radioactivity, and evaluated by autoradiography using a BAS-5000 system (Fuji Film, Tokyo).

**Immunohistochemistry**

Six micrometer sections of frozen muscle tissue from biopsies were prepared. The sections were incubated with monoclonal mouse anti-neural cell adhesion molecule (NCAM) antibodies (Leica, Wetzlar) diluted 1:25, polyclonal rabbit anti-HMGCR antibodies (Sigma) diluted 1:125 and serum samples diluted 1:40. After incubation with the primary antibodies for 16h, the sections were incubated for 2h with a fluorescein isothiocyanate-conjugated anti-mouse, anti-rabbit or anti-human IgG antibody (Jackson Immuno-Research), and the sections were examined with a fluorescence microscope (Eclipse E-800, Nikon, Tokyo).

**RESULTS**

**Anti-HMGCR ELISA**

Since the cut-off value was set as the mean + 5 × SD of 30 healthy control sera, the cut-off of anti-HMGCR index was 0.48. Positivity for the anti-HMGCR antibody was observed in 8 of 26 the patients with necrotizing myopathy (Figure 1). However, only one of the 24 patients with sporadic inclusion body myositis had a slight elevation of anti-HMGCR index. There was no positivity of anti-HMGCR antibodies in the 25 patients with polymyositis or dermatomyositis, or in the 25 patients with Duchenne muscular dystrophy. The

| Patients no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|-------------|---|---|---|---|---|---|---|---|
| Age/sex     | 75/M | 75/F | 70/M | 79/F | 64/M | 57/M | 55/F | 49/M |
| Statin exposure | (+) | (+) | (+) | (-) | (-) | (-) | (-) | (-) |
| Disease duration (mo) | 3 | 2 | 1 | 1 | 2 | 4 | 15 | 3 |
| Neurological examination | 4–5/5 | 3–4/4 | 5/4 | 3/3–4 | 4/4–5 | 3/4 | 4/5 | 5/4 |
| Upper/lower limbs | | | | | | | | |
| Neck weakness | (-) | (-) | (-) | (+) | (-) | (+) | (-) | (-) |
| Dysphagia | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) |
| Muscle atrophy | (-) | (-) | (+) | (+) | (-) | (+) | (+) | (+) |
| Myalgia | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) |
| Deep tendon reflex | D | D | D | D | N | D | D | N |
| Laboratory data | | | | | | | | |
| Creatine kinase (IU/L, nl: 60–250) | 9695 | 9680 | 10452 | 3028 | 6603 | 7238 | 8510 | 6694 |
| Aspartate aminotransferase (IU/L, nl: 10–35) | 196 | 235 | 317 | 110 | 244 | 154 | 262 | 146 |
| Alanine aminotransferase (IU/L, nl: 5–40) | 357 | 353 | 246 | 209 | 325 | 248 | 454 | 199 |
| Lactate dehydrogenase (IU/L, nl: 120–220) | 1248 | 762 | 788 | 898 | 772 | 925 | 1436 | 683 |
| C-reactive protein (mg/dL, nl: 0–0.35) | 0.1 | 8.1 | 0.1 | 0.1 | 0.6 | 0.5 | 0.1 | 0.1 |
| Electromyography | | | | | | | | |
| Spontaneous activity | (+) | (+) | (+) | (-) | (+) | (+) | (+) | n/a |
| Low-amplitude, short-duration MUPs | (+) | (+) | (+) | (+) | (+) | (+) | (+) | n/a |
| Histology | | | | | | | | |
| Variation in fiber size | Marked | Moderate | Mild | Moderate | Marked | Marked | Moderate | Moderate |
| Necrosis fiber | Some | Scattered | Some | Many | Many | Scattered | Some | Scattered |
| Cell infiltration | (+) | (-) | (+) | (-) | (-) | (-) | (+) | (+) |
| Endomysial fibrosis | Minimal | Minimal | Minimal | Minimal | Minimal | Mild | Minimal | Minimal |
| MHC class I expression | (-) | (-) | (+) | (+) | (+) | (+) | (-) | (-) |
| MHC class II expression | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) |
| Treatment | mPSL, PSL | PSL, IVlg | mPSL | mPSL, IVlg | mPSL | mPSL, PSL, IVlg | mPSL, IVlg | n/a |
| Modified Rankin scale | | | | | | | | |
| Pre-treatment | 3 | 3 | 2 | 4 | 2 | 3 | 2 | 2 |
| 2-year follow-up | 0 | 2 | 0 | 2 | 0 | 0 | 0 | n/a |

D = decreased, IVlg = intravenous immunoglobulin, MHC = major histocompatibility complex, mPSL = high-dose methylprednisolone plus therapy, MRC = Medical Research Council, MUPs = motor unit potentials, n/a = not available, N = normal, nl = normal values, PSL = prednisolone.
seropositivity rate in the 26 necrotizing myopathy patients was significantly higher compared with those of the 49 patients with other inflammatory myopathies (31% vs 2%, \( P = 0.001 \)).

**Protein Immunoprecipitation Assay**

We analyzed autoantigens immunoprecipitated by anti-HMGCR-positive sera using the protein immunoprecipitation assay. Representative results obtained from 6 patients with anti-HMGCR antibodies detected by anti-HMGCR ELISA are shown in Figure 2A. Anti-HMGCR-positive serum immunoprecipitated the doublet autoantigens located around 50 kDa (lanes 1–6). However, no immunoprecipitates were found in sera without anti-HMGCR antibodies (lanes 7 and 8). Moreover, we added an excess of the recombinant HMGCR protein (50 ng) to the patient 1’s serum at the incubation with protein A-Sepharose. The 50-kDa doublet autoantigens were clearly absorbed (lane 2 in Figure 2B).

We determined the sensitivity and specificity of the ELISA using this cutoff relative to the protein immunoprecipitation.4,5 Among 75 patients with inflammatory myopathies, 8 sera immunoprecipitated HMGCR protein and all of them were positive by anti-HMGCR ELISA. Conversely, among 9 sera positivity by anti-HMGCR ELISA, 8 were positive by protein immunoprecipitation. Therefore, the sensitivity and specificity of the anti-HMGCR ELISA are 100% and 98.5%, respectively."

**Immunohistochemistry**

We next performed immunohistochemistry using the muscle tissues obtained from patient 3 (Figure 2C). Regenerated muscle fibers were clearly detected by anti-NCAM antibody. In addition, HMGCR was expressed in the regenerated fibers. Anti-HMGCR-positive sera produced similar staining on the muscle fibers of patient’s sera (left panels, Fig. 2C). In contrast, the anti-HMGCR antibody and patient’s sera did not show any staining on the muscle fibers of control muscle.

**Clinical Features of Patients with Anti-HMGCR Antibodies**

The clinical features of eight patients (five men and three women) with anti-HMGCR-positive necrotizing myopathy are summarized in Table 1. Their mean age was 66 years, ranging from 49 to 79 years. All but patient 7 deteriorated within two months with a markedly increase level of creatine kinase. The clinical course suggested the initial diagnosis of rhabdomyolysis. Atorvastatin were administered in 3 patients who were over 70 years’ old. The diseases did not recover after the cessation of the statin treatment. Neurological examinations showed symmetrical and proximal limb weakness. Arms and legs were equally affected. The severe limb weakness with the grade \( \leq 2/5 \) assessed by manual muscle strength (Medical Research Council scale grade) was not observed. No patients had dysphagia. Electromyography also indicated myopathic motor unit potentials (MUPs) in all patients.

With regard to the histology, all patients showed necrotic and regenerating muscle fibers without inflammatory cell infiltration. Endomyosial fibrosis was minimal. MHC class I and class II expression were detected in 50% and 25% of the 8 anti-HMGCR-positive patients, respectively. The 2-year follow-up was available in 7 patients. All patients required immunotherapy and responded well. The recovery of muscle weakness was observed several weeks after the therapy. Since the creatine kinase persisted in higher levels, intravenous immunoglobulin therapy was added in 4 patients. None of the 7 patients experienced disease relapse. Neurological outcome evaluated using the modified Rankin scale showed that 5 of the 7 patients were able to return to their normal daily lives.

Muscle magnetic resonance images (MRIs) were useful for evaluating the distribution of inflammation. Short T1 inversion recovery images in particular showed high signal intensities in all 8 patients. Focal or diffuse abnormal signals were seen in trunk and limb muscles (Figure 3). In contrast to the neurological examination, asymmetry was found on muscle MRI.

**Statin Exposure and Anti-HMGCR Antibodies in MG Patients**

The profiles of 251 patients with MG are indicated in Table 2. Of the 251 patients with MG, 23 (9%) including the 5 early-onset, 10 late-onset, and 8 thymoma-associated MG received statins at the disease onset. Statin brands were atorvastatin in 9 patients, pravastatin in 4, fluvastatin in 4, simvastatin in 3, pivalvastatin in 2, and rosuvastatin in 1 patient. In contrast, only 1 late-onset MG patient experienced MG worsening after statin exposure (Figure 4). Briefly, this 68-year-old woman had a diagnosis of ocular myasthenia at the age of 62 years. Her diplopia and ptosis were well controlled by pyridostigmine and achieved 18-month remission. However, she developed diplopia and ptosis after a 4-week treatment with atorvastatin at the age of 66 years. Her quantitative MG score was increased to 8 with an elevation titer of anti-AChR antibody. Since pyridostigmine was not fully effective, she required prednisolone at a daily dose of 10 mg.

We examined the presence of anti-HMGCR antibodies by conducting our ELISA, using 251 serum samples from the patients with MG. Only 1 (0.4%) early-onset female patient was found to be seropositive for anti-HMGCR antibodies (anti-HMGCR index: 0.6). She had mild generalized MG (MG Foundation of America class 2A) with no history of statin exposure. With regard to the histology, she showed necrotic and regenerating muscle fibers without inflammatory cell infiltration. Endomyosial fibrosis was minimal. MHC class I and class II expression were detected in 50% and 25% of the 8 anti-HMGCR-positive patients, respectively. The 2-year follow-up was available in 7 patients. All patients required immunotherapy and responded well. The recovery of muscle weakness was observed several weeks after the therapy. Since the creatine kinase persisted in higher levels, intravenous immunoglobulin therapy was added in 4 patients. None of the 7 patients experienced disease relapse. Neurological outcome evaluated using the modified Rankin scale showed that 5 of the 7 patients were able to return to their normal daily lives.

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**FIGURE 1.** Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) ELISA. Antibodies reactive with recombinant HMGCR protein by ELISA in sera from inflammatory myopathy patients, Duchenne muscular dystrophy patients, and healthy controls. The cut-off level for positivity is indicated by the broken line (anti-HMGCR index: 0.48).
DISCUSSION

We established an anti-HMGCR ELISA and showed the following clinical relevance of its use:

(i) anti-HMGCR autoantibodies were specifically detected in necrotizing myopathy,
(ii) myopathy associated with anti-HMGCR antibodies was characterized by mild limb weakness and favorable response to immunotherapy with or without statin exposure;
(iii) of 251 MG patients, 1 woman (0.4%) with no history of statin therapy had anti-HMGCR antibody.

The molecular weight of HMGCR is 97-kDa. Original reports indicated that a 100-kDa doublet precipitates detected in the serum sample containing anti-HMGCR antibodies (lanes 1–6). (B) Arrows indicate the 50-kDa doublet precipitates detected in the patient 1 sera (lane 1), but not in a healthy control (lane 3). The autoantigens were absorbed in the presence of recombinant HMGCR protein (lane 2). The panel has been cropped between lanes 2 and 3 to exclude immunoprecipitations that are irrelevant to the current study. (C) Muscle sections were obtained from patient 3 (left panels) and control (right panels). Sections were stained with hematoxylin-eosin (HE), polyclonal anti-neural cell adhesion molecules (NCAM) antibody, polyclonal anti-HMGCR antibody, and anti-HMGCR-positive sera. Scale bar = 50 μm.

**FIGURE 2.** Confirmation of the HMGCR immunoreactivity. (A) Autoradiograms of immunoprecipitated $^{35}$S-labeled RD extracts from serum samples are shown. Immunoprecipitated materials were analyzed on SDS-7.5% polyacrylamide gels. The positions of the molecular weight standards are at the left. Arrows indicate the 50-kDa doublet precipitates detected in the serum sample containing anti-HMGCR antibodies (lanes 1–6). (B) Arrows indicate the 50-kDa doublet precipitates detected in the patient 1 sera (lane 1), but not in a healthy control (lane 3). The autoantigens were absorbed in the presence of recombinant HMGCR protein (lane 2). The panel has been cropped between lanes 2 and 3 to exclude immunoprecipitations that are irrelevant to the current study. (C) Muscle sections were obtained from patient 3 (left panels) and control (right panels). Sections were stained with hematoxylin-eosin (HE), polyclonal anti-neural cell adhesion molecules (NCAM) antibody, polyclonal anti-HMGCR antibody, and anti-HMGCR-positive sera. Scale bar = 50 μm.
exposure. This prevalence was consistent with that in a European cohort (44%).

Taken these findings together, we emphasize that anti-HMGCR antibodies can be regarded as the second serological marker of necrotizing myopathy as well as a marker of statin-induced myopathy.

Importantly, there were clear differences in the clinical characteristics associated with autoantibodies to SRP and HMGCR in our investigation. The neurological manifestations of the anti-HMGCR-positive patients were mild limb weakness with good response to immunotherapy. Older patients tended to have anti-HMGCR antibodies. In contrast, anti-SRP myopathy was characterized by severe limb weakness and atrophy as well as bulbar and trunk muscle involvement. Younger patients showed severe clinical deficits.

Previous reports revealed the clinical features of 15 patients with statin-associated MG. The ages were ranged as 41 to 71 years (average 58 years) and the sex ratio was 11:4 (M:F). Newly-onset MG was observed in 8 patients and worsening of MG in 7 patients. The patients experienced MG symptoms after 1 to 16 weeks after the statin exposure (average, 4 weeks and within 2 weeks in 8 patients). Ocular MG was observed in 3 patients and generalized MG in 12 patients. The

![FIGURE 3. Muscle MRI of patients with anti-HMGCR antibodies. (A–C) Patient 2. Increased short T1 inversion recovery (STIR) signal abnormalities involving deltoid, infraspinatus muscles (A), biceps brachii and triceps brachii (B), and forearm muscles (C). (D–F) Patient 3. Images of thighs on T1 images (D), T2 images (E), and STIR images (F). High intensity in biceps femoris and semitendinosus muscles on STIR images. (G, H) Patient 4. Increased T2/STIR signal abnormalities in posterior calves. (I) Patient 6. Increased STIR signal in trapezius muscle. (J–L) Patient 7. STIR images of pelvis (J) and enhancement in vastus lateralis and obturator internus muscles (K). Increased signal with enhancement of triceps brachii on STIR images (L).](image)

![TABLE 2. Profiles of 251 Patients with Myasthenia Gravis](table)

| Age | mean ± SD (range) | 50 ± 17 (16–88) |
| --- | --- | --- |
| Disease subtypes |  |  |
| Early-onset | 121 (48%) |  |
| Late-onset | 70 (28%) |  |
| Thymoma-associated | 60 (24%) |  |
| Classification of Myasthenia gravis Foundation of America |  |  |
| Class I | 73 (29%) |  |
| Class II | 89 (35%) |  |
| Class III | 54 (22%) |  |
| Class IV | 11 (4%) |  |
| Class V | 24 (10%) |  |
| Autoantibody status |  |  |
| Acetylcholine receptor positive | 198 (79%) |  |
| Muscle-specific tyrosine kinase positive | 6 (2%) |  |
| Seronegative | 47 (19%) |  |

SD – standard deviation.
antibodies status was AChR-positive in 10 patients, muscle-specific tyrosine kinase-positive in 4, and seronegative in 1 patient. Discontinuation of statins and initiation of pyridostigmine were effective, but immunotherapy was necessary in 8 patients.

In our case series, it is likely that statins were less involved in the new onset of MG in 23 patients because myasthenic symptoms did not develop within several weeks after the start of the statin therapy. However, 1 patient’s MG worsened after 4 weeks of statin use, after an 18-month MG remission. Her symptoms were limited to ocular myasthenia, but prednisolone was necessary to control her disease.

Oh et al. reported that MG worsening occurred in 6 (11%) of their 54 MG patients with statin treatment. However, the actual incidence of statin-associated MG exacerbation seems to be lower. In clinical practice, we also feel that statins should be used in patients with MG for the same indications as in individuals without MG.23 Statins should be withdrawn if exacerbation of MG occurs, or if the anti-AChR antibody concentration increases markedly.

A limitation of the present study is that anti-HMGCR antibodies were evaluated in only 1 statin-associated MG patient, although the cases of 251 MG patients were examined. However, we think that anti-HMGCR antibodies do not affect the function of neuromuscular transmission. We regard seropositivity with a low titer of anti-HMGCR antibodies in 1 MG patient as a non-specific phenomenon. In a previous report, positivity with a low titer of anti-HMGCR antibodies in 1 MG patient was necessary to control her disease.

In conclusion, anti-HMGCR antibodies are a relevant clinical marker of necrotizing myopathy with or without statin-exposure, but they are not associated with the onset or deterioration of MG.

FIGURE 4. Clinical course of a 68-year-old woman with MG worsening after statin treatment. Anti-AChR = anti-acetylcholine receptor antibody, QMG = quantitative myasthenia gravis.
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