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Successful Pregnancies During Ongoing Eculizumab Therapy in Two Patients With Complement-Mediated Thrombotic Microangiopathy

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In patients with pregnancy-associated complement gene variant–mediated thrombotic microangiopathy (cTMA), terminal complement blockade is used for treatment of cTMA flares during pregnancy or following delivery. We report pregnancy and delivery outcomes of 2 genetically high-risk patients with cTMA, including 1 kidney transplant recipient, during ongoing eculizumab therapy. In both patients, the first manifestation of cTMA occurred independent from pregnancy. One patient has a history of 2 uneventful pregnancies with prophylactic plasma infusions, and the other has a history of early abortion during long-term eculizumab therapy following kidney transplantation. Overall, pregnancy and delivery outcomes under ongoing eculizumab therapy in our 2 patients with preserved kidney function were excellent as compared with other patients reported in the literature. Eculizumab plasma concentrations were maintained in the therapeutic range during pregnancy and were also detectable in cord blood. Results of cord blood analysis showed deficient complement activity, with low factor and regulator levels, most likely reflecting the age of the neonates and presence of eculizumab in cord blood. In conclusion, pregnancy during ongoing eculizumab treatment appeared to be safe in 2 women with a history of high-risk genetic cTMA and excellent kidney function, even following kidney transplantation.

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INTRODUCTION

A history of complement gene variant–mediated thrombotic microangiopathy (cTMA) bears an increased risk for TMA relapse during pregnancy, leading to miscarriage, poor delivery outcomes, and end-stage kidney disease.[1-3] Pregnancy is generally discouraged in these women. Therefore, preventive plasma therapy has been used in the past during pregnancy for several patients who wanted to have children despite discussions of the risks involved.[4,5]

More recently, eculizumab was used to treat cTMA flares during pregnancy (Table S1) and after delivery (Table S2), but also in a preventive setting, in which patients with cTMA became pregnant during ongoing eculizumab therapy.[6,7] Servais et al[6] reported 5 pregnancies in 3 women during ongoing eculizumab therapy and showed rather poor pregnancy and delivery outcomes. Complications included 1 abortion and 2 growth retardations, and all 4 neonates were small for gestational age. Each of the reported women experienced either HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome or, in 2 cases, preeclampsia.[6] Duval et al[7] recently reported another pregnancy during ongoing eculizumab treatment in a patient who delivered a preterm child by caesarean section that was performed due to signs of moderate eclampsia and fetal distress at week 32 of gestation. Furthermore, Fontana et al[8] described a patient with cTMA who presented with severe preeclampsia as of week 26 of gestation during ongoing eculizumab therapy (low dose with 900 mg fortnightly) that resulted in a caesarian section at gestational week 27 with plasma and higher dose eculizumab rescue therapy.

From the Vienna TMA cohort (Fig S1), we identified pregnancies in patients with cTMA and we report excellent pregnancy and delivery outcomes of 2 pregnancies in 2 genetically high-risk patients with cTMA with well-preserved kidney function, including a kidney transplant recipient, during ongoing eculizumab therapy.

CASE REPORTS

Case 1

A white woman with an approximate 10-year history of cTMA underwent kidney biopsy for worsening kidney function in her late 20s. This biopsy showed acute and chronic glomerular and interstitial arteriolar TMA and she acutely required dialysis. Despite plasma exchange, she remained dialysis dependent and received a deceased donor kidney graft 4 years later. Molecular genetic analysis revealed the presence of: (1) a rare variant in *CFH* (p.C1032X, heterozygous), (2) the *CD46*ggaac risk haplotype (homozygous), and (3) the *CFH* H8 haplotype (heterozygous). Due to the genetically high-risk scenario, she received peritransplantation plasma exchange followed by fortnightly plasma infusions for prevention of cTMA recurrence. Kidney function was excellent within a few days after surgery (serum creatinine, 1.5 mg/dL 7 days after transplantation). She remained on treatment with blood pressure–lowering medication using a triple combination of antihypertensive drugs. Three months after

Table 1. Delivery Outcomes of 3 Pregnancies in 2 Patients With a History of cTMA During Ongoing Eculizumab Therapy

Case	Pregnancy	Age at Delivery, y	Outcome	Sex	Gestational Age at Birth/ Abortion, wk	Mode of Delivery	Birth Weight, g	Birth Height, cm	Head Circumference, cm	Assessment
1	1	20s	Abortion	—	<12 + 0	—	—	—	—	—
1	2	20s	Live birth	Male	37 + 0	Vaginal	3,082	50	34	AGA[a]
2[b]	1	20s	Live birth	Male	40 + 3	Vaginal	3,720	52	35	AGA[a]

Abbreviations: AGA, appropriate for gestational age; cTMA, complement gene variant–mediated thrombotic microangiopathy.
[a]Neonatal outcome at 4 weeks after delivery was unremarkable in both cases.
[b]Two previous pregnancies of this patient with preemptive plasma therapy are not included in this table and were reported previously by Gaggl et al[4] (case A.1).

transplantation, allergic reactions with recurrent severe maculopapular rush prompted a switch from plasma therapy to complement inhibition with eculizumab (900 mg every week for 4 weeks followed by 1,200 mg fortnightly). Serum creatinine level was in the reference range at this time (0.89 mg/dL).

Shortly after transplantation, the patient wanted to become pregnant. The risks for the mother and baby, such as pregnancy in kidney transplant recipients and pregnancy with a history of cTMA, were discussed extensively with the patient and the family. Immunosuppressive therapy was switched from tacrolimus to cyclosporine A because of hair loss and later from mycophenolate mofetil to azathioprine for prevention of miscarriage and congenital defects. Three months after conversion, immunosuppression included cyclosporine A at 75 mg twice daily (trough level, 50-80 ng/mL), azathioprine at 25 mg once daily, and prednisolone at 5 mg once daily. Kidney function was excellent (serum creatinine remained between 0.9 and 1.1 mg/dL and urinary protein-creatinine ratio, <200 mg/g) and blood pressure was well controlled (<130/80 mm Hg) with triple blood pressure–lowering therapy. Her first pregnancy was diagnosed at 7 weeks of gestation, but unfortunately ended with a spontaneous abortion around 12 weeks of gestation. Clinical and laboratory details are summarized in Tables 1 and 2.

Five months later, the patient reported her second pregnancy at 7 weeks of gestation. The frequency of eculizumab doses was increased in the second trimester (900 mg every week starting during gestational week 17). Kidney function remained stable but proteinuria increased to protein excretion > 1 g/24 h, and the need for antihypertensive medications increased at the same time at 36+0 weeks of gestation. However, the SFLT1/PLGF (soluble fms-like tyrosinkinase 1 to placental growth factor) ratio in serum, a risk marker for preeclampsia, remained low. She delivered a healthy child by vaginal delivery the following week at 37+0 weeks of gestation (Table 1). The clinical course and results of laboratory tests during and after pregnancy are indicated in Tables 2 and 3.

Case 2

A white woman with a history of hemolytic uremic syndrome starting at 3 years old became pregnant for the third time in her mid-20s. Since age 3 years, she had experienced multiple episodes of acute kidney injury attributed to TMA. These resolved without plasma therapy, with a return of kidney function to baseline. At age 14 years, the 23rd TMA episode resulted in acute kidney failure and necessitated a total of 6 plasma exchanges until normalization of kidney function. Later, her first 2 pregnancies in her late teens and early 20s were managed with prophylactic plasma therapy (case A.1, Gaggl et al,[4] 2018) and resulted in vaginal delivery of 2 healthy children. During both pregnancies, she showed no signs of complement activation as evidenced by microangiopathic hemolysis, but she developed proteinuria with protein excretion > 1 g/24 h at the end of the second pregnancy that did not resolve completely after delivery. However, serum creatinine level remained normal. Antihypertensive therapy was not necessary during her first pregnancy, although during the second pregnancy she received nifedipine, which was replaced by lisinopril after her second delivery due to proteinuria. Genetic testing revealed disease-causing variants in *CFI* (p.G342E; heterozygous) and *CD46* (p.D257Vfs*41; heterozygous), as well as the *CFH* H3 haplotype (heterozygous). Furthermore, she carries the p.R102G/p.P314L haplotype in *C3*, which is a risk factor for dense deposit disease.

One year after the patient's second delivery, she presented with acute TMA accompanied by persistent proteinuria. Shortly before her third pregnancy, she agreed to undergo a kidney biopsy owing to proteinuria and another TMA flare triggered by a gastrointestinal infection. Pathologic examination revealed signs of chronic and also acute TMA, as well as C3, immunoglobulin M, and C1q deposits. At this time, complement inhibition with eculizumab was initiated (900 mg every week for 4 weeks followed by 1,200 mg fortnightly) and urinary protein-creatinine ratio significantly decreased from 1,727 to 509 mg/g thereafter.

Eculizumab treatment was continued with 1,200 mg fortnightly during the patient's third pregnancy in the same year, which was confirmed at gestational week 8. Proteinuria increased to protein excretion of ~1 g/24 h at the end of pregnancy. However, the SFLT1/PLGF ratio remained low. Blood pressure–lowering medication was changed from lisinopril to methyldopa before pregnancy and was not changed during pregnancy. At gestational week 40+3, she delivered a healthy child after an uneventful pregnancy (Table 1). The clinical course and results of laboratory tests during and after this pregnancy are indicated in Tables 2 and 3.

Table 2. Time Course of Laboratory Results and Clinical Details of 3 Pregnancies During Ongoing Eculizumab Therapy in 2 Patients With cTMA

	Patient 1 (KTX), Pregnancy 1	Patient 1 (KTX), Pregnancy 2					Patient 2, Pregnancy 1				
Time of blood test, gestational wk[a]	8	12	24	36	Del	Del+12	12	24	36	Del	Del+12
SBP, mm Hg	127	104	141	133	122	149	135	124	121	146	122
DBP, mm Hg	76	70	89	86	87	99	69	73	91	81	94
Serum creatinine, mg/dL	0.97	0.88	0.91	1.02	—	0.97	0.82	0.72	0.76	0.96	0.82
Urinary PCR, mg/g	76	101	269	1,818	—	1,651	390	359	1,386	ND	1,355
Platelets, $\times 10^3/\mu L$	250	257	279	263	—	302	217	204	187	221	304
Lactate dehydrogenase, U/L	ND	163	154	161	—	179	159	213	ND	187	220
Haptoglobin, mg/dL	37.4	366	<12	<12	—	56.4	94.8	84.6	77.6	ND	146
SFLT1/PLGF	ND	50	5.43	6.7	—	ND	ND	2.68	ND	ND	ND
TCA, classical pathway, CH50/mL	9	14	14	4	9	9	2	2	ND	ND	11
TCA, alternative pathway, %	0	1	0	0	0	1	0	1	ND	ND	0
Complement C3, g/L	0.73	0.88	1.19	1.31	1.15	0.91	1.31	1.09	ND	ND	1
Complement C4, g/L	0.24	0.33	0.37	0.3	0.3	0.41	0.42	0.33	ND	ND	0.38
Complement factor H antigen, mg/L	239	345	256	319	267	356	1,107	738	ND	ND	441
Complement factor I antigen, %	53	93	96	101	79	94	100	98	ND	ND	88
Complement factor B antigen, %	63	96	85	101	102	75	94	91	ND	ND	71
sC5b-9, ng/mL	697	554	307	245	385	1,128	233	320	ND	ND	401
Serum free eculizumab level, µg/mL	ND	81	240	157	120	116	60	76	ND	ND	95
Medication, daily dose, mg											
Cyclosporine A	150	200	200	250	250	250	—	—	—	—	—
Azathioprine	25	25	25	25	25	25	—	—	—	—	—
Steroid	5	5	5	5	5	5	—	—	—	—	—
Nifedipine	60	60	60	60	60	60	—	—	—	—	—
Metoprolol	75	75	0	100	100	100	—	—	—	—	—
Labetolol	300	300	300	300	300	300	—	—	—	—	—
Methyldopa	—	—	—	—	—	—	500	500	500	500	500

Note: Conversion factor for units: serum creatinine in mg/dL to µmol/L, ×88.4.
Abbreviations: cTMA, complement gene variant–mediated thrombotic microangiopathy; DBP, diastolic blood pressure; Del, delivery; KTX, kidney transplantation; ND, not done; PCR, protein-creatinine ratio; SBP, systolic blood pressure; sC5b-9, soluble terminal complement complex; SFLT1/PLGF, soluble fms-like tyrosinkinase 1 to placental growth factor ratio; TCA, total complement activity.
[a]±2 weeks.

DISCUSSION

Our center's experience based on 52 pregnancies in women with cTMA and now 2 further successful pregnancies under maintenance eculizumab therapy strongly suggests that pregnancies in women with cTMA have an excellent prognosis, even in women with high-risk mutations.

However, data for the therapeutic use of eculizumab during pregnancy or breastfeeding in patients with cTMA are scarce (see also Tables S1 and S2).[9] Limited data for malformations indicate no increased risk compared with non–eculizumab-treated mothers. However, eculizumab may cross the placental barrier and may cause terminal complement inhibition in the fetal circulation. To date, no evidence exists that eculizumab is excreted in human breast milk. Therefore, an individual risk-benefit analysis is recommended before starting and during treatment of pregnant or breastfeeding women with eculizumab.[10]

The primary concern with terminal complement blockade is increased susceptibility to infection with encapsulated organisms, particularly *Neisseria* species infections. Meningococcal vaccination is considered mandatory and long-term antibiotic prophylaxis is recommended for the duration of treatment and up to 3 months after withdrawal. This issue was discussed with our patients and according to the standard of care at our institution, both were vaccinated together with antibiotic prophylaxis given for 2 weeks at the start of eculizumab therapy. Other concerns include hepatotoxicity in association with eculizumab therapy as reported in children and adults.[11] Furthermore, deposition of eculizumab has been reported in individuals with C3 glomerulopathy or cTMA and its significance is currently unknown.[12,13]

Most recently, a 10-year pharmacovigilance study of eculizumab reported 434 cases of eculizumab exposure in pregnant women. Among 260 cases with known outcomes, 70% resulted in live births.[14] With respect to eculizumab exposure of newborns, only 2 studies reported eculizumab concentrations in cord blood or in neonates born to women with cTMA, one of which was negative.[6,15] In our 2 babies, eculizumab could be detected in cord blood (Table 3), but further analysis was not done on the neonates. Results of complement-related tests in cord blood showed deficient complement activity, with low

Table 3. Results of Complement Laboratory Analyses From Cord Blood of 2 Neonates Born to Mothers With cTMA Under Ongoing Eculizumab Therapy

Outcome	Case 1	Case 2	Adult Reference
TCA classical pathway, CH50/mL	14	26	48-103
TCA alternative pathway, %	0	0	70-105
Complement C3, g/L	0.5	0.71	0.9-1.8
Complement C4, g/L	0.09	0.11	0.15-0.55
Complement factor H antigen, mg/L	64	179	250-880
Complement factor I antigen, %	68	54	70-130
Complement factor B antigen, %	59	49	70-130
sC5b-9, ng/mL	139	130	110-252
Serum free eculizumab level, μg/mL	29	3	NA
Time since last eculizumab therapy, d	3	4	NA
Genetic variants of the newborns			
CFH	p.C1032X, het	—	
CFH haplotype	H3, het	—	
CFI	—	p.G342E, het	
CD46	—	—	
CD46 haplotype	ggaac, hom	ggaac, het	

Abbreviations: —, no variant found; cTMA, complement gene variant–mediated thrombotic microangiopathy; het, heterozygous; hom, homozygous; NA, not applicable; sC5b-9, soluble terminal complement complex; TCA, total complement activity.

factor and regulator levels in the absence of overactivation, reflecting most probably the age of the neonates and the presence of eculizumab in cord blood (Table 3). We recommend close monitoring of the child in the postpartum period because possible neonatal consequences of complement blockade are unknown. Histologic examination of placentas from both patients showed no pathologic finding.

Recurrence is high, with an incidence of 20% in women with preexisting cTMA, which causes significant maternal mortality and morbidity.[3] However, in our genetically high-risk patients with cTMA with preserved kidney function, administration of eculizumab during the whole pregnancy was well tolerated and associated with excellent pregnancy and delivery outcomes. Though our patients had gene mutations, it is worth mentioning that the presence or the nature of complement gene mutations on the course of pregnancy-associated cTMA appears to be variable. Some data support that women with complement gene mutations progressed more frequently to dialysis-dependent kidney failure.[3,16]

Patient 1 had a previous spontaneous abortion despite eculizumab therapy, which may be attributed to inherent risks of immunosuppression in a kidney transplant recipient, as well as possible subtherapeutic eculizumab levels. During her second pregnancy, the dosing frequency of eculizumab was increased during week 17 of gestation because of the previous abortion and low haptoglobin serum concentrations, which might indicate subclinical hemolysis in the absence of other signs of microangiopathic hemolysis. Of note, low haptoglobin serum concentrations were reported in normal pregnancies in the absence of hemolysis[17,18] and thus may not inform ongoing hemolysis in a pregnant patient with a history of cTMA. Overall, pregnancy and delivery outcomes in our 2 patients were better as compared with the 3 patients reported by Servais et al.[6] This contrast is most likely related to the decreased kidney function, more severe proteinuria, and hypertension in the patients of Servais et al,[6] which certainly poses further risks for poor pregnancy outcomes among these women with preeclampsia-related cTMA possibly complicating the picture.[19]

It is also important to point out that although the safety of eculizumab in pregnancy has been established, especially given its use in patients with paroxysmal nocturnal hemoglobinuria and a few cases of cTMA in pregnancy, we cannot lose sight of the cost of treatment. An alternate strategy includes expectant management with immediate treatment with eculizumab should an episode of cTMA occur. This seems to be gaining traction.[20]

In conclusion, ongoing eculizumab treatment appeared to be safe in 2 pregnant women with a history of genetically high-risk cTMA, even following kidney transplantation. Pregnancy and delivery outcomes were excellent in these 2 reported pregnancies.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Patient disposition in the Vienna TMA cohort as of September 2019

Table S1: Eculizumab therapy for p-cTMA flare during pregnancy

Table S2: Eculizumab therapy for p-cTMA flare after delivery or abortion

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