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HIGHER DOSES OF ECULIZUMAB MAY BE BENEFICIAL IN PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA IN PREGNANCY

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ABSTRACT

Introduction: Paroxysmal nocturnal haemoglobinuria (PNH) is a rare bone marrow failure disorder that results in complement-mediated haemolysis (mostly intravascular), thrombosis and bone marrow suppression. Terminal complement inhibitors, such as eculizumab, have improved outcomes in pregnant and non-pregnant individuals. However, the optimal management of PNH during pregnancy has not been fully established.

Case description: We describe the case of a 30-year-old Caucasian woman with classical PNH who became pregnant while on eculizumab therapy. Despite complete terminal complement blockade, as confirmed by appropriately suppressed functional C5 levels and elevated C5 antigen levels, the patient experienced recurrent breakthrough haemolysis and transfusion dependence during the first trimester. Her eculizumab dose was escalated beyond the standard recommended doses, which improved haemoglobin levels and reduced transfusion requirements, although lactate dehydrogenase (LDH) levels remained elevated. The patient delivered a healthy infant via elective caesarean section at term without complications. Postpartum, she transitioned to a combination of eculizumab and pegcetacoplan to address ongoing haemolysis, likely due to C3b mediated opsonisation.

Conclusion: The case illustrates the complexity of managing PNH during pregnancy and highlights the importance of individualised therapy and close monitoring to achieve optimal foetomaternal outcomes. Our experience suggests that despite appropriately suppressed complement levels, pregnant patients with continued transfusion dependence and elevated LDH levels may benefit from higher than standard doses of eculizumab. Given the paucity of data, detailed reporting of such cases is essential to inform treatment strategies for pregnant patients.

KEYWORDS

Paroxysmal nocturnal haemoglobinuria (PNH), pregnancy, complement-mediated haemolysis, terminal complement inhibitors, breakthrough haemolysis

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LEARNING POINTS

- Pregnant patients with classical paroxysmal nocturnal haemoglobinuria need individualised treatment and frequent monitoring.
- Even with appropriate terminal complement blockade, pregnant patients may have significant breakthrough haemolysis burden, likely due to C3b mediated opsonisation.
- Higher than standard doses of eculizumab may help control breakthrough haemolysis in pregnant patients.

INTRODUCTION

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare bone marrow failure disease resulting from a clonal abnormality of haematopoietic stem cell from a somatic mutation in the PIG-A gene. This leads to a loss of the glycosylphosphatidylinositol (GPI) anchor and hence loss of GPI-anchor bound proteins – CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis) [1]. This leads to unchecked activation of the complement system by the alternative pathway, and eventual formation of the membrane attack complex against the CD55 and CD59 deficient red blood cells and subsequent intravascular haemolysis. A minority of the affected red blood cells undergo extravascular haemolysis (EVH) by opsonisation due to C3b[1]. PNH also affects the platelets and leukocytes as they too lack these regulatory proteins, which leads to their overactivation and subsequent thromboembolism at atypical sites, general morbidity and decreased life expectancy[1].

Eculizumab, a humanised monoclonal C5 antibody which inhibits membrane attack complex formation, was the first agent used to treat PNH patients. Ravulizumab is another such agent – a C5 monoclonal antibody with FcRn-receptor-mediated recycling, which increases the duration between two infusion doses, and decreases pharmacokinetic breakthrough haemolysis (BTH) compared to eculizumab. But with these distal inhibitors, there is an increase in C3b-mediated EVH (i.e. iatrogenic EVH) because of the increased survival of type III erythrocytes[1]. Thus, proximal inhibitors were developed – C3 inhibitor pegcetacoplan, oral direct inhibitors of Factor B – iptacopan and Factor D – danicopan[2]. Pregnancy is a hyper complemented state and increases the risk for dilutional anaemia and thrombotic complications[3]. Although complement system inhibitors have dramatically improved foetomaternal outcomes, large scale data remains scant, and treatment-individualisation is needed. We present a case of a PNH patient who became pregnant and had worsening of the disease course, requiring higher than approved doses of eculizumab.

CASE DESCRIPTION

The patient is a 30-year-old Caucasian woman, G4P2012 (pregnant four times, has two children who were born at term, no premature births, one abortion and two living children), with a past medical history significant for PNH, who presented for management of PNH during pregnancy. When diagnosed initially, she was started on eculizumab and then ravulizumab, but she continued to suffer from transfusion-dependent BTH. With the intention to become pregnant, she was in the process of switching from ravulizumab to eculizumab, but she miscarried before this switch. She was nonetheless put on eculizumab in anticipation of her next pregnancy.

The patient soon became pregnant after her last miscarriage, and was managed on 900 mg biweekly eculizumab, enoxaparin 40 mg once daily for venous thromboembolism prophylaxis and penicillin V 500 mg twice daily for meningococcal prophylaxis. Complete blood count, lactate dehydrogenase and total bilirubin were drawn prior to each eculizumab dose *(Table 1)*. The efficiency of eculizumab was assessed by period measurements of total complement levels (CH 50), serum functional C5 complement levels and serum C5 complement antigen levels. Absent C5 function with normal or elevated total C5 completed antigen levels indicates complete C5 blockade by eculizumab, which was consistently achieved throughout her pregnancy. However, even with complete C5 blockade, the patient continued to suffer from BTH. Hence, her eculizumab dose was increased to 1,200 mg biweekly at gestation age of 9 weeks and 6 days. Haemoglobin levels initially improved, but with increasing lactate dehydrogenase (LDH) levels and pharmacokinetic BTH, the eculizumab dose was increased to 1,500 mg biweekly, with incomplete control of haemolysis. At 39 weeks and 1 day of gestation, the patient underwent an elective caesarean section without any complications and was discharged on postoperative day two. Immediately postpartum, the eculizumab dose was decreased to 900 mg biweekly with pegcetacoplan overlap for four weeks. The patient was also continued with enoxaparin until six weeks postpartum.

DISCUSSION

Management of PNH is challenging in pregnancy due to increased disease activity and paucity of data regarding the use of anti-complement agents during pregnancy.

Kelly et al. reported the largest series of pregnant patients with PNH – sixty-one patients with seventy-five pregnancies who were treated with eculizumab[4]. Six patients miscarried during the first trimester, and three stillborn cases occurred. Sixty-seven pregnancies progressed to delivery, and thirty-six of them suffered from BTH, requiring either an increase in the dose or frequency of eculizumab. Alashkar et al.

Eculizumab dose	Haemoglobin (12–16 g/dl)	Lactate dehydrogenase (94–250 U/l)	CH50* (30–75 U/ml)	C5 complement functional (29–53 U/ml)	C5 complement antigen (10.6–26.3 mg/dl)
900 mg	10.2	226	-	-	-
	7.6	249	-	-	-
	8	-	-	-	-
	8	247	-	-	-
	-	-	3	<5	37.9
1,200 mg	8.4	-	-	-	-
	7.5	-	-	-	-
	9.7	-	-	-	-
	7.6	464	<3	<5	37.9
	9.1	355	-	<5	52.1
	8.5	396	<3	<5	56.5
	8.8	410	-	-	-
	8.5	437	<3	<5	54.7
	7.5	395	-	<5	50.9
	9.0	467	<3	<5	53.2
	8	459	-	<5	52.4
	8.1	-	-	-	-
	7.4	-	-	-	-
	9.4	-	-	-	-
	9.1	447	-	<5	54.9
	-	466	<3	-	-
	8	-	-	-	-
	8.1	473	-	-	-
	8.7	572	4	-	-
	-	-	6	<5	34.5
	7.2	-	-	-	-
1,500mg	7.6	555	6	<5	35.7
	9	481	4	<5	35.8
	10.6	-	-	-	-
	9.4	405	-	-	-
	10.2	-	-	-	-

*Total complement levels.

Table 1. Eculizumab dosing and markers of haemolysis and complement activity during the patient's third pregnancy. Eculizumab was given every fourteen days. Not all laboratory data were collected at each visit.

reported sixteen pregnancies in nine patients with classical PNH; thirteen of these pregnancies were managed with eculizumab, and four ended in spontaneous abortion or stillbirth[5]. The other three pregnancies without the use of eculizumab resulted in unfavourable outcomes; placental examination of two patients with stillbirth revealed placental insufficiency with thrombosis and fibrosis. Six patients suffered from BTH, requiring an increase in the weekly eculizumab dose from 900 mg to 1,200–1,800 mg. Manning et al. reported their experience with the use of eculizumab in thirty-seven pregnant patients[3]. Twenty patients required an increase in the eculizumab dose due to BTH (1,050–1,800 mg biweekly). Five pregnancies had unfavourable outcomes; no maternal or foetal deaths were reported. There is no randomised study comparing regular vs increased doses of eculizumab in pregnant PNH patients, but these results indicate that titrating the dose of eculizumab to achieve a low-BTH state during pregnancy may improve maternal and foetal outcomes. Our single-patient experience adds to this body of evidence *(Table1, Appendix)*[3].

Experience with ravulizumab is limited during pregnancy. A recent retrospective analysis included five women with PNH who were treated with ravulizumab prepartum and whose pregnancies and postpartum periods were the same; four of them breastfed[6]. All the ravulizumab pregnancies had favourable outcomes with completed pregnancies with healthy children; in the same cohort, there were a total of six eculizumab pregnancies prior to their use of ravulizumab, and three of them resulted in either a miscarriage or termination. Our patient also experienced a miscarriage while on eculizumab, which may be attributable to uncontrolled PNH. Hence, data regarding the use of ravulizumab in pregnant PNH patients are urgently needed.

EVH becomes the prominent mechanism of continued haemolysis, transfusion dependence and symptom burden in PNH patients treated with C5 inhibitors[1]. C5 inhibitors are also associated with life-threatening infections caused by encapsulated pathogens, especially *Neisseria meningitidis*, despite appropriate vaccinations prior to their initiation. The degree of complement inhibition required to curb PNH-mediated thrombosis also significantly inhibits the competent-mediated immune process[7]. The use of C3b antagonist pegcetacoplan can reduce the incidence of iatrogenic EVH caused by C5 inhibitor use[1]. Kelly et al. recently reported a three-year post marketing experience with pegcetacoplan in PNH patients and reported comparable efficacy in preventing thrombosis, with no incidence of encapsulated pathogen infection[8]. Du and Mei also recently used pegcetacoplan in pregnant patients[9]. This patient had a history of two miscarriages and BTH with eculizumab and therefore was managed with pegcetacoplan prepartum, which continued after she became pregnant. She developed abruptio placentae and BTH at 30 weeks of gestation, requiring an emergency C-section and a short-term intense dose of pegcetacoplan and eculizumab, which controlled BTH. The infant was premature with no congenital anomalies. Current experience with the use of pegcetacoplan in pregnant patients remains acutely limited, and any decision to use pegcetacoplan in this patient population should be individualised.

An LDH level less than 1.5 times the upper limit of normal has been used as a marker of appropriate control of intravascular haemolysis[10]. This metric may be used for pregnant PNH patients for dose titration of eculizumab, but LDH levels are elevated in normal pregnancies and hence potentially muddling this process[10]. Our patient frequently breached this limit, and during the third trimester the LDH levels were frequently two times the upper limit of normal, requiring eculizumab dose escalation, but this decision was made in conjunction with low haemoglobin levels and consistent transfusion dependence. Hence, for pregnant PNH patients, transfusion dependence and significantly elevated LDH may serve as a marker for the need for increased eculizumab dosage. Another metric for eculizumab dose titration is complement system activity, as measured by total complement levels (CH50), serum functional C5 complement levels and serum C5 complement antigen levels. Low functional C5 levels with normal or elevated total C5 complement antigen levels would indicate complete distal complement blockade by eculizumab, and any residual haemolysis thereafter is likely EVH. Thus, if a patient still exhibits signs of haemolysis on eculizumab with effective inhibition of the C5 pathway, then incremental dosing of eculizumab may yield diminishing returns. In our patient, the C5 pathway was consistently suppressed, but she consistently remained transfusion dependent. Since there was no experience using ravulizumab or pegcetacoplan during pregnancy during this patient's care, her eculizumab dose was titrated with LDH and haemoglobin levels, and she had no untoward pregnancy outcomes.

CONCLUSION

The management of PNH during pregnancy remains arduous. However, with increasing experience with the use of agents such as ravulizumab and pegcetacoplan, pregnant patients with BTH may benefit from dual blockade of the complement system. Complete blood count, LDH, and functional and total C5 levels may be used for monitoring and dose titration of eculizumab, especially if BTH is primarily intravascular. There is an urgent need for collating data regarding the management of PNH during pregnancy, including individual patient experiences such as ours, and assimilating this data for the collective benefit of PNH patients during pregnancy.

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APPENDIX

Reference	Eculizumab initiation	Biweekly eculizumab dose range* (mg)	Method of titration
Alashkar et al.	Prior to conception for most patients	900-1,800	Haemoglobin >8 g/dl
Manning et al.	Prior to conception for most patients	900-1,800	LDH > 1.5–2 times ULN, and/or clinical cues (dyspnoea, dark urine, fatigue)
Danilov et al.	30 weeks of gestation	900	No titration
Gessoni et al.	Prior to conception	450-1350	PRBC transfusion requirement
Sharma et al.	Prior to conception	900-1800	Serum eculizumab levels, pharmacodynamic assay
Vekemans et al.	Prior to conception	900	No titration
Miyasaka et al.	Prior to conception	900	No titration
Lauritsch-Hernandez et al.	Prior to conception	900#	Haemoglobin level, LDH level and PRBC transfusion requirement
Bastos et al.	Prior to conception	900-2,400	Haemoglobin level, LDH level and reticulocyte count
Li et al.	Prior to conception	900	No titration
Al-Dosari et al.	Prior to conception for most patients	600-1200	Haemoglobin level, haptoglobin level, LDH level and total bilirubin level
Fassett et al.	Prior to conception	900-1,800	Haemoglobin level and PRBC transfusion requirement
Bortolotti et al.	After conception	900-1,500	Haemoglobin level, total bilirubin level, LDH level and reticulocyte count

*Weekly 900 mg eculizumab dose may be reported as 1,800 mg eculizumab biweekly.
#900 mg eculizumab doses were administered every 10–14 days depending on the level of haemolysis.
Abbreviations: LDH, lactate dehydrogenase; ULN, upper limit of normal PRBC, packed red blood cells.

Table 1. Eculizumab dosing regimen, and titration methods for pregnant patients with paroxysmal nocturnal haemoglobinuria. Our patient was on 900 mg–1,500 mg biweekly eculizumab, which was titrated using levels of total complement (CH 50), serum functional C5 complement, serum C5 complement antigen, haemoglobin and lactate dehydrogenase.

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