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CASE REPORT

Increased eculizumab requirements during pregnancy in a patient with paroxysmal nocturnal hemoglobinuria: case report and review of the literature

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Key Clinical Message

Paroxysmal nocturnal hemoglobinuria (PNH) results from reduced complement regulatory proteins on hematopoietic cells, predisposing patients to intravascular hemolysis, thrombophilia, and cytopenias. Women diagnosed in pregnancy can experience significant maternofetal complications. Trials of eculizumab in PNH excluded pregnant women. Here, we report the first Canadian patient taken through pregnancy on eculizumab.

Keywords

Aplastic anemia, eculizumab, hemolysis, PNH, pregnancy.

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired clonal disorder of hematopoietic stem cells. These cells have somatic mutations in the X-linked phosphatidylinositol glycan (*PIG*)-A gene, which encodes an integral step in production of glycosylphosphatidylinositol (GPI) membrane anchor proteins. Without these anchors, GPI-linked proteins such as the complement regulatory elements CD55 and CD59 are deficient, causing cells to be exquisitely susceptible to complement-mediated lysis [1]. Classical manifestations of PNH include Coombs-negative intravascular hemolysis, thrombophilia, and bone marrow failure. Other common symptoms include fatigue, abdominal pain, pulmonary hypertension, erectile dysfunction, and renal insufficiency [1, 2]. Patients with PNH have traditionally been treated supportively with transfusions, folic acid, and anticoagulation; in PNH with severe aplastic anemia (SAA), antithymocyte therapy may be used, with or without bone marrow transplant. The introduction of eculizumab, a humanized monoclonal antibody that binds complement protein C5, led to considerable advances in the long-term management of PNH, with significant improvements in hemolysis, thrombosis, quality of life, and overall survival [2–4].

The median age at diagnosis of PNH is in the third decade, with a slight female preponderance [5]. As such, there is a risk of obstetrical complications. Indeed, retrospective analysis has suggested that 25% of women are diagnosed with PNH during pregnancy [6]. This may be, in part, due to the increased activity of complement noted even in normal pregnancy, which could provide a trigger [7]. In active PNH, cytopenias and thromboembolism can cause significant morbidity to mother and fetus, with thrombosis being the leading cause of death in pregnant women. Reports of pregnant PNH patients in the preeculizumab era describe maternal and fetal mortality rates of 8–12% and 4–7%, respectively [8, 9]. However, as pregnancy was an exclusion criterion for the clinical trials, randomized controlled data for pregnant women

are unavailable [3, 4]. Case reports and series in the published literature document several patients who have been treated with eculizumab during some portion of their pregnancy and/or postpartum [10–13].

Physiologic changes during pregnancy can affect drug metabolism, including altered plasma volume, total body water, plasma proteins, and organ blood flow. Eculizumab pharmacokinetic testing was assessed in 40 nonpregnant adult patients with PNH using a one-compartment model, without taking pregnancy-associated changes into account. Pharmacodynamic analysis demonstrated near-complete inhibition of hemolysis with a sustained trough of ≥35 μg/mL [14]. Eculizumab metabolism has not been explicitly tested in pregnancy. In the largest case series of pregnant PNH patients, only three of the seven had documented eculizumab levels (range: 63.2–116.1 μg/mL) [11]. Those who had levels measured either continued eculizumab antepartum/postpartum or were started in later trimesters and into the postpartum period. Two patients required an increase in infusion frequency to manage breakthrough hemolysis [11].

We report here on the first Canadian PNH patient taken through a pregnancy. Eculizumab was administered without interruption in the antepartum period but required increased dosing and frequency of infusions for management of breakthrough disease.

Case Report

In 2001, an 18-year-old female with pancytopenia was referred to our clinic and diagnosed with SAA. She had no histocompatible siblings so was treated with horse antithymocyte globulin (ATG) and cyclosporine. Investigations revealed no evidence of a PNH clone. Due, in part, to noncompliance with cyclosporine, only a partial response was achieved, and she continued to require intermittent transfusions. A second course of horse ATG was administered for worsening disease in 2006, again with only a partial response. In January 2007, flow cytometric evaluation demonstrated the first evidence of a PNH clone (23% of granulocytes) with evidence of compensated intravascular Coombs-negative hemolysis, worsening fatigue, and multiple episodes of dysuria, many culture-negative. Consistent with this, her lactate dehydrogenase (LDH), which was normal at diagnosis, became modestly elevated in mid-2006 and rose further near the end of the year, with levels between 563 and 619 U/L (normal range: 100–220 U/L). Hemolysis continued to worsen (LDH 1000–2000 U/L), and transfusion requirements increased to 4–10 units of red cell concentrate (RCC) per month. Although our patient also had mild thrombocytopenia and occasional heavy menstrual periods, no platelet transfusions were required. Her neutrophil count was consistently within normal range.

Due to progressive hemolysis, the application for eculizumab was submitted in September 2009. She was immunized against meningococcus with a quadrivalent vaccine, and eculizumab was started in early December 2009. Following induction, she was maintained on the standard fortnightly dose of 900 mg. Evidence of hemolysis resolved within a week (LDH 200–300 U/L), with marked improvement in fatigue and dysuria. She had a moderate reduction in transfusion requirements (2–4 units RCC per month) with no increase in LDH or hemoglobinuria, likely reflecting extravascular hemolysis and the underlying SAA. Ongoing transfusions led to the development of transfusion-related iron overload and the eventual initiation of iron chelation therapy (deferasirox). Interestingly, erythropoiesis improved and she became transfusion independent in February 2011, coinciding with the start of deferasirox. This is similar to results seen in some patients with myelodysplastic syndrome early after initiation of iron-chelation therapy [15].

In February 2013, our patient became pregnant and was referred to high-risk obstetrics for comanagement. Risks and benefits were discussed, and the decision was made to continue both cyclosporine and eculizumab throughout pregnancy, to initiate low-molecular-weight heparin (LMWH) prophylaxis (tinzaparin 4500 units daily), and to discontinue deferasirox. The first trimester was uneventful. In the second trimester, she developed symptomatic anemia without overt evidence of hemolysis and again required regular RCC transfusions. Because of previously published experience with pregnancy [11] and the increased plasma volume anticipated in the second trimester, her eculizumab was increased from 900 to 1200 mg fortnightly in June 2013. In August 2013, despite the increased dose, she had her first episode of frank intravascular hemolysis with hemoglobinuria since starting eculizumab (LDH 1073 U/L). Therefore, the interval between infusions was decreased to every 12 days. Facilities for monitoring drug levels were unavailable.

During obstetrical assessment, a diagnosis of placenta previa was made. Accordingly, elective Caesarian section was chosen as the delivery plan. One week before the planned delivery, she experienced antepartum hemorrhage with frequent contractions and required an urgent C-section. A healthy female infant was delivered approximately 4-week premature, with a normal age-adjusted preterm complete blood count. Our patient's preoperative hemoglobin was 99 g/L and her platelets, 73×10^9/L. Intraoperatively, the hemoglobin dropped to 79 g/L with an estimated blood loss volume of 800 mL. Two units of RCC were subsequently transfused. In all, 25 RCC units were required during the pregnancy. Four eculizumab

infusions were given at the increased dose and frequency (including two postpartum), with no further evidence of hemolysis, and then reduced back to her standard schedule. There were no thromboembolic episodes, and the LMWH was discontinued 6 weeks postpartum. Her hemoglobin since delivery has increased to the prepregnancy baseline (Hgb 100–115 g/L). She decided not to breastfeed the infant, who continues to develop appropriately.

Discussion

We report here the first case of a Canadian PNH patient on eculizumab followed through pregnancy. Although no overt complications occurred, it was clear that pregnancy coincided with a return of transfusion dependence and overt intravascular hemolysis. Increased transfusion requirements and hemolysis during pregnancy have been reported by other groups as well [6, 11]. Fortunately, no thromboembolic events or infections occurred in our patient, despite the increased frequency of both being reported in PNH pregnancies [6, 8]. As well, similar to previous reports, no adverse fetal outcomes were noted with eculizumab exposure [11].

Our case highlights the importance of regular, and perhaps more frequent, monitoring of hemolytic parameters to detect early disease activity. Preemptive increases in eculizumab dose and/or frequency may prevent serious clinical manifestations of PNH and minimize maternal and fetal complications. Such an anticipatory strategy could be assisted further by the ability to quantify eculizumab drug levels. Data on eculizumab in pregnant PNH patients, monitored prospectively, will help in developing guidelines for treating this patient population. Eculizumab could also be monitored in these cases via umbilical cord sampling, as previously reported in select cases [11], although the engineered IgG2 backbone should minimize placental transfer. Such data would enrich the global registry and serve to improve care of pregnant PNH patients in the future.

Conflict of Interest

CP is the recipient of an unrestricted educational grant from Alexion. CP and BL have participated in advisory boards for Alexion.

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