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Eculizumab in Early-Stage Pregnancy

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INTRODUCTION

An intact complement system is essential for the normal development of both the placenta and the fetus. However, its excessive activation during pregnancy may induce severe adverse events, including thrombotic microangiopathy (TMA).[1] In conditions such as paroxysmal nocturnal hemoglobinuria and atypical hemolytic-uremic syndrome (aHUS), in which involvement of a dysregulated complement system are well established, pregnancy can act as the trigger of the disease, leading to maternal and fetal morbidity and mortality.[S1] An imbalance by overactivity of the complement system can be detected in relapses of antiphospholipid syndrome (APS), systemic lupus erythematosus (SLE), and sickle cell anemia during pregnancy.[2] IgA nephropathy is another entity that has been recently recognized as a TMA trigger.[S2] Furthermore, complement system overactivity has been reported in pregnancy-specific disorders, such as preeclampsia (PE) or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. All of these conditions are currently included within the expanded spectrum of TMA syndromes, which are characterized by a severe injury of the vascular endothelium, microangiopathic hemolytic anemia, a variable degree of thrombocytopenia, and organ damage.[S3]

Eculizumab is a monoclonal antibody that inhibits the activation of complement C5 and has drastically changed the prognosis of TMA syndromes. Several studies have shown its beneficial effect in patients with paroxysmal nocturnal hemoglobinuria[S4] and aHUS,[S5] and preliminary evidence suggests that this effect is extended to pregnant women suffering these diseases, with a good safety profile for the fetus.[3] However, limited information exists about the use of eculizumab in pregnant women in TMA associated with PE, HELLP, or APS.[4] We present 2 cases of patients with signs of TMA during the early stages of pregnancy who were treated with eculizumab aiming to prolong their pregnancy. Informed consent was obtained from both patients and the Case Reporting[S6] guidelines were closely followed for the report of these cases.

CASE PRESENTATIONS

Case 1

A 35-year-old woman with no relevant medical history except for headaches of unknown etiology was hospitalized with malignant hypertension with grade IV hypertensive retinopathy, proteinuria, and severe kidney injury. Antihypertensive treatment was started and at hospital discharge serum creatinine was 2.7 mg/dl (estimated glomerular filtration rate 20 ml/min per 1.73 m^2) and proteinuria 0.5 grams per 24 hours. Eighteen months later she became pregnant and was admitted to the hospital at both 9 and 17 weeks because of hypertensive crises that required intravenous antihypertensive treatment. The 20-week pregnancy ultrasound (US) showed increased uterine arterial resistances. A 24-week US revealed fetal growth restriction. Blood pressure was 135–145/85–95 mm Hg with antihypertensive treatment and superimposed PE was suspected. The maternal soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio was 21, normal for gestational age.[5]

At 27 weeks and 6 days of pregnancy she was hospitalized with an intense headache, hypertension

(208/104 mm Hg), anemia (hemoglobin 10 g/l), lactate hydrogenase (LDH) of 282 IU/l, microhematuria, and proteinuria (1.6 g/24 hours), with a stable kidney function (serum creatinine 2.3 mg/dl) and normal coagulation tests. Given these findings, the diagnosis of early onset superimposed PE with severe features was made. US showed fetal hemodynamic stability and an estimated fetal weight of 850 g. The hypertensive crisis was controlled and corticosteroids were prescribed for fetal maturation. In the following 2 days, worsening of anemia (hemoglobin 8.3 g/l), increased LDH (306 IU/l), hypocomplementemia (C3 73 mg/dl), and impaired renal function (serum creatinine 3.0 mg/dl) with normal platelet count were observed. Peripheral blood smear showed the presence of 2 to 3 schistocytes per high power field. Homocysteine and ADAMTS13 activity were normal. Give the extreme fetal prematurity, data suggesting TMA, and the normal value of the sFlt-1/PlGF ratio, eculizumab together with continuous fetal monitoring was proposed to prolong the pregnancy and improve neonatal outcomes. The patient signed an informed consent accepting the off-label indication of eculizumab and received a first dose of 900 mg after the administration of oral penicillin 400 mg (daily during the whole treatment with eculizumab) and meningococcal and pneumococcal vaccination. Two additional doses were infused (900 mg 1 week later and 1200 mg on the day of delivery) with no reported side effects. TMA markers and kidney function showed improvement (hemoglobin 10 g/l, LDH 250 IU/l, and serum creatinine 2.1 mg/dl). After reaching 30 weeks and 0 days of pregnancy (13 days after starting eculizumab), US showed fetal deterioration, consistent with worsening placental function, also reflected by an increased sFlt-1/PlGF ratio of 134 (Figure 1). At this point, delivery was indicated by caesarean section, delivering a male weighing 1090 g with a favorable outcome.

During the immediate puerperium, blood pressure was optimally controlled, and no analytic abnormalities were noted. After the administration of the fourth and last dose of eculizumab, 7 days after delivery, the patient was discharged. Placental histology revealed decidual vasculopathy and altered

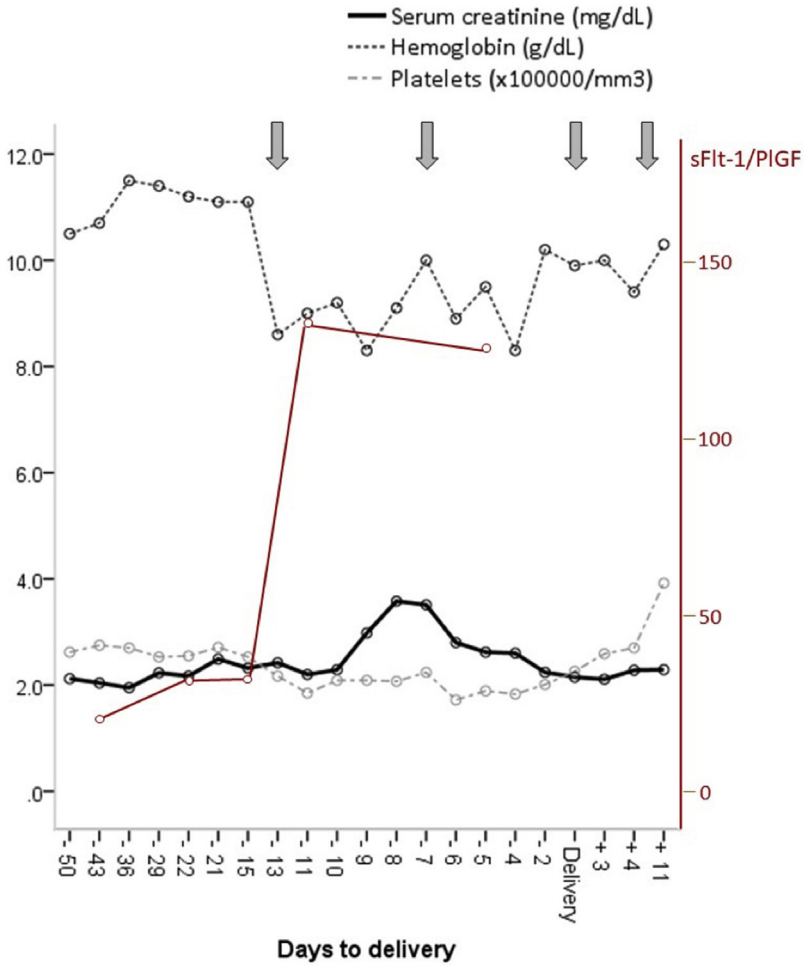

Figure 1. Evolution of the levels of maternal serum creatinine, hemoglobin, platelets, and soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio in case 1. Arrows indicate the administration of eculizumab.

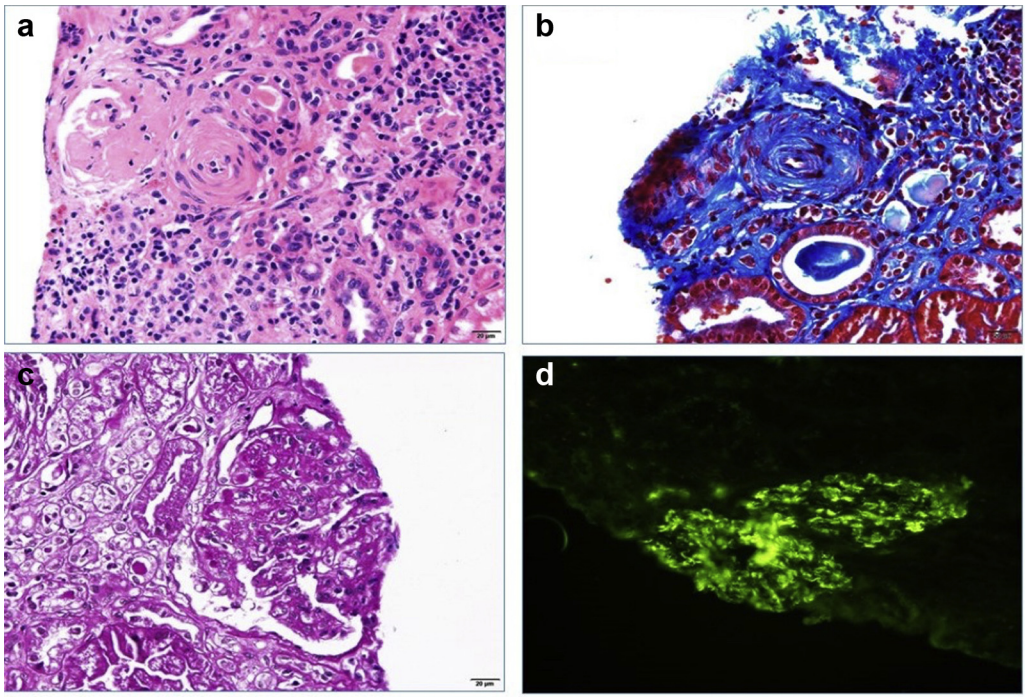

Figure 2. Kidney biopsy specimen from case 1. (a) Hematoxylin and eosin stain (original magnification ×40) and (b) Masson trichrome staining (original magnification ×40) show a renal arteriole with hyperplastic arteriolosclerosis (thickening of the arteriolar wall caused by the concentric proliferation of smooth muscle cells with an "onion skin" appearance). (c) Periodic acid–Schiff stain (original magnification ×40) displays a glomerulus with mesangial expansion and segmental hyaline lesions. (d) IgA immunofluorescence (original magnification ×40) shows an image of direct immunofluorescence with intense (+++/+++) mesangial IgA deposits in 2 glomeruli. All histologic images were taken on an Olympus BX53 microscope with an Olympus DP73 camera (Olympus Corporation, Shinjuku, Japan).

trophoblastic invasion with small areas of infarction, as usually observed in PE/HELLP syndrome. Staining for complement membrane attack complex (C5b-9) was negative.

Two months after delivery, a new decline of kidney function was observed, along with increasing proteinuria and microhematuria, hypocomplementemia (C3 58.9 mg/dl), and elevated serum IgA (926 mg/dl). A renal biopsy specimen was obtained (Figure 2), establishing the diagnosis of long-standing IgA mesangial nephropathy with chronic TMA signs. The genetic complement study showed homozygous deletion of *CFHR1* and *CFHR3*. Treatment with corticosteroids and mycophenolate sodium was initiated. Two years later, the clinical and analytic responses are excellent with stable renal function (serum creatinine 1.8 mg/dl), resolution of microhematuria, and marked proteinuria decrease to 0.4 grams per 24 hours.

Case 2

A 27-year-old woman with a history of SLE and APS with anti-Ro and anti-La antibodies and multiorganic repercussion was referred to our center at 8 weeks of pregnancy. Initial treatment included low-dose aspirin, heparin, azathioprine, hydroxychloroquine, prednisone, and vitamin D supplements. A routine analysis performed at 21 weeks of pregnancy showed signs of TMA (hemoglobin 9.0 g/dl, platelets 109,000 cells/μl, LDH 316 UI/l, 2 schistocytes per high power field in the peripheral blood smear, and haptoglobin <5.8 mg/dl) with a negative Coombs test, normal coagulation, serum creatinine 0.5 mg/dL, a protein/creatinine ratio of 0.40, microhematuria, normal homocysteine, vitamin B_{12} levels, and a sFlt-1/PlGF ratio of 10. Serologic testing revealed elevated anti–double-stranded DNA antibodies (36, cut-off 30) and normal complement levels. The patient was admitted to the hospital and a multidisciplinary team recommended increasing the dosage of her immunosuppressive therapy in addition to the administration of eculizumab. After informed consent, 2 weekly doses of 900 mg and 4 biweekly doses of 1200 mg were administered until delivery. Improvement of the hematologic parameters was observed from the first weeks, with stable renal function and no reported side effects. Fetal growth was normal throughout the pregnancy, as well as the sFlt-1/PlGF ratio, with in-range results of 7 and 3 and 25 weeks and 5 days and 28 weeks and 3 days of pregnancy, respectively.

At 27 weeks and 3 days of pregnancy, the patient was admitted for progressive dyspnea and severe pulmonary hypertension. Treatment with epoprostenol and sildenafil

was initiated with marked improvement. Fetal maturation with corticosteroids was completed. After reaching 31 weeks and 2 days' gestation, a caesarean section was performed and a male weighing 1700 g was delivered without any severe morbidity and favorable outcome at 7 months. The maternal postoperative course was complicated by development of hemoperitoneum that required transfusion and temporary discontinuation of anticoagulation. Treatment with high doses of corticosteroids and rituximab was initiated and the patient was discharged 20 days after delivery.

DISCUSSION

There are scarce data on the use of complement inhibitor drugs during gestation to treat TMAs, such as aHUS, APS, or PE/HELLP syndrome, threatening the course of pregnancy. In clinical practice, the presence of common characteristics among these entities makes reaching a precise diagnosis difficult. In PE/HELLP syndrome, the elevation of the sFlt-1/PlGF ratio[5] and their clinical resolution after delivery can be of help in differential diagnosis.[6] aHUS usually develops postpartum, whereas PE/HELLP syndrome usually occur during the second half of pregnancy.[S7] Regardless of the definitive diagnosis, whenever TMA is found along with compromised fetal viability the use of eculizumab could potentially prolong the pregnancy.

Currently, the first-line treatment for PE/HELLP syndrome is delivery of the fetus and placenta. Nevertheless, this approach may not be easy during the earlier stages of pregnancy. Despite the evidence, the role of the complement system may be a mediator in its pathophysiology. The experience with eculizumab in PE/HELLP syndrome is limited. Burwick *et al.*[7] first described a case where HELLP syndrome with TMA features was treated with eculizumab at 26 weeks, allowing pregnancy prolongation for 3 more weeks with excellent results for the mother and the fetus. Recently, another patient with TMA case starting at 20 weeks was treated with eculizumab allowing the pregnancy to continue successfully until 27 weeks.[8] In our first case, even though the patient was initially diagnosed of PE with severe features, the presence of renal damage, anemia, LDH increase, C3 hypocomplementemia, and severe hypertension also suggested the presence of TMA, even in the absence of thrombocytopenia.[9] Moreover, the kidney biopsy specimen obtained postpartum confirmed signs of chronic TMA together with the presence of IgA mesangial nephropathy, a condition in which complement overactivation is involved. In the second case, TMA occurred in a predisposed SLE/APS pregnant woman before viability was achieved. Despite the severity of the life-threatening condition of this case, the administration of eculizumab allowed pregnancy continuation until 31 weeks without features of PE/HELLP syndrome.[S8]

Table 1. Teaching points

Established facts
TMA can affect the course of pregnancy. TMA features overlap with pre-eclampsia, HELLP syndrome, or SLE, and all of them should be considered in the differential diagnosis
Novel insights
Eculizumab can prolong pregnancy in TMA syndromes that develop early in pregnancy. Angiogenic biomarkers could be of aid in differential diagnosis of TMA, pre-eclampsia, and SLE

HELLP, hemolysis, elevated liver enzymes, and low platelet count; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy.

Eculizumab's safety profile during pregnancy has been proven across different reports, mostly in women with PHN. In our experience, we confirmed the absence of severe neonatal infectious complications.[S9] Moreover, both patients found treatment with eculizumab acceptable with no side effects.

The main limitations of this study are those related to case reports, which are subject to selection and publication bias. However, our findings support the conviction that the complement system is closely intertwined with TMA physiopathology in different scenarios that occur during pregnancy, such as PE/HELLP syndrome or APS/SLE.[S10] Given this premise, it seems reasonable to consider the use of complement-blocking agents in short cycles of treatment, maintaining them until delivery, as a plausible option to prolong pregnancy in those situations that debut early on the pregnancy and in which the complement plays a key role in their development (Table 1).

DISCLOSURE

EM has received lecture fees from Alexion Pharmaceuticals. IH has received lecture and consultation fees from Alexion Pharmaceuticals and Roche Diagnostics. CV has received lecture fees from Roche Diagnostics. AG has received lecture fees from Roche Diagnostics. All the other authors declared no competing interests.

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Approval by the local Ethics Committee was obtained prior to publication. Informed consent was obtained from both patients prior to publication. Data available from the corresponding author on reasonable request. All information is registered in the electronic clinical history of our center (Electronic Health Care Resources HCIS).

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplemental References.

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