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Safety and Effectiveness of Eculizumab throughout Three Pregnancies in a Patient with Refractory Generalized Myasthenia Gravis: A Case Report

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Abstract
We describe maternal and fetal outcomes in a patient who had three successful pregnancies while being treated with eculizumab for AChR+ gMG. This is a follow-up to our previously published report describing outcomes with this C5 complement inhibitor during the patient's first pregnancy. Eculizumab conferred adequate gMG disease control during these pregnancies, although there were instances of increased gMG symptoms during the first trimester and postpartum period without requirement for rescue therapy. The patient experienced disseminated gonococcal infection once during her second pregnancy, a serious adverse event that was likely related to complement inhibition by eculizumab. The patient additionally experienced two nonserious and treatment responsive yeast infections. There were no negative outcomes reported with any of the pregnancies in fetal, neonatal, or infantile periods. In the context of the existing literature, this report provides additional insight on potential outcomes with use of eculizumab in patients with gMG. While the report suggests favorable effectiveness and fetal outcomes, it also highlights potential for adverse events, namely, maternal infections. Additional reports on clinical outcomes in pregnancy in patients with gMG are needed to guide risk-benefit stratification for eculizumab.

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Introduction

Complement-mediated tissue damage is implicated in the pathogenesis of neurologic and non-neurologic autoimmune diseases [1, 2]. Elucidation of these mechanisms has led to expanded application of complement-targeted therapies. As these autoimmune conditions are common among women of child-bearing age, the effects of these medications on pregnancy and pregnancy-related outcomes are of utmost importance to inform clinical management. This subject becomes especially complex given amplified complement activity in the physiology of pregnancy itself [3].

Eculizumab is a humanized monoclonal antibody that binds complement protein C5 and prevents membrane attack complex formation [1, 4]. In the USA, eculizumab and ravulizumab are FDA-approved for acetylcholine receptor antibody-positive generalized myasthenia gravis (AChR+ gMG), anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4+ NMOSD), paroxysmal nocturnal hemoglobinuria (PNH), and atypical hemolytic uremic syndrome (aHUS).

To date, most clinical data informing safety of eculizumab in pregnancy exist within populations with PNH [4, 5]. In patients with PNH treated with eculizumab, maternal mortality was dramatically improved and fetal mortality was similar to that reported prior to the availability of eculizumab [4]. The results of a systematic review and meta-analysis of pregnancies in PNH with and without eculizumab treatment in a recently published abstract showed a higher rate of fetal survival, fewer spontaneous miscarriages, and lower rate of premature birth [6]. Additionally, published case reports in aHUS, antiphospholipid antibody syndrome, HELLP syndrome, and sickle cell disease also suggest favorable maternal and fetal outcomes with eculizumab use [2]. Studies have shown that eculizumab does not achieve any clinically meaningful concentration in breast milk or placental plasma [4, 5].

While the safety data in other diseases are encouraging, their translatability to the gMG and NMOSD population is not fully established. Patients with PNH, for example, are particularly susceptible to consequences of pregnancy-induced complement activation and concomitant increased intravascular hemolysis, including spontaneous abortion, prematurity, thromboembolism, and early preeclampsia [7]. In AChR+ gMG, however, complement activation results in postsynaptic membrane destruction in striated muscle and clinically presents as myasthenic symptoms [1]. Thus, the locus of disease in gMG is not only distinct, but the pathophysiologic mechanisms of gMG are also less likely to bear the same degree of consequence related to pregnancy physiology and outcomes compared to diseases like PNH and aHUS.

There is a significant paucity of reported outcomes in patients on eculizumab during pregnancy in both gMG and NMOSD. Published data on outcomes with eculizumab in gMG are limited to our previously reported case and 1 other case describing patients with treatment-refractory gMG on eculizumab, both of whom had relatively uncomplicated pregnancies with good fetal outcomes and adequate gMG control [8, 9]. There has been one published report on outcomes in two cases with eculizumab in NMOSD, both of whom also had uncomplicated pregnancies with good fetal outcomes and adequate disease control [10]. In this case report, we provide follow-up of our patient with gMG who had two additional pregnancies with good fetal outcomes and well-controlled gMG. In contrast to other published reports of eculizumab use during single pregnancies, this case report is unique in that it demonstrated eculizumab's durable therapeutic effects for more than 6 years and safety throughout multiple pregnancies. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000543216).

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Case Report

The patient was diagnosed with AChR+ gMG between the age of 5–6 years old. Throughout her disease course, she failed multiple first- and second-line treatments due to inadequate disease control or intolerability, and was ultimately enrolled at age 19 in the treatment arm of the phase 3 placebo-controlled REGAIN study, in which she demonstrated significant improvement in disease control and quality of life with eculizumab [8]. In total, she had three successful pregnancies while on eculizumab, the first of which we described in a previously published report [8]. During each pregnancy, the patient was on pyridostigmine 120 mg three times daily and eculizumab infusions every 2 weeks.

The patient had her first pregnancy at 23 years-old, and about 7 months of postpartum, she described increased fatigue, intermittent generalized weakness, and intermittent ptosis without bulbar or respiratory symptoms. Her exam was stable, and her symptoms were attributed to interrupted sleep and high demands of newborn care.

At 24 years of age, she became pregnant for the second time (G2P1000). Routine prenatal evaluations demonstrated normal fetal development. Her pregnancy was complicated only by one episode of candida vulvovaginitis, successfully treated with one dose of fluconazole 150 mg. Otherwise, her gMG symptoms remained well-controlled (documented consistently at obstetric visits and at a neurologic visit during the third trimester [MG-ADL = 7]). She presented with contractions at 38w1d and progressed to the second stage of labor, which lasted 10 min. She delivered by expectant management without maternal or fetal complications. She had an episode of acute on chronic leg weakness at approximately 3 months postpartum; however, rescue therapy was not deemed indicated.

At 25 years of age, she became pregnant again (G3P2000). Routine prenatal evaluations demonstrated normal fetal development. At a neurologic visit during her first trimester, she reported fluctuating fatigue, diplopia, and ptosis without other symptoms (MG-ADL = 6 and MGQoL15 = 16/30); rescue therapy was deemed not indicated. Her second trimester was complicated by disseminated *Neisseria gonorrhea* infection presenting as joint pain mostly in her toes and knees. She also had painful erythematous areas and purpuric lesions her arms and legs (shown in Fig. 1). She had elevated WBC (16.03×10^3/mL), CRP (14.96 mg/dL) and ESR (77 mm/h), and normal PT/PTT and platelet count. She was ultimately treated with ertapenem due to concern for amoxicillin resistance and ceftriaxone allergy with full recovery. Her third trimester was additionally complicated by a yeast infection treated with clotrimazole. She presented with contractions at 38w0d and delivered by expectant management without maternal or fetal complications. To date, there have been no complications reported in any of the three children (currently ages 4, 3, and 2 years).

Discussion

This case report provides additional data on effectiveness and safety of eculizumab for mother and fetus during pregnancy in AChR+ gMG patients. For the vast majority of patients with gMG, peripartum and postpartum disease state mirror prepartum disease state, though increased risk of myasthenic exacerbations during the first trimester and postpartum period have been noted [11]. These observations are consistent with our patient's course, as she experienced worsening of gMG symptoms 6 weeks of postpartum after her first pregnancy, 3 months of postpartum after her second pregnancy, and during the first trimester of her third pregnancy.

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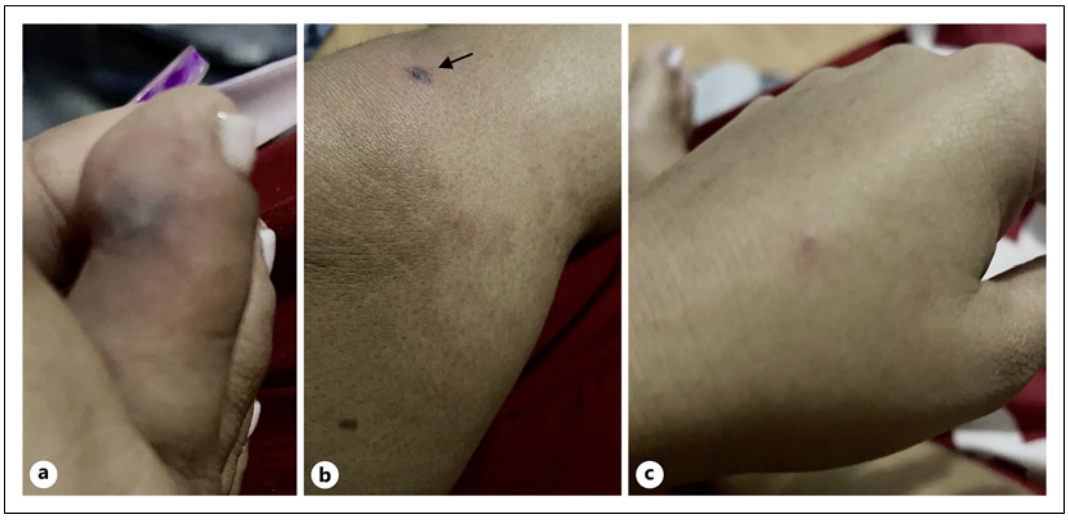

Fig. 1. Skin lesions associated with disseminated gonococcal infection. **a** Painful swelling and erythema over toe joint. **b** Ecchymosis over knee and erythematous and scattered painful papules with central purpuric area (arrow). **c** Macule on dorsum of hand.

In gMG, while uterine tone (given its smooth rather than striated muscle composition) is unaffected, there is potential for fatigable weakness during the second and third stages of the labor process [11]. Our patient exhibited no weakness or other difficulties with these stages of labor in any of her pregnancies.

Eculizumab dose is not weight-based, but it is conceivable that adjustments of eculizumab dosage or frequency of administration may be necessary at certain stages of pregnancy. There are no published data on pregnancy-related changes in pharmacokinetics and pharmacodynamics or both with eculizumab in the pregnant gMG population. Eculizumab remained effective during pregnancy in our patient with otherwise refractory gMG. Despite some episodes of symptomatic exacerbation, she did not require rescue therapy.

Prescribers of complement inhibitors should be aware of the increased risks for gonococcal infection in patients treated with complement inhibitors. Eculizumab confers increased susceptibility to meningococcal and disseminated gonococcal infection as it inhibits formation of the MAC, which is critical in neutralizing encapsulated *Neisseria* bacteria. Signs and symptoms of this infection include genital discharge, pain, and swelling, dysuria, joint pain, rash, and fever [12]. The arthritis-dermatitis syndrome (co-occurrence of joint involvement, cutaneous lesions, and tenosynovitis) is a well-described presentation of disseminated gonococcal infection [13]. In a 10-year pharmacovigilance analysis in patients with PNH or aHUS, serious, non-meningococcal infections occurred at a rate of 7.9 per 100 patient years, 1.7% of which were disseminated gonococcal infections [14]. While there is no vaccine against *N. gonorrhea* to date, there is some evidence of cross-protection with vaccination against *Neisseria meningitidis* due to underlying genetic similarities [15]. However, in the same pharmacovigilance study, nearly all meningococcal infections reported occurred despite meningococcal vaccination [14]. Our patient contracted disseminated gonococcal infection during the second trimester of her second pregnancy. Fortunately, she responded well to antibiotic therapy with no long-term complications.

In the context of the existing literature, this report provides additional insight on potential outcomes with use of eculizumab in patients with gMG. While the report suggests favorable effectiveness and fetal outcomes, it also highlights potential for adverse events,

namely, maternal infections. Additional reports on clinical outcomes in pregnancy in patients with gMG are needed to guide eculizumab risk-benefit stratification. Of note, due to the paucity of data on pregnancy outcomes in patients with gMG on complement inhibitors, these agents are currently not specifically a part of any MG treatment guidelines.

Statement of Ethics

Ethical approval is not required for this study in accordance with USF guidelines. Per the USF IRB, a case report or limited case series is a description of the characteristics, evaluation, and/or treatment(s) of a single individual or a small group of individuals that share a common condition but did not involve activities defined as research. The retrospective review of records for publication of a single case report or a limited case series involving data from three (3) or fewer individuals is not considered to be research involving human subjects; and therefore, such a report does not require IRB review and approval. The patient gave permission for the publication of this report. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

T.H. Vu was an investigator in the REGAIN study, sponsored by Alexion Pharmaceuticals, Inc., and serves on Alexion's speakers' bureau and advisory board. He is also the USF Site Principal Investigator for MG clinical trials sponsored by Alexion/AstraZeneca Rare Disease, Argenx, Amgen, Cartesian Therapeutics, COUR, Dianthus, Immunovant, Johnson & Johnson, NMD Pharma, Regeneron, and UCB. He receives speaking and/or consulting honoraria from Amgen, Argenx, CSL Behring, Dianthus, Johnson & Johnson, and UCB. J. Farias was a subinvestigator in the REGAIN study, sponsored by Alexion Pharmaceuticals, Inc. She has received compensation for participation in a speakers' bureaus for CSL Behring, Argenx, and UCB Biopharma SRL, as well as consulting for Argenx, Catalyst Pharmaceuticals, Inc., Amylyx Pharmaceuticals, Inc., UCB Biopharma SRL, PCON (Point of Care Network, LLC), and Rare Disease Connect in Neurology. N. Khalil, C. Guerra Hernandez, K. Murray, N. Suresh, and C. Gooch have no relevant disclosures.

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Author Contributions

N.K. drafted the manuscript. T.H.V. is the patient's primary physician. N.K., C.G., J.F., K.M., N.S., C.G., and T.H.V. made substantial contributions to the conception of the work, reviewed the work critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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