Eculizumab treatment in pregnant women with paroxysmal nocturnal hemoglobinuria: A Polish experience

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Abstract

Background. Eculizumab is an antibody targeting the C5 complement protein. Clinical trials suggest that eculizumab significantly reduces transfusion requirements and prevents disease complications in patients with paroxysmal nocturnal hemoglobinuria (PNH).

Objectives. To analyze the outcome of pregnancies among Polish women with PNH treated with eculizumab as a part of the Polish National Health Fund program.

Materials and methods. We report the outcomes of 3 pregnancies among women treated with eculizumab between 2017 and 2020. For 1 of these woman, it was the 1st pregnancy, while the remaining 2 patients had previously had 1 previous successful pregnancy each.

Results. All 3 mothers survived pregnancy, and all children were born alive. One of the patients had a vaginal delivery. Another required cesarean delivery at the 34th week due to a decreasing platelet count. In 1 case, premature rupture of the fetal membranes occurred at week 36, followed by artificial labor induction. All children were born without any inborn defects. The 2 prematurely born babies required a prolonged hospital stay.

Conclusions. Treatment with eculizumab seems to reduce the risk to a mother and a child associated with PNH. However, more data are necessary to confirm this notion.

Key words: pregnancy, eculizumab, PNH

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Background

Paroxysmal nocturnal hemoglobinuria (PNH) is an uncommon, acquired clonal disorder characterized by venous and arterial thromboembolism, chronic hemolysis, and a broad spectrum of other symptoms related to terminal complement activation.[1] The progressive character of the disease seriously affects the prognosis, with a median survival varying from 1 to 3 decades.[2,3] Pregnancy among affected women has been universally discouraged due to the tendency for the disease to aggravate hemolysis, and because of transfusion requirements and an increased risk of thromboembolic complications.[4] In some reports, maternal mortality is as high as 20%, with most deaths observed postpartum.[5] Fetal morbidity and mortality are also high, reaching nearly 10%, primarily due to premature births.[2–6]

Eculizumab is a humanized IgG2/4 antibody targeting the C5 complement protein. It blocks complement cleavage to C5a and C5b.[7] Clinical trials suggest that eculizumab treatment in patients with PNH significantly reduces transfusion requirements, prevents disease complications and improves the quality of life.[8–10] There are limited data regarding the management of pregnant patients with eculizumab. The published series differ regarding the timing of the introduction of eculizumab, administered doses, infusion frequencies, and the type of anticoagulation used.[11–18]

Objectives

Pregnancy among women with PNH has been discouraged due to the risk of thromboembolic complications in mothers and significant fetal morbidity and mortality. However, there are only sporadic reports describing the treatment results in pregnant women in the era of monoclonal antibody-controlled PNH. Therefore, this study aimed to assess the risks related to pregnancy pregnancy for mothers while being treated with eculizumab, as well as risks for babies, and to consider possible changes in the recommendations regarding pregnancy among affected women.

Materials and methods

Information was collected from 3 patients who became pregnant during treatment with eculizumab or started treatment while pregnant between 2017 (the beginning of the Polish National Health Fund program) and 2020. They were selected from a total of 74 patients who qualified for the eculizumab treatment program. Among the treated patients, there were 46 females, 28 of whom were younger than 55 years. The treating physician provided detailed information about each patient. Eculizumab was administered using the standard treatment protocol: 600 mg intravenously weekly for the first 4 weeks, followed by 900 mg intravenously every 2 weeks.

Despite the retrospective nature of the study, the protocol had to receive approval from the Bioethics Committee of Collegium Medicum, Nicolaus Copernicus University in Toruń, Poland (approval No. KB 674/2021), and the study was performed in compliance with the Declaration of Helsinki.

Results

The 1st patient was diagnosed with a mild form of aplastic anemia at the age of 26. At that time, the PNH granulocyte clone size was 3.8%. Before the treatment with eculizumab started, she had had 1 successful pregnancy. At the time of her 2nd pregnancy, her PNH clone increased to 38.9%; thus, the treatment with eculizumab was introduced at week 20. She was also receiving prophylactic enoxaparin. A drop in the platelet count occurred after the initiation of eculizumab, reaching a nadir of 17×10^9/L at the time of delivery. Otherwise, her pregnancy remained uncomplicated. She had a vaginal delivery in the 39th week with platelet transfusion support. No complications were observed during the postpartum period.

The 2nd patient was diagnosed with PNH with the presence of a 20.6% PNH clone at the 25 years of age. Soon after the diagnosis was established, the patient started treatment with eculizumab due to an aggravation of anemia. Later on, she developed immune thrombocytopenia that required steroid treatment. A bone marrow biopsy ruled out aplastic anemia. One year after diagnosis, she became pregnant and, at that time, the PNH clone increased to 24.1%. She continued the eculizumab infusions throughout her pregnancy. Artificial labor induction was necessary due to a premature rupture of the fetal membranes at week 36.

The 3rd patient was diagnosed before her pregnancy at the age of 30. Previously, she had had 1 successful pregnancy despite not being treated with eculizumab. At the time of her 2nd pregnancy, she had already started eculizumab treatment with the standard dose. She received anticoagulation prophylaxis with low-dose aspirin alone. At week 34, she had an uncomplicated cesarean section due to a falling platelet count. None of the above patients required blood transfusion during pregnancy.

All children were born without any inborn defects and scored 10 points on the Apgar scale. Two prematurely born babies (born at weeks 36 and 34) required a prolonged hospital stay. Their birth weight was 2650 g and 1920 g, respectively. The third baby (2830 g) born at week 39 was discharged as planned.

Discussion

The introduction of eculizumab for the treatment of PHN allows affected patients to lead a relatively normal life and start a family. In this study, we confirm the safety

of eculizumab treatment during pregnancy both in mothers and their babies, with minimal morbidity observed. All our patients gave birth to healthy babies. No significant maternal mortality was observed in the patients treated with eculizumab, which means a certain progress in comparison with the pre-eculizumab era. De Guibert et al. observed 2 fatal postpartum thromboses among 27 pregnancies in 22 women at 10 French Society of Hematology centers between 1978 and 2008.[5] In other retrospective series, the percentage of fatalities among mothers related to thrombosis ranged from 11.6% to 22.2%.[6,19] Fetal mortality in the same groups varied from 4% to 7.2%. The introduction of eculizumab resulted in a substantial improvement in the pregnancies of affected mothers. Kelly et al. summarized a questionnaire survey investigating the outcome of pregnancies in 75 patients with PNH treated with eculizumab, which was reported to the International PNH Interest Group and Registry.[11] No maternal deaths occurred, and only 2 episodes of postpartum thrombosis were reported. Maternal thrombocytopenia and premature rupture of the fetal membranes were the leading causes of premature birth in 2 of our patients. In the report to the International PNH Interest Group and Registry, premature births occurred in 29% of cases (22 of 75 pregnancies). Thrombocytopenia that resulted in replacing enoxaparin with aspirin monotherapy did not cause any thrombotic complications. It resulted in premature cesarean sections, but otherwise was uncomplicated. Thrombocytopenia is common in pregnancy, affecting 27% of patients, and often requires platelet transfusions.[19] We did not observe any significant worsening of anemia with the aggravation of hemolysis that would have required an increase in the dose of eculizumab in any of the patients. No thrombotic complications were observed, possibly due to the decreased platelet count in our patients. The morbidity observed among babies was related to prematurity. According to data from the UK, the prevalence of premature births among patients with PNH is 4 times higher than in the normal population.[11] The most frequent causes of premature delivery were planned cesarean delivery, a decreased maternal platelet count, intrauterine growth retardation, and preeclampsia. In the group described by Kelly et al., fetal morbidity and mortality remained high despite eculizumab treatment, with 3 deaths (4%) and 2 stillbirths from the same mother, and the loss of a twin in another pregnancy.[11] In our study, 2 out of 3 babies were born prematurely and required a prolonged hospital stay.

Limitations

Despite the fact that all the pregnant patients treated with eculizumab found by National Health Fund were included in the study, the number of patients remains limited. Only an international collaboration could provide more data regarding this critical subject. On the other hand, even a limited number of patients can provide vital information that will influence our clinical practice.

Conclusions

Based on our observations and the previous data, we can assume that treatment with eculizumab can be used safely in pregnant women with PNH. This treatment reduces the risk of maternal morbidity and mortality. However, more evidence is required regarding the use of eculizumab and other C5 inhibitors in this setting.

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