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CASE REPORT

Management of refractory generalized myasthenia gravis with eculizumab during pregnancy and puerperium: a case report

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Abstract

Myasthenia gravis (MG) mostly affects women of childbearing age. Since the disease course may be affected during pregnancy and postpartum, monitoring and appropriate treatment of MG in pregnant women are crucial. Current treatment options for pregnant women with refractory MG are limited by possible teratogenicity and inadequate lactation data. This case report describes a successful pregnancy in a patient who received eculizumab for refractory generalized MG that was difficult to manage during the pre-pregnancy period. We also report the experience of preterm labour and neonatal MG and the 1-year follow-up of the neonate. Considering the risk–benefit balance, eculizumab can be recommended during pregnancy and postpartum, especially in women with refractory generalized MG.

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Introduction

Myasthenia gravis (MG) is an acquired autoimmune disease characterized by weakness in the ocular, bulbar, extremity or respiratory muscles that increases with activity. Acetylcholine receptor (AchR) antibodies (AchRAb), which are detected in 80–90% of patients with MG, cause neuromuscular junction dysfunction through AchR blockade and disrupt the postsynaptic membrane structure through membrane attack complex-mediated damage as a result of complement activation.[1] MG can occur at any age, with female predominance in the second and third decades.[2] Because MG more frequently affects women of reproductive age, pregnancy for both the course of the disease and the health of the mother and baby. Whilst MG exacerbation rates in pregnancy tend to be higher than remission rates, a significant proportion of cases remain stable.[3] Exacerbations are usually mild to moderate, and myasthenic crisis during pregnancy is rare.[3] Although most generalized MG (gMG) can be controlled with pyridostigmine with/without immunosuppressants, such as oral corticosteroids, azathioprine, mycophenolate mofetil, methotrexate or rituximab, 10–15% of cases do not respond to these treatments and are called 'refractory gMG'.[4] Eculizumab, a humanized monoclonal antibody targeting complement C5, has been shown to be effective and well tolerated in patients with refractory AchRAb-positive gMG.[5,6] However, its use in pregnant women with MG is not well documented. There are only two cases and five pregnancies in the literature of eculizumab use in pregnant women with MG, and we anticipate that experiences will increase in the future.[7–9] Treatment management during pregnancy and postpartum can be challenging, especially in refractory gMG cases, and current treatment options are limited by potential

teratogenicity and lack of lactation data. In this case report, we present the successful management of a patient with refractory gMG who continued eculizumab treatment during pregnancy and postpartum with favourable fetal and neonatal outcomes.

Ethics statement

No information is reported that could enable the patient to be identified; therefore, no patient consent was required. This manuscript was prepared according to CARE guidelines.

Case report

A 28-year-old female patient who presented with symptoms of diplopia and ptosis in 2013 was diagnosed with anti-AchRAb-positive MG. Pyridostigmine and oral corticosteroids were started as initial treatment. Computed tomography of the chest revealed evidence of thymic hyperplasia, and she underwent thymectomy a year following the diagnosis. One month later, the patient received intravenous immunoglobulin (IVIG) treatment at a dosage of 0.4 g/kg/day for 5 days due to weakness in the extremities and difficulty in swallowing. There was partial improvement in her symptoms, and azathioprine (100 mg/day gradually) was started in addition to monthly IVIG treatment.

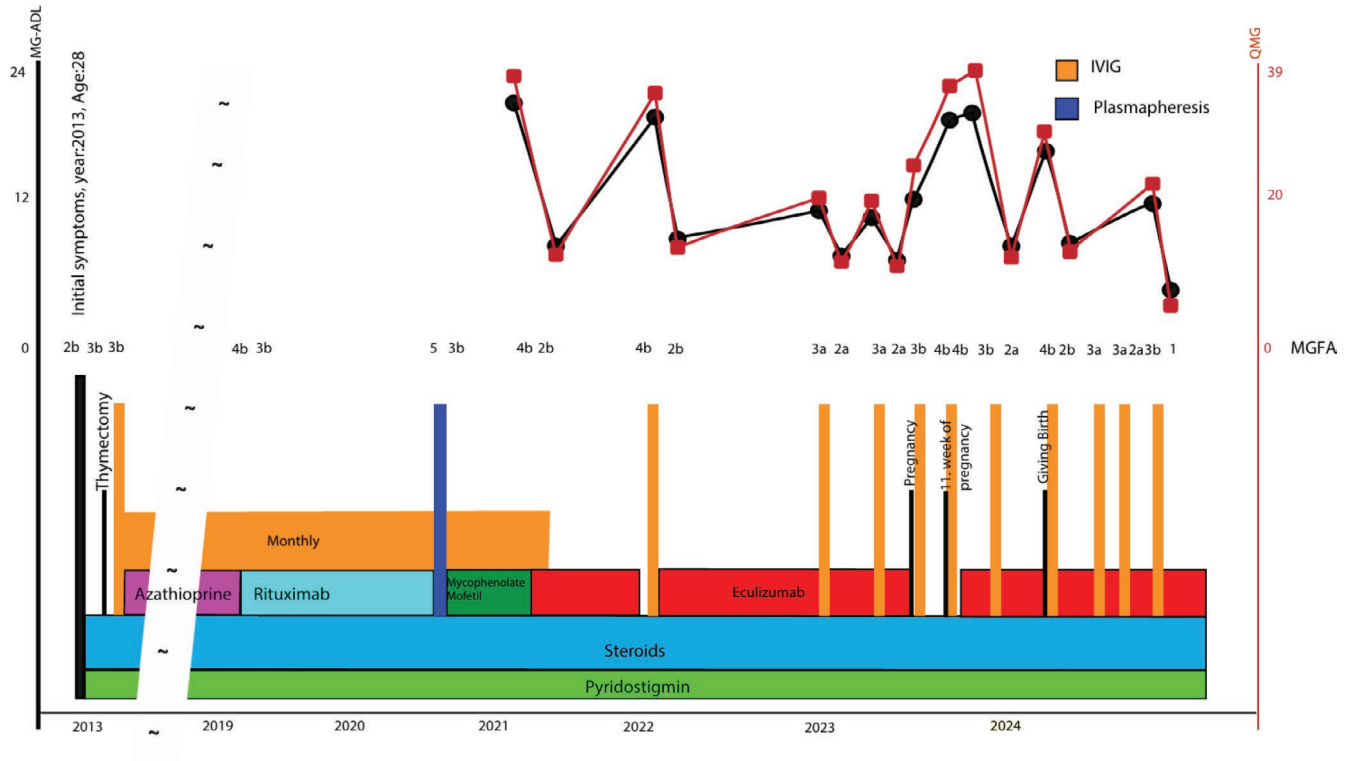
In February 2019, due to continued attacks in the setting of bulbar and generalized weakness, azathioprine was switched to intravenous rituximab 375 mg/m^2. The patient had an attack of myasthenic crisis requiring hospitalization whilst under treatment with rituximab, methylprednisolone 64 mg/day, pyridostigmine 480 mg/day and monthly IVIG 0.4 g/kg for 6 months. Her neurological examination at that time revealed bilateral ptosis, limited gaze, 3/5 muscle strength in the upper extremities and 2/5 muscle strength in the lower extremities, and the need for a nasogastric (NG) feeding tube. She could only count to eight on one breath. After seven sessions of plasmapheresis, the extremity weakness improved partially, but the patient was still fed with an NG feeding tube. Rituximab was discontinued, and mycophenolate mofetil (2000 mg/day) was added to oral methylprednisolone 40 mg/day and monthly IVIG.

Despite 4 months of mycophenolate mofetil treatment, attacks of bulbar weakness occurred. In March 2021, a decision was made to switch the patient to eculizumab treatment whilst continuing methylprednisolone 64 mg/day and pyridostigmine 480 mg/day. The patient was vaccinated for meningococcal meningitis before receiving eculizumab. At that time, her pre-treatment Myasthenia Gravis Foundation of America (MGFA) score was calculated as Class 4b, the Myasthenia Gravis – Activities of Daily living (MG-ADL) score was 21 and the quantitative MG (QMG) score was 39. A few days after receiving the first dose of eculizumab in March 2021, her dysphagia improved, and her NG feeding tube was removed. In the first week after the first dose, the patient, who had been in a wheelchair for months, was able to walk with one-sided support. The MG-ADL score regressed to 8 and QMG to 11. As reflected in her MG metric scores, eculizumab was effective and well tolerated. Oral methylprednisolone was reduced to 8 mg/day and pyridostigmine to 240 mg/day, and monthly IVIG treatment was discontinued. The patient had no significant symptoms other than mild ptosis whilst receiving eculizumab 1200 mg every 2 weeks until she experienced a mild COVID-19 infection in December 2021.[10] She had to stop treatment for 1 month during the COVID-19 infection and relocated to another city. Subsequently, she was then admitted to our clinic for the first time with ocular bulbar and generalized weakness. Neurological examination revealed bilateral ptosis, gaze paralysis and quadriparesis. She was being fed with an NG feeding tube and could count up to 10 in a single breath. IVIG administered at a dose of 0.4 g/kg/day for 5 days provided partial improvement. Eculizumab was restarted in February 2022. Immediately after restarting eculizumab, the NG feeding tube was removed with a dramatic improvement in swallowing difficulty within 48 hours of the eculizumab dose. The patient was stable for about 1 year with methylprednisolone 40 mg/day, pyridostigmine 240 mg/day and eculizumab every 2 weeks. The patient experienced worsening of myasthenic symptoms triggered by psychological stress and required IVIG twice in January and May 2023.

In July 2023, when an unplanned pregnancy occurred, eculizumab treatment was discontinued because the patient did not want to use it during pregnancy. In August 2023, at 11 weeks' gestation and without taking three doses of eculizumab (after 7–8 weeks without treatment), she was hospitalized with ocular, severe bulbar and generalized weakness, and received IVIG 0.4 g/kg/day for 5 days. After evaluating the risks and benefits with the patient, it was decided to continue eculizumab treatment. She responded dramatically to the restarted eculizumab and was quickly weaned off the NG feeding tube. She gave birth to a healthy male baby by an unplanned caesarean section at 35 weeks in February 2024 due to rupture of membranes. Immediately after birth, IVIG 0.4 g/kg/day for 5 days was given again due to myasthenic exacerbation and eculizumab was continued every 2 weeks.

During the postpartum period, the patient needed IVIG three more times, approximately 2 months apart. The premature baby, weighing 2725 g, was admitted to the neonatal intensive care unit with an APGAR score of 8/9. He was not intubated. On the second day of his life, AchRAb was >8 mg/dL. He was evaluated as having neonatal MG

Figure 1. Time diagram of the patient's myastenia gravis clinical state scores and treatment.



IVIG, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis – Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America clinical classification; QMG, Quantitative Myasthenia Gravis score.

and was fed via an NG feeding tube for the first week. In the second week, he was able to feed with a bottle and spoon and was discharged after 15 days of hospitalization. After a few months of breastfeeding, he continued to be fed with milk-adapted formula because the mother's milk supply decreased. The infant's height and weight were found to be in the 50th percentile, and systemic and neurological examinations were normal at the 6-month follow-up. At the current age of 10 months, his weight is 9200 g (25–50 percentile), height is 76 cm (75 percentile) and he has no myasthenic symptoms. Our patient is currently receiving eculizumab every 2 weeks, pyridostigmine 240 mg/day, and methylprednisolone 40 mg/day and has no symptoms other than bilateral orbicularis oculi muscle weakness. MG metric scores were calculated as MG-ADL score 4 and MGFA score Class 1. A time diagram of the patient's MG clinical state scores and treatments is shown in Figure 1.

Discussion

This case report presents the pregnancy and puerperium experience under eculizumab in a patient with refractory gMG and the 1-year follow-up of the baby. The safety of treatment during pregnancy and the puerperium is important because, consistent with our patient, exacerbations may occur during the first trimester of pregnancy and the puerperium in patients with gMG. Hormonal, immunological and stress mechanisms have been suggested as explanations for MG exacerbations. The most common first-line immunosuppressants for MG, prednisone/prednisolone and azathioprine, are regarded as safe during pregnancy.[3] Rituximab, a monoclonal antibody that crosses the placenta, is currently contraindicated in pregnancy because the drug binds to B lymphocytes in the developing child. Mycophenolate mofetil should not be used during pregnancy because of an association with an increased number of congenital malformations. IVIG and plasma-exchange represent safe treatment options during pregnancy.[3] Mycophenolate mofetil and methotrexate are also not compatible with breastfeeding due to their teratogenic potential. Maternal treatment with prednisone, azathioprine and pyridostigmine is not a contraindication to breastfeeding. Breastfeeding is probably also safe for rituximab, as the concentration in breast milk is 200 times less than in serum.[3]

Clinical data indicating the safety of eculizumab use in pregnancy have been reported in various indications, especially in cases of paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome

(aHUS). Eculizumab is associated with higher maternal and infant survival in pregnancies with PNH and aHUS, with no reported maternal deaths and low rates of infant deaths.[11,12] In a 10-year post-marketing safety analysis of eculizumab-treated patients with PNH or aHUS, the rate of congenital malformations and the overall rate of miscarriage in pregnancy with eculizumab exposure were considered to be within the range of the general population.[13] Safety data regarding the use of eculizumab during pregnancy and lactation in patients with gMG are limited. To our knowledge, our case is the third case in the literature regarding the use of eculizumab during pregnancy and puerperium. Eculizumab was not detected in breast milk, suggesting it might be safe for breastfeeding mothers.[14] Although no data on breastfeeding were reported in either of the previous case reports in which gMG was treated with eculizumab through pregnancy,[7,8] our patient was able to breastfeed her baby for a few months. There was no safety problem with eculizumab, and favourable maternal and foetal outcomes were observed.

Although it is not possible to predict how MG will progress during pregnancy, women with MG who are well controlled before pregnancy can be expected to have a stable pregnancy and postpartum period.[15] MG pregnancies should preferably be planned in the phase when MG is stable. The first case report presents a successful pregnancy in a young woman with refractory MG well controlled with eculizumab before, during and after pregnancy. The treatment was associated with a favourable benefit–risk profile with no observed adverse effects on the mother or the newborn.[7] Another report highlighted the potential for infectious adverse events as the same patient contracted disseminated gonococcal infection during her third pregnancy under eculizumab.[9] In the second case, which had been stable for 2 years with eculizumab before pregnancy, a successful pregnancy was reported with eculizumab monotherapy.[8]

Our patient responded well to eculizumab treatment during her illness, but worsened when the medication was discontinued due to an access problem or pregnancy. Around 10% of babies of mothers with gMG have transient neonatal MG. No direct correlation was found between the risk of neonatal MG and severity of disease and antibody concentration in the mother.[3] Whilst no preterm labour or neonatal MG was observed in the other reported MG pregnancies under eculizumab treatment,[7–9] both occurred in our case. There are no minor or major malformations in the baby, and his growth and development are compatible with his age. On the other hand, a significant number of preterm births have been reported in pregnant women with PNH and aHUS under eculizumab treatment;[14] however, these preterm births may be related to the nature of the diseases during pregnancy rather than the treatment itself. Women with MG also have an increased risk of preterm birth compared with the general population, often associated with preterm premature rupture of membranes, especially in those with exacerbations during the pregnancy, as was observed in our case.[16,17] In a report presenting the pregnancies of two patients with aquaporin 4-positive neuromyelitis optica spectrum disorders under eculizumab treatment, it was stated that both pregnancies resulted in full-term and healthy babies despite patients with these disorders being at an increased risk of pregnancy complications.[18]

Conclusion

Our case provides additional data on the use of eculizumab during pregnancy and lactation. Whilst efficacy and safety outcomes were favourable for mother and baby, this report also highlights the importance of planned pregnancy in gMG as in other autoimmune diseases. Data from eculizumab-treated pregnancies with PNH and aHUS and from a small number of reported pregnant women with refractory MG under eculizumab treatment indicate that eculizumab may be safe for mother and baby; however, long-term follow-up is needed to determine the safety profile of eculizumab in pregnancy and lactation.

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