Successful pregnancy outcome in paroxysmal nocturnal hemoglobinuria (PNH) following escalated eculizumab dosing to control breakthrough hemolysis

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Case report

Successful pregnancy outcome in paroxysmal nocturnal hemoglobinuria (PNH) following escalated eculizumab dosing to control breakthrough hemolysis

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1. Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired clonal stem cell disorder characterized by intravascular hemolysis and thrombophilia. Pregnancy in PNH is associated with increased maternal and fetal morbidity and mortality due to thromboembolism, infection and premature birth [1]. Therefore, PNH has been considered a relative contraindication for pregnancy. The terminal complement cascade inhibitor eculizumab has become the standard treatment in patients with symptomatic PNH. There are limited published data regarding the use of eculizumab in pregnancy in either animal studies or in humans. We report a patient with PNH who became pregnant while on eculizumab, required dose escalation during the third trimester to control breakthrough hemolysis, and successfully delivered a healthy baby.

2. Materials and methods

Eculizumab levels were measured at Cambridge Biomedical using a manual ELISA method in which the microtitre plates are coated with C5, then blocked. Standards, controls, and unknowns were added. After incubation and washing, mouse anti-human IgG4 horseradish peroxidase (HRP) was added as the conjugate. Then the substrate 3,3',5,5'-tetramethylbenzidine (TMB) was added and the color reaction was halted using a stop reagent. The results were read spectrophotometrically at 450 nm using a plate reader [2]. The pharmacodynamics of eculizumab were determined by measuring the capacity of the patient’s serum to lyse chicken erythrocytes in a standard total human serum-complement hemolytic assay [3].

2.1. Case report

A 30 year old Chinese female presented with pancytopenia and direct antoglobulin negative hemolytic anemia in 2010. She was diagnosed with hypoplastic myelodysplastic syndrome due to dysplastic features noted on the bone marrow aspirate and biopsy, although with normal cytogenetics. A PNH clone was identified by flow cytometry with type I RBC 93.9% (reference range – 99.0 to 100.0%), type II RBC 0.10% (reference range – 0.00 to 0.99%) and type III RBC 6.00% (reference range – 0.00 – 0.01%). Her granulocyte clone size was 52.93% (reference range – 0.00 – 0.01%). She was treated with cyclosporine, horse anti-thymocyte globulin, steroids and standard dose eculizumab with a good response. Her lactate dehydrogenase (LDH) levels returned to normal with a simultaneous improvement in her hemoglobin level from 6 g/dl to 12 g/dl. She no longer required blood nor platelet transfusion. She had no thrombotic events. She was advised against pregnancy and urged to use non-hormonal contraceptives. Two years after the initial diagnosis, she was noted to have a decline in hemoglobin from 12 g/dl to 7 g/dl with a simultaneous rise in LDH to 1027 U/L and undetectable haptoglobin (Fig. 1). A repeat bone marrow aspiration and biopsy showed focal erythroid hyperplasia, mild dyserythropoiesis, normal myelopoiesis, small lymphoid aggregate, and increased iron stores.

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anemia (Fig. 1). At week 30, her serum eculizumab level was clearly subtherapeutic, re-
ed to 900 mg every 2 weeks. She required an average of 1 unit of packed red blood cell transfusion per week for symptomatic treatment. Her eculizumab level had been sub-therapeutic and a pharmacodynamic assay demonstrated the absence of complement blockade. Rather than reducing the time interval between doses, we opted to escalate the dose of eculizumab. Higher doses of eculizumab have been needed to control atypical hemolytic uremic syndrome (aHUS) [8] and catastrophic antiphospholipid syndrome [9]. In aHUS, the recommended dose of eculizumab is 33% higher than for PNH in order to completely block the complement cascade [10]. Utilizing this escalated dose of eculizumab, we successfully achieved therapeutic eculizumab levels with adequate complement blockade (Fig. 2) and controlled the patient’s hemolysis (Fig. 1). This dose of eculizumab was also recently reported in a pregnant patient with aHUS and found to be safe [11].

Pregnancy activates the complement cascade, with increased terminal complex formation in the third trimester [12]. We hypothesize that loss of control of complement-mediated hemolysis with eculizumab during the second and third trimester appears to be due to the physiologic expansion of intravascular volume which occurs during pregnancy. Our patient’s serum eculizumab level was clearly subtherapeutic, reflecting the dilution which had occurred. Dose escalation restored the level to therapeutic range and controlled hemolysis.

Eculizumab levels were not detectable in our patient’s cord blood nor breast milk. It therefore does not appear to cross the placenta nor be excreted in breast milk, which is consistent with previous reports [4–7]. Forty-five percent of pregnancies in women with PNH result in spontaneous miscarriage and 6% in maternal mortality due to fatal thrombotic events [13]. Because of the risk of life threatening thrombotic complications, pregnant women with PNH should receive full anticoagulation during pregnancy and for at least 4–6 weeks postpartum [14]. Our case highlights that breakthrough hemolysis can occur early in gestation and that pregnant patients with PNH require close monitoring. It appears that eculizumab can be safely used throughout pregnancy. Many PNH patients require either a shortening of dose interval or treatment with higher doses of eculizumab in order to control hemolysis as pregnancy progresses.

3. Discussion

The median age at diagnosis of PNH is 34 years, so affected females are often in the reproductive age group. PNH is not known to adversely affect female fertility. There are 6 reported cases of successful pregnancies in PNH patients being treated with eculizumab [4–7]. Kelly et al. described the first 3 women who received eculizumab during pregnancy [4]. Two of these patients suffered from breakthrough hemolysis in the third trimester. Breakthrough hemolysis manifested itself with patients experiencing hemoglobinuria prior to their next scheduled dose of eculizumab. Both of these patients were treated by reducing the interval between subsequent doses from 14 days to 12 days in one case and to 7 days in the other case. The third patient delivered at 28 weeks due to preeclampsia. Three other cases have been described [5–7]. One of them suffered breakthrough hemolysis and was treated by reducing the duration between eculizumab doses to 7 days [7].

We describe the seventh case of successful pregnancy in the era of eculizumab. Our patient was stable on standard dose eculizumab until the second trimester. It has been noted that the dose of eculizumab required to block complement during the latter stages of pregnancy is greater than in the non-pregnant state [4]. Our patient developed breakthrough hemolysis in the second trimester despite standard eculizumab administration. Her eculizumab level was sub-therapeutic and a pharmacodynamic assay demonstrated the absence of complement blockade. Rather than reducing the time interval between doses, we opted to escalate the dose of eculizumab. Both of these patients were treated by reducing the dose of eculizumab. Further evidence that PNH patients require higher doses of eculizumab in pregnancy is greater than in the non-pregnant state [4–7].

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Fig. 1. Trend of LDH and hemoglobin measured at Baseline, 4 weeks (calculated retrospectively), 20 weeks, 27 weeks, 30 weeks and 35 weeks. Red cell transfusion indicated by red arrows. Small black arrows represent eculizumab 900 mg every 2 weeks. Large black arrows represent eculizumab 900 mg weekly x 4 doses followed by 1200 mg every 2 weeks.

Fig. 2. Complement activity by pharmacodynamic assay (PD) shown on left Y axis. Eculizumab level by pharmacokinetic assay (PK) shown on right Y axis. Graph depicts fully active complement system with subtherapeutic eculizumab level before re-induction (week 0) and complete blockade of complement activity with therapeutic eculizumab levels.
**Contribution**

All authors were involved in drafting the article or revising it critically for important intellectual content. All authors approved the final version.

**Conflict-of-interest disclosure**

The authors declare no competing financial interests.

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**References**


