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Complement inhibition in seropositive generalized myasthenia gravis as rescue therapy in impending and effective treatment in frequently recurring impending myasthenic crisis—a case series

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***Abstract*:** In seropositive myasthenia gravis (MG), complement inhibition has been shown to be an effective and a fast-acting therapeutic option. Myasthenic crisis (MC), usually preceded by impending MC, is a life-threatening complication requiring highly effective treatments with rapid onset of action. Currently used treatment options of MC are limited, consisting mainly of symptomatic and immune therapies, that is, intravenous immunoglobulins and plasma exchange/immunoadsorption. So far, there is only very limited data on complement inhibitors in impending or manifest MC or termination of frequently recurring impending crises. Here, we report three cases of acetylcholine receptor antibody positive MG, two with impending and one case suffering from high-frequency impending MC, where complement inhibition with eculizumab or ravulizumab resulted in a rapid and sustained remission. Meningococcal vaccination, mandatory when using complement inhibitors, did not result in symptom-worsening or manifest MC.

Keywords: complement inhibition, eculizumab, meningococcal vaccination, myasthenia, ravulizumab

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Introduction

Generalized myasthenia gravis (gMG) is an autoimmune disorder affecting neuromuscular transmission due to antibodies to postsynaptic targets in seropositive cases and is characterized by fluctuating exertional weakness of voluntary muscles.[1] In the majority (85%–90%) of gMG patients, antibodies against the nicotinic acetylcholine receptors (AChR) can be detected, other postsynaptic antigens comprise muscle-specific receptor tyrosine kinase and low-density lipoprotein receptor-related protein 4. In seronegative gMG, at present undetectable antibodies may be of pathogenic relevance.[1]

Autoantibodies against the AChR lead to complement pathway activation and destruction of the neuromuscular junction by accumulation of antibodies.[2] There is plenty of evidence that activation of the complement system is critical to the pathology of myasthenia gravis (MG). Complement inhibitors target the component C5 with the goal of blocking terminal complement activation, preventing the pro-inflammatory effects of C5a and C5b and the subsequent formation of the terminal complement component or membrane attack complex (C5b-9).[3]

The approval of the terminal complement inhibitors eculizumab and ravulizumab for AChR-positive gMG has broadened the therapeutic spectrum.[1] Both humanized monoclonal antibodies inhibit the cleavage to C5a und C5b, thus preventing the cascade of events leading to the destruction of the neuromuscular junction.[2]

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Complement inhibitors have been found to be fast-acting. In the phase III CHAMPION MG study, therapeutic serum ravulizumab concentrations were achieved immediately, and clinical response (defined by ⩾5-point improvement in quantitative myasthenia gravis (QMG)) was observed within 1 week after the first dose of ravulizumab.[4] In the REGAIN study, clinical response was achieved in 19.4% within 1 week after the first eculizumab application.[5]

Up to 20%–25% of patients with MG experience at least one myasthenic crisis (MC) during their lifetime.[6] Triggers such as infections, pregnancy, dose failures, or certain medication (e.g., antibiotics) can lead to an acute worsening of weakness resulting in a life-threatening MC.[6,7] A manifest myasthenic crisis (mMC) is characterized by rapidly progressive weakness of the respiratory and bulbar muscles, culminating in aspiration and respiratory insufficiency necessitating intensive care treatment and (non)invasive ventilation.[6,8] An impending myasthenic crisis (iMC) is defined by a rapid clinical worsening of MG that, in the opinion of the treating physician, could lead to MC in the short term (days to weeks).[8]

Currently recommended treatment options in MC are plasma exchange (PE)/immunoadsorption (IA), intravenous immunoglobulins (IVIG), and steroid pulse therapy.[9]

So far, there is no robust evidence for the use of complement inhibitors in mMC or iMC with only few case reports for eculizumab[10–13] and even less for ravulizumab.[14]

In the REGAIN phase III study,[15] only 7/62 eculizumab treated participants were classified as Myasthenia Gravis Foundation of America (MGFA) IV. To our knowledge, the use of eculizumab in treatment refractory MC ($n=14$) or severe MG ($n=4$, MGFA classes III–IV[16]) has been reported in a total of 18 AChR-antibody positive cases until now.[10–13,16–18] Apart from PE/IA or IVIG, 2 of these 18 cases received rituximab[13,17] approximately 2 months before eculizumab, impeding the interpretation of the subsequent clinical course. In the report by Oyama et al.,[16] 9 of 11 patients received tacrolimus, 1 patient cyclosporine additionally to prednisolone given in all cases. In 3 of 18 cases,[12,13,17] azathioprine had been given before, in 1 case mycophenolate mofetil.[17]

Six of 86 ravulizumab-treated patients in the CHAMPION phase III trial[19] were classified as MGFA IV. To our knowledge, there is only one case report regarding the successful use of ravulizumab in MC.[14] Of note, in this report, the patient did not undergo ventilation and was classified as MGFA IV, per definition not fulfilling the criterion of MC. As a possible limitation, the authors discussed that the long-term stability over 19 weeks might not only be attributed to ravulizumab initiation but also to rituximab given 1 week before.

A known drawback of phase III studies is that included participants often do not reflect clinical situations.

In the phase III REGAIN study[15] and its open-label extension,[20] treatment refractory patients were included characterized by lacking symptom control in MGFA II–IV, who have received at least two immunosuppressive therapies or at least one immunosuppressive therapy plus IVIG or PE for at least 12 months. However, patients with IVIG or PE within 4 weeks before randomization, rituximab within 6 months before screening or patients with a history of thymoma were excluded.

In phase III CHAMPION-MG study[19] and its open-label extension,[21] treatment refractory disease course was not an inclusion criterion, patients who had received IVIG or PE in the previous 4 weeks, rituximab in the previous 6 months, or previous treatment with eculizumab were excluded.

For the risk of meningococcal infection due to complement inhibition, before the administration of eculizumab or ravulizumab, vaccination is mandatory. In urgent cases, where vaccination is postponed or has not yet resulted in protection, the administration of prophylactic antibiotics is necessary.[9]

Here, we present two cases (1 and 2) of AChR-antibody positive gMG with iMC and one patient (case 3) with frequently recurring iMC and refractory disease course showing a rapid and sustained clinical response to eculizumab and/or ravulizumab. The role of meningococcal vaccination as potential trigger for myasthenic worsening will also be discussed.

Case series

Case 1

A 57-year-old woman presented in February 2018 with first iMC with dyspnea, ptosis, limb weakness, and double vision as her first manifestation of AChR-antibody positive (44.4 nmol/l) gMG (MGFA IV B).

Treatment with pyridostigmine, prednisolone, and eight PE resulted in a marked improvement. Subsequently, the patient received IVIG at 2 g/kg body weight, followed by 0.4 g/kg body weight monthly. Thymectomy was performed 6 months after diagnosis (no thymoma). With IVIG, the patient was stable except for symptom exacerbation in January 2019, treated with up-titration of IVIG. In October 2019, the second iMC occurred with dyspnea and reduced vital capacity, treated with increasing prednisolone doses, and continuous infusion of pyridostigmine at our intensive care unit with no evidence of increased respiratory tract secretion. Azathioprine, given additionally, had to be discontinued after a few weeks due to a hypersensitivity reaction, so IVIG was continued with 0.4 g/kg body weight monthly.

In August 2022, the third iMC occurred with bulbar symptoms, dyspnea, ptosis, and limb weakness, treated with higher doses of pyridostigmine and prednisolone, seven PE, and, due to lack of treatment response, IVIG at 2 g/kg body weight. Therefore, treatment with eculizumab was introduced in September 2022. Myasthenic symptoms rapidly improved and stabilized over nearly 2 weeks, but the clinical course was complicated by cardiac arrest 3 days after second eculizumab dose, regarded as unrelated to eculizumab, followed by aspiration pneumonia, septic shock, multiorgan failure, and insertion of a percutaneous enterogastrostomy tube, independent of MG. After recovery from intensive care complications, there was a gradual and sustained improvement. In December 2022, treatment was switched to ravulizumab, resulting in stable disease for 19 months with only mild exertional dyspnea (at last visit: QMG: 3 points, myasthenia gravis activities of daily living (MG-ADL): 1 point, myasthenia gravis-quality of life 15 (MG-QoL15): 6 points). Treatment and clinical course are presented in Figure 1.

Case 2

A 72-year-old male presented with progressive exertional dysphagia, fluctuating dysarthria, and neck flexor paresis in September 2023. After the diagnosis of AChR-antibody positive (39.6 nmol/l) gMG (MGFA IV B), prednisolone and pyridostigmine were initiated. Computed tomography scan could not verify thymoma. Azathioprine, started after diagnosis, had to be stopped for liver toxicity. After initial improvement under up-titration of prednisolone and pyridostigmine without increased respiratory tract secretion, there was a clinical deterioration of dysphagia with a high risk of aspiration indicating the first iMC, requiring six PE, and leading to clinical improvement. However, immediately afterward, a SARS-CoV-2 infection resulted in a rapid increase in bulbar symptoms with severe dysphagia (second iMC). Ravulizumab was initiated in October 2023, which led to a rapid and sustained clinical improvement. The patient was discharged from hospital without dysphagia and with only slight dysarthria. Under continued complement inhibition, the patient is stable (at last visit: QMG: 2 points, MG-ADL: 4 points, MG-QoL15: 25 points, due to concomitant depression). Treatment and clinical course are presented in Figure 1.

Case 3

A 47-year-old woman presented in June 2020 with double vision, ptosis, dysarthria, and dysphagia. After diagnosis of AChR-antibody positive (5.9 nmol/l) gMG (MGFA IV A) presenting with first iMC, treatment with prednisolone and pyridostigmine resulted in a transient improvement of myasthenic symptoms, followed by myasthenic worsening with severe limb weakness, double vision, and bulbar symptoms (second iMC). Despite administration of IVIG (1 g/kg body weight) and up-titration of pyridostigmine, there was no relevant improvement necessitating seven PE, another IVIG administration (2 g/kg body weight), and higher prednisolone doses. After a brief incomplete remission, dysphagia and limb weakness increased (third iMC), treated with six PE, followed by IVIG (1 g/kg body weight). The patient underwent thymectomy in September 2020 (WHO Type A thymoma, Masaoka stage I). Due to postoperative worsening (double vision and ptosis), IVIG

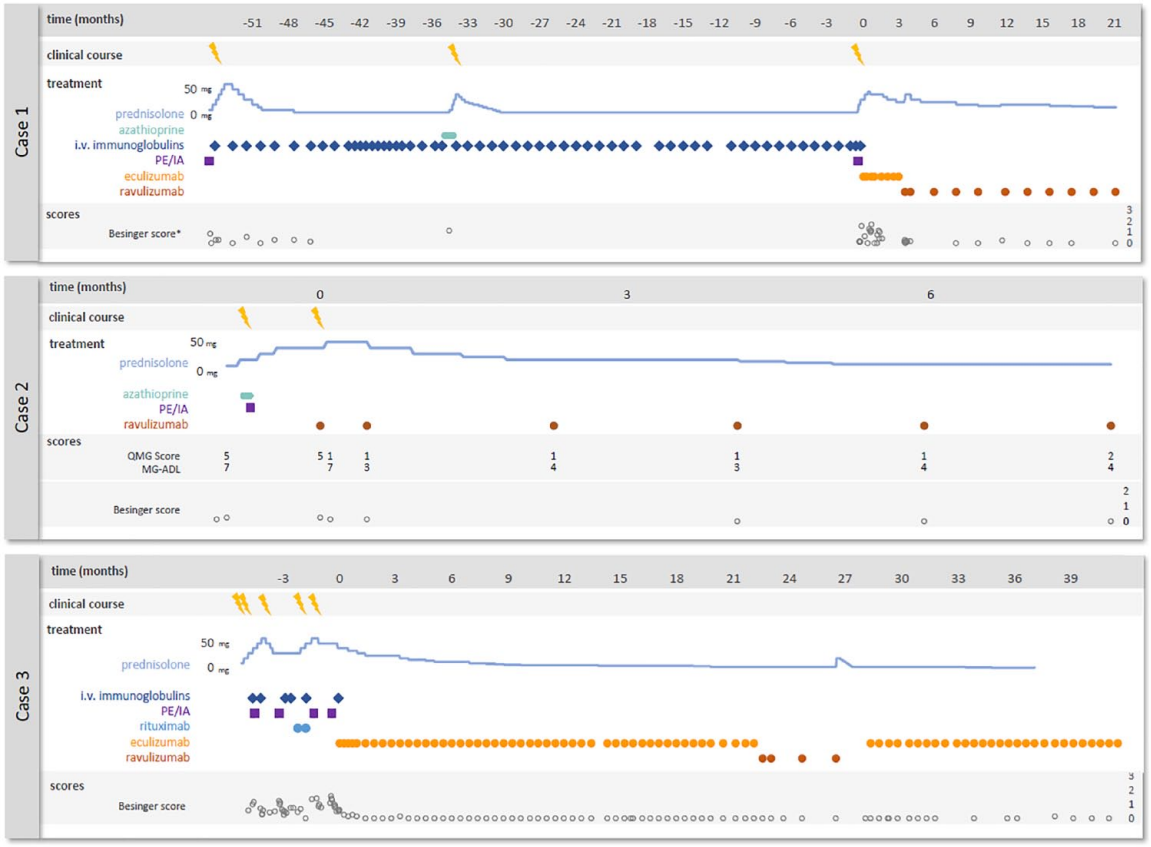

Figure 1. Treatment and clinical course of cases 1–3; from top to bottom: time (in months) = 0 at initiation of complement inhibition, impending myasthenic crisis (zigzag arrow), immunotherapies, clinical scores (case 1–3: Besinger score; case 2: QMG and MG-ADL score).
*Besinger score without vital capacity.
IA, immunoadsorption; MG-ADL, myasthenia gravis-specific activities of daily living; PE, plasma exchange; QMG, quantitative myasthenia gravis.

(1 g/kg body weight) was administered, and rituximab was initiated (2 × 1 g, 2 weeks apart). Despite peripheral depletion of B-cells, further (fourth and fifth) iMC were again treated with seven PE and seven IA, respectively, leading to a remarkable improvement, but with residual mild dysphagia and stress-related double vision. For recurrent iMC, eculizumab was initiated in December 2020, 7 days after the last IA (MGFA III A), leading to a rapid, sustained, and nearly complete remission. In December 2022, eculizumab was switched to ravulizumab for longer infusion intervals. In April 2023, ravulizumab was again changed to eculizumab due to arthralgia and back pain. Since treatment with complement inhibition, the patient is in nearly complete remission with no further iMC occurring (at last visit: QMG: 0 points, MG-ADL: 1 point, MG-QoL15: 0 points). Treatment and clinical course are presented in Figure 1.

Meningococcal vaccination, cases 1–3

As required according to the prescribing information,[22,23] and the recommendations of the German Standing Committee on Vaccination (STIKO),[24] all patients received vaccination against *Neisseria meningitidis* serogroup A, C, W, Y (Nimenrix®) and serogroup B (Bexsero®, administered twice with a 1 month interval) between 6 days (case 1) and 1 day (case 2) before and 2 days (case 3) after initiating complement inhibition. Revaccination for serogroup B was performed 1 year later (case 1). Vaccination was tolerated well without any worsening of MG. The prednisolone dose at the time of vaccination ranged between 20 and 40 mg daily.

Antibiotic prophylaxis with depot Penicillin G Benzathine (Tardocillin® 1,200,000 units i.m.) for meningococcal infection was once administered between 2 and 5 days prior to initiation of complement inhibition and was continued for 13–106 days (see below) after completion of vaccination.

In case 3, 1 month after completing meningococcal vaccination at a prednisolone dose ranging between 30 and 40 mg daily, antibody testing for serogroup A, C, W, Y using a rabbit serum bactericidal assay revealed no protective antibodies (titers < 4 with titers ≥ 8 being considered protective). The antibody titer for serogroup B could not be measured under eculizumab therapy due to interactions between the antibody and the human complement used in the test.[25] After re-vaccination against all five serogroups after 2.5 and 3.5 months, protective antibodies were still not detectable (prednisolone daily dose between 17.5 and 20 mg). Antibiotic prophylaxis was subsequently discontinued due to potential side effects. B-cells, after rituximab treatment, were depleted at that time (1/µl).

In all cases, there have been no signs or symptoms of meningococcal infection so far.

Discussion

Here, we report two cases with iMC refractory to currently recommended treatment options in iMC or mMC (glucocorticosteroids, PE/IA, IVIG), and one case with frequently recurring iMC showing a rapid and sustained clinical response to complement inhibition with a durable effect between more than 6 and beyond 36 months after treatment start. Eculizumab was well tolerated. In case 3, when treated with ravulizumab, arthralgia, and back pain, known from the phase III trial in around 15% and 16%, respectively,[21] occurred, prompting a treatment change back to eculizumab.

The cases reported here confirm the efficacy of eculizumab in severe MG. In case 3, rituximab had been given approximately 2 months before eculizumab. Although a therapeutic effect of rituximab on the disease course cannot be excluded, the nearly complete remission over the subsequent 3 years under eculizumab as most recent immune-monotherapy argues for the effectiveness of complement inhibition. The same applies to case 1 receiving no other immunotherapy other than glucocorticosteroids and IVIG in more than 30 months before eculizumab was started.

In most cases reported in the literature, a marked improvement was noted after eculizumab; however, in two cases intermittent ventilation was still necessary.[10,17]

Case 2 reported here, did not receive immunosuppression before, apart from prednisolone and azathioprine for only 3 days that had to be stopped due to liver toxicity. To our knowledge, our report with an observation period of more than half a year is the second[14] on the use of ravulizumab with rapid and sustained efficacy in iMC. Characterized by the same mode of action, ravulizumab has the major advantage of longer infusion intervals compared to eculizumab (8 vs. 2 weeks, respectively).

A limitation of our report is the small number of only two cases refractory to currently recommended treatment options for iMC but responding very favorably to complement inhibition. However, since clinical trials in iMC or mMC are lacking, our cases contribute to the few reports on the efficacy of eculizumab and ravulizumab in these challenging clinical situations.

Patients with active or untreated thymoma, a history of thymic carcinoma, or thymic malignancy (unless deemed cured by adequate treatment with no evidence of recurrence for 5 years or more before screening), were excluded from the CHAMPION MG phase III trial.[19] In the REGAIN study with eculizumab, a history of thymoma or thymic neoplasms was an exclusion criterion.[15] In the case series of Oyama et al.,[16] 5 of 11 patients were diagnosed with thymoma, with favorable response to eculizumab. In case 3 reported here, WHO type A thymoma was diagnosed with no recurrence so far. Together with this patient also responding to complement inhibition, the presence of a thymoma does not seem to argue against the use of complement inhibitors.

Since the risk for meningococcal infection is increased under complement inhibitors, anti-meningococcal prophylaxis by vaccination, and/or, if postponed, antibiotic prophylaxis is obligatory. Inactivated and subunit vaccines are regarded as safe in MG. Although some of them,

such as anti-SARS-CoV-2 vaccine, might uncommonly cause MG exacerbations, a recent review suggests that benefits still outweigh by far the potential risks.[26]

To date, there are no published data on the risk of meningococcal vaccination regarding myasthenia worsening. In the three cases reported here, vaccination was commenced between 6 days before and 2 days after complement inhibition with no signs of symptom worsening. The exact timing of vaccination has not been described in the reports published so far. Where mentioned, vaccination was performed within few weeks before or after eculizumab treatment.[11,13,16,17] Worsening of myasthenic symptoms after vaccination has not been reported.

Of interest, in neuromyelitis optica spectrum disorders, the proportion of patients with a physician-reported relapse within 4 weeks after meningococcal vaccination and before complement inhibition or randomization to placebo, was 3.1% in eculizumab and 10.6% in placebo treated patients.[27] Further studies, however, are necessary to obtain meaningful data on potential negative effects of vaccination on autoimmune conditions.

In patient 3 repeated analyses of protective antibodies against meningococci revealed negative results. This may be explained by the preceding immune therapies (prednisolone, IVIG, and rituximab). In cases like this, it remains open, to what extent, or if at all, repeated vaccination provides protection against meningococcal infections. Of note, in patients undergoing eculizumab treatment, it is not possible to determine vaccination titers after immunization with protein-based serogroup B vaccines due to interactions between the antibody and the human complement used in a commonly performed test.[25] This may be circumvented by different test procedures.

In a recent integrated analysis of postmarketing surveillance in Japan in patients with paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, or gMG, four cases of meningococcal infection with an event rate of 0.10 per 100 patient-years were reported, but none in MG. Two patients died from meningococcal sepsis, with a mortality rate of 0.05 per 100 patient-years.[28] This highlights the importance of education for the early detection of signs indicating a meningococcal infection.

In conclusion, complement inhibitors like eculizumab and ravulizumab are an option as rescue treatment in iMC and mMC as well as recurrent iMC based on published and our cases reported here. Zilucoplan, another complement inhibitor given subcutaneously,[29] recently approved for seropositive MG, may be another option, but data for its use in MC are lacking.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The patients have provided a written informed consent for publication of this article.

Author contributions
Martina Menacher: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Markus Naumann: Writing – review & editing.

Antonios Bayas: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Availability of data and materials

Patient information or materials cannot be shared for privacy reasons.

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Appendix

Abbreviations

AChR	acetylcholine receptor
gMG	generalized myasthenia gravis
IA	immunoadsorption
iMC	impending myasthenic crisis
IVIG	intravenous immunoglobulins
MC	myasthenic crisis
MG	myasthenia gravis
MG-ADL	myasthenia gravis activities of daily living
MGFA	Myasthenia Gravis Foundation of America
MG-QoL15	myasthenia gravis-quality of life 15
mMC	manifest myasthenic crisis
PE	plasma exchange
QMG	Quantitative Myasthenia Gravis