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Letter to the Editor

# Eculizumab improved weakness and taste disorder in thymoma-associated generalized myasthenia gravis with anti-striational antibodies: A case report

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*Dear Editor*

Myasthenia gravis (MG), an autoimmune disease, is characterized by physical exhaustion and weakness caused by autoantibody-induced dysfunction of the neuromuscular junction. MG is frequently accompanied with thymoma, and approximately 25% of patients with thymoma-associated MG exhibit at least one non-motor symptom (taste disorder, myocarditis, neuromyotonia, limbic encephalitis, pure red cell aplasia, immunodeficiency, or alopecia areata) [1]. Further, approximately 74%–88% of patients with MG have anti-acetylcholine receptor (AChR) antibodies that bind to postsynaptic membrane and induce complement-mediated injury [2]. Moreover, anti-striational antibodies are often detected in patients with thymoma-associated refractory MG [3, 4], which putatively induce complement activation [5].

Herein, we report the case of refractory thymoma-associated generalized MG with anti-AChR and anti-striational antibodies. The motor symptoms remarkably improved by the administration of eculizumab, a humanized monoclonal antibody that targets the terminal complement protein C5 [6]. Moreover, taste disorder was alleviated, suggesting the involvement of complement activation in the onset of taste disorder in patients with MG.

## 1. Case report

A 34-year-old male presented to our hospital after 3 months of the onset of limb weakness, bilateral ptosis, diplopia, and dysphagia. A diagnosis of thymoma-associated generalized MG was established based on positive serum anti-AChR antibodies (51 nmol/L) and detection of thymoma by computed tomography. Among anti-striational antibodies, anti-titin and anti-Kv1.4 antibodies were positive, whereas serum anti-RyR antibody was negative. The patient had no arrhythmia or heart failure. Serum IgG was 1873 mg/dL, and the patient had no past history of immunodeficiency. Although treatment with oral prednisolone was initiated prior to performing extended total thymectomy, the patient exhibited rapid aggravation of dysphagia and dyspnea. Eventually, mechanical ventilation was required due to myasthenic crisis. Following treatment with intravenous high-dose immunoglobulin (IVIg, 400 mg/kg bodyweight for 5 days) and intravenous methylprednisolone (IVMP, 1000 mg/day for 3 days) followed by oral prednisolone, thymectomy was performed [7]. Postoperatively, the patient was treated with oral prednisolone (60 mg/day) with tacrolimus. Although prednisolone dose tapering was attempted, the patient experienced relapse of MG every 3–6 months; the prednisolone dose could not be reduced below 20 mg/day. Approximately 10 months following the onset, the patient gradually developed impairment of taste sensation and diffuse alopecia areata. Each relapse of MG was repeatedly treated with IVIg, IVMP, intravenous cyclophosphamide, and plasmapheresis. However, long-term remission of motor symptoms could not be achieved with prednisolone and tacrolimus therapy, and there was a gradual worsening of taste disorder and alopecia areata.

Eighteen months following the onset, the patient developed pulmonary infection with *Mycobacterium avium complex*, ostensibly owing to the long-term immunosuppressant therapy. To taper predonisolone dose, eculizumab was introduced as a maintenance therapy for refractory MG. Eculizumab administration was initiated after antibiotics against the *M. avium complex* had been administered for at least 1 year and chest X-ray showed signs of remission.

Just before eculizumab administration was initiated, the patient was receiving predonisolone (20 mg/day) and tacrolimus (2.5 mg/day) and exhibited severe physical exhaustion and bilateral ptosis. The quantitative myasthenia gravis (QMG) score was 13 and Myasthenia Gravis Activities of Daily Living (MG-ADL) score was 18. The induction dosing schedule of eculizumab was 900 mg on day 1 and weeks 1, 2, and 3; the maintenance dose was 1200 mg every second week after week 4. Eculizumab substantially improved the motor symptoms, and prednisolone could be safely tapered; the QMG score reduced to 4 and MG-ADL score to 5 at week 12 with 2.5 mg/day tacrolimus and 12.5 mg/day prednisolone. Remarkably, the taste disorder and motor symptoms together showed improvement, whereas alopecia areata did not improve. Following the introduction of eculizumab and tapering of steroids, there was no deterioration in the *M. avium complex* infection. At week 26, the QMG score was 3 and MG-ADL score was 2 with 2.5 mg/day tacrolimus and 8 mg/day prednisolone. After week 34, the patient exhibited minimal manifestations with 3 mg/day tacrolimus and 5 mg/day prednisolone.

## 2. Discussion

Eculizumab blocks complement-mediated injury to postsynaptic AChR [6] and has been used for patients with anti-AChR antibody-

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associated refractory generalized MG [2]. Although in the REGAIN study, the change in the MG-ADL score from baseline to week 26 did not significantly differ between the eculizumab and placebo arms, additional prespecified sensitivity and secondary analyses suggested the efficacy of eculizumab [2]. However, patients with a history of thymoma or thymic neoplasms were excluded from the REGAIN study, and the patients were not investigated for anti-striational antibodies. The present case suggests that eculizumab is effective in patients with thymoma-associated generalized MG who have anti-striational antibodies.

Anti-striational antibodies can recognize the epitopes on skeletal and cardiac muscle tissues. Among these, antibodies against titin, RyR, and Kv1.4 are frequently observed in patients with anti-AChR antibody-positive thymoma-associated MG [4]. Presence of these antibodies is associated with severe manifestations of MG including complications of myositis and cardiomyositis [8]. Anti-striational antibodies have been implicated in complement activation and the subsequent muscle dysfunction [4,5]. In the present case, eculizumab possibly inhibited complement activation mediated by anti-striational antibodies, which resulted in a favorable clinical course.

In addition, this case is unique in that taste disorder improved following eculizumab administration, although no improvement in alopecia areata was observed. Among the non-motor symptoms of MG, taste disorders are putatively autoantibody-mediated disorders and typically respond to immunotherapy in parallel with the disease activity of MG [1,9]. Conversely, alopecia areata is considered to be due to CD8 T-cell cytotoxicity and independently develops of the clinical course of MG [1]. Although further studies are needed, the present case suggests that complement activation is involved in the causation of taste disorder, but not of alopecia areata, in patients with MG.

We cannot eliminate the possibility that the long-term immunotherapy administered prior to the use of eculizumab contributed to the remission; however, MG did not relapse after the induction of eculizumab for more than 12 months and prednisolone was successfully tapered. We hypothesize that eculizumab inhibited complement-mediated damage triggered by anti-AChR antibodies and anti-striational antibodies and that it is effective in patients with anti-striational antibodies associated MG.

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## Declarations of interest

None.

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