Three months interval therapy of Eculizumab in a patient with atypical hemolytic uremic syndrome with hybrid CFHR1/CFH gene

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Abstract

Pregnancy-associated atypical hemolytic uremic syndrome (P-aHUS) is a rare condition. It is characterized by very high maternal mortality and morbidity. Most cases of P-aHUS (79%) manifest in the postpartum period; this is probably due to the complement's involvement in aHUS pathogenesis. Eculizumab is approved for aHUS treatment, but its use is limited due to cost, unknown duration of treatment, and vague dose intervals to keep patients in remission. In this case report, we present a 26-year-old female with P-aHUS with hybrid CFHR1/CFH gene. Eculizumab was initiated after 5 weeks of being on hemodialysis and plasmapheresis sessions. Full remission successfully achieved after 6th dose of Eculizumab, within 13 weeks of onset of aHUS. Due to financial issues and inability to financially cover the cost, Eculizumab was set in hold. Within 6 months, she suffered recurrence of the disease and Eculizumab was re-instated. After re-inducing full remission, the patient was switched to Eculizumab every 3 months instead of the recommended manufacture dose interval of every 2 weeks. We followed this patient for 3 years and she continued to be in remission based on clinical and laboratory data. In conclusion, achievement of successful and maintenance of remission of P-aHUS in this patient who had limited access to Eculizumab raise the attention of the efficacy of Eculizumab at longer time intervals. However, it is time to consider conducting a long-term study to learn about the safety and efficacy of this approach, which may have a major financial advantage for patients.

Keywords Eculizumab · aHUS · Complement dysregulation nephropathy · Pregnancy-aHUS

Introduction

Thrombotic microangiopathy (TMA) is a relatively rare condition, but is a definite medical emergency, requiring immediate intervention to avoid irreversible organ damage or death [1]. This group of diseases has traditionally been divided on clinical grounds by affected organs in thrombotic–thrombocytopenic purpura (TTP) and hemolytic–uremic syndrome (HUS), and the latter being termed atypical if not preceded by diarrhea [2]. A definitive diagnosis of aHUS is made when the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury

(AKI) is present. The disease should not be associated with Shiga toxins, and TTP should also be excluded [3]. Patients negative for Shiga toxin-producing *E. coli* (STEC) are categorized as having atypical HUS (aHUS), which is related to an increased risk of complement mutations and a poorer prognosis compared with typical HUS [4].

Case presentation

A previously healthy 26-year-old female was transferred from another hospital with picture of postpartum acute kidney injury, thrombocytopenia, and microangiopathic hemolytic anemia; she received renal replacement therapy in the form of hemodialysis. Peripheral blood smears showed thrombocytopenia and schistocyte 4–5/HPF. She never had diarrhea during her current illness, and stool cultures were negative on admission. She had seizures and was diagnosed with posterior reversible encephalopathy syndrome as a neurological complication of aHUS. Laboratory work-up to rule out other causes of thrombotic microangiopathy (TMA) is

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shown in Table 1. As such, she was immediately started on plasmapheresis after sending out ADAMTS-13, which came back normal (73%). She received 10 sessions of plasmapheresis with improvement of her platelets and lactate dehydrogenase (LDH) but no improvement of kidney function.

Kidney biopsy was done, a single core of cortical renal tissue containing up to 11 glomeruli. These glomeruli are showing features of thrombotic microangiopathy. These include segmental thickening of the glomerular membrane. Fibrinoid necrosis and intra-capillary fibrin thrombi, focal mesangiolysis and fibrillary appearance of the mesangium, and focally congested glomerular capillary. The podocytes and the endothelial cells are also swollen. The arterioles show foci of fibrinoid necrosis and fibrin thrombi. The tubules were unremarkable. The interstitium shows edema but no significant fibrosis or interstitial inflammation. JMS stain shows focal

mesangiolysis and focal wrinkling of the glomerular basement membrane. Segmental tram-tracking of the glomerular basement membrane and Masson Trichrom stain reveal interstitial edema but no fibrosis (Fig. 1). After 22 days from her admission, Eculizumab 900 mg intravenously was given on a weekly basis for 4 weeks, then 1200 mg every 2 weeks. After the 6th dose of Eculizumab, she enjoyed improvement of renal function, LDH, and normal platelets. Her serum creatinine slope was coming down and she maintained good renal function independent from hemodialysis (Fig. 2). Because of financial inability to cover her medication costs, she was lost in follow-up without Eculizumab for 6 months and presented with picture of recurrent aHUS with thrombocytopenia (platelets 58,000/ μ l) and slightly elevated serum creatinine of 123 μ mol/l. She had an evidence of hemolysis during recurrence based on blood film revealed

Table 1 Laboratory work-up for the case upon presentation to the hospital

The patient's result	Normal range in our hospital
Hemoglobin (Hb): 9.1	11.7–15.5 g/dl
Platelets count: 69	150–400 $10^3/\mu$ l
LDH: 4800	125–220 u/l
Haptoglobin: <0.08	0.35–2.5 g/l
Serum iron: 21	9–30.4 μ mol/L
Ferritin 4868.71	4.6–204 ng/ml
Coombs test (direct and indirect): negative	
Creatinine: 1105	48.6–90.1 mmol/l
BUN 157	1–14 mg/dl
PH 7.306	7–18.7 mg/dl
HCO ₃ : 11.4	
Pt 12.3	10–14 s
PTT 25.77	24–41 s
INR 1.13	0.01–1.6 INR
Fibrinogen 3.5	1.8–3.5 g/l
ALT 96	0–55 u/l
AST 56	5–34 u/l
Alkaline phosphatase 106	40–150 u/l
GGT 30	9–36 u/l
Bilirubin 1.7	0.2–1.2 mg/dl
Serum albumin 2.2	3.5–5 g/dl
Uric acid 16.09	2.6–6 mg/dl
C3: 0.75	0.83–1.93 g/l
C4: 0.143	0.15–0.57 g/l
ANA: negative	<20
Anti DS DNA: negative	<1:10
Anticardiolipin, Lupus anticoagulant and beta 2 glycoprotein were negative	
Hepatitis B surface Antigen(HBsAG): negative	–
Hepatitis C virus antibodies: negative	
HIV Ag/Ab: negative	
ADAMTS-13: normal	–
Stool culture: negative

Fig. 1 Histopathological features of the renal biopsy. **a** Focal mesangiolysis and fibrillary appearance of the mesangium, and focally congested glomerular capillary. **b** Fibrinoid necrosis and intra-capillary fibrin thrombi. **c** Jone's methenamin silver (JMS) stain shows focal

mesangiolysis and focal wrinkling of the glomerular basement membrane, segmental tram-tracking of the glomerular basement membrane. **d** Masson Trichrome stain reveals interstitial oedema but no fibrosis

Fig. 2 Clinical profile shows the level of serum creatinine, LDH, and platelet counts in relation with hemodialysis and plasmapheresis sessions, as well as Eculizumab doses; all was spotted in relation with the doses interval

significant schistocytes, thrombocytopenia, undetectable haptoglobin, and elevated LDH peaked at 395 u/l (normal 220 u/l) during that period. A patient sample was sent for molecular genetic work-up (Bioscientia Institute for Medical Diagnostics GmbH, Germany), and NGS analysis did not reveal a clearly pathogenic sequence variation. Furthermore, the patient does not carry the haplotypes CFH-H3 and ***MCP-H2 and the CFHR1*B polymorphism each associated with an increased risk for aHUS. The C5 variants c.2653C>T (p.Arg885Cys) and c.2654G>A (p.Arg885His) for which a poor response in patients with paroxysmal nocturnal hemoglobinuria (PNH) to the therapeutic antibody Eculizumab has been reported and could not be identified in the patient. MLPA analysis revealed a heterozygous duplication of CFH exon 22 (3' UTR). Further upstream regions of CFH exon 22 might probably also be comprised by the duplication; however, incomplete probe coverage concerning CFH exons 19–21 does not allow further assessment. In addition, a heterozygous deletion of CFHR3 and a partial deletion of CFHR1 comprising exons 5 and 6 were detected. The result was confirmed by an independent MLPA analysis. The regulators of complement activation (RCA) gene cluster on chromosome 1 comprise in order of their chromosomal location the genes CFH, CFHR3, CFHR4, CFHR2, and CFHR5. These genes share a high degree of sequence identity resulting from large-scale genomic duplications which promotes chromosomal re-arrangements by non-allelic homologous recombination (NAHR). Besides the common CFHR1/CFHR3 deletion, different hybrid genes have been reported (CFH/CFHR1, CFH/CFHR3, CFHR1/CFH, CFHR1/CFHR3, and CFHR2/CFHR5) in patients with complement disorders.

The MLPA result indicates an NAHR event in the RCA gene cluster comprising the genes CFH, CFHR1, and CFHR3 which likely results in the deletion of CFHR3 and the formation of a CFHR1/CFH hybrid gene, in which exons 5 and 6 of CFHR1 (SCR 4–5) are replaced by the highly homologous CFH exons 21 and 22 (SCR 19–20). This hybrid gene has already been described in the literature [5]. The exact breakpoints of the detected gene conversion could not be identified with the method applied here. Biochemical studies on CFHR1/CFH hybrid genes known so far showed an interference with cell-surface regulation of the alternative complement pathway by competition with CFH. Thus, the detected CFHR1/CFH hybrid is most likely pathogenic. Anti-CFH antibody was negative. Eculizumab was immediately resumed and full remission was re-possessed. After financial meditation with her insurance, she was approved to receive Eculizumab for only 4 doses of 1200 mg per year. Following that regimen for 3 years, she was enjoying full remission with no single episode of recurrence.

Discussion

Pregnancy-associated atypical hemolytic uremic syndrome (P-aHUS) is also a rare condition, affecting 1 of every 25,000 pregnancies; P-aHUS is characterized by very high maternal mortality and severe morbidity, as stated. In a review of published literature, it suggests that more than half of all patients with P-aHUS eventually develop end-stage renal disease in less than 1 month if left untreated, with most cases of it (79%) developing in the postpartum period. In a normal pregnancy, uncontrolled complement activation is prevented by three regulatory proteins: DAF, MCP, and CD59 [6]. Serum concentrations of C3, C4, and CH50 gradually increase during pregnancy by 10–50%. After the inflammation of delivery (as well as postpartum infections, hemorrhage, and the release of fetal cells in the maternal circulation), they abate; these factors eventually lead to systemic activation of the alternative pathway, which, in the absence of effective regulatory mechanisms, induces postpartum aHUS [6, 7]. P-aHUS is correlated with uncontrolled complement alternative pathway activation and complement-mediated damage to the microvascular endothelium. As such, pregnancy in the postpartum period has recently been identified as a high-risk period for aHUS development in women carrying inherited defects in complement genes or autoantibodies against complement regulatory proteins [6].

The initial approval of Eculizumab for treatment of aHUS was based due to its efficacy on prospective open-label case series, where Eculizumab was administered intravenously at a dose of 900 mg per week for 4 weeks, a dose of 1200 mg 1 week later, and a maintenance dose of 1200 mg every 2 weeks [8]. There are limited data in the literature of aHUS cases treated with Eculizumab in pregnancy; in an article published by Servais et al., they analyzed its use for the treatment of aHUS during five pregnancies in three patients and studied an additional pregnancy without it. All pregnant patients with aHUS were closely monitored by both nephrology and obstetric specialists. They concluded that Eculizumab displayed no overt safety issues and its reversal of adverse outcomes was debatable.

The optimal duration of Eculizumab treatment in aHUS and the decision to stop treatment remain under debate [9, 10]; after reviewing the largest retrospective study that included 108 patients with aHUS, all patient discontinued dialysis after management and enjoyed dialysis-free, median duration of treatment was 17.5 months, data indicate that the presence and type of complement gene variants detected do not affect one's response to it, but are major predictive factors for aHUS relapse after termination [11]. The risk of relapse after Eculizumab discontinuation was the highest in patients with CFH variants (72%), reflecting that the decision to discontinue or not should take into account the high risk of relapse, unlike the patient with no identified

complement gene or pathogenic variants, or those with MCP pathogenic variants—where discontinuation of the treatment might be considered; however, kidney biopsy still plays a role in assessing subclinical renal damage after treatment discontinuation or subsequent relapse [10]. Our approach has advantage over the traditional approach of stopping Eculizumab and retreat in case of relapse. It is planned, cheaper, and less doses of Eculizumab required maintaining remission in comparison with induction doses in case of relapse. It protects patient against risk of tissue injury and loss of nephrons associated with relapse.

The risk of P-aHUS is highest during a woman's second pregnancy [8, 12]. It is difficult to exclude that complement dysregulation could be involved in other pregnancy complications, such as preeclampsia and fetal losses. Counseling of young female patients with documented C3 dysregulation who wish to undergo another pregnancy is crucial. On the basis of the literature review, patients with a complement dysregulation should be informed of the relatively high risk (20%) of P-aHUS, along with the pregnancy being closely monitored [8, 13]. No sufficient information available about the secretion of Eculizumab in human milk, the milk production process, or the effects on infant after breastfeeding. Breastfeed while female on Eculizumab is not prohibited, because Eculizumab is a large protein molecule; absorption is unlikely, because it is probably destroyed in the infant's gastrointestinal tract. No adverse effects attributable to Eculizumab have been reported in infants who were breastfed during maternal therapy [14, 15].

In conclusion, we cannot determine if this patient has active subclinical TMA that might induce kidney insult over time without a significant detectable change in serum creatinine. Performing a kidney biopsy to rule out subclinical TMA might be necessary if one is unable to afford Eculizumab as per the manufacturer's recommended doses. Our experience with this patient with financial restrains should not be taken as a recommendation to increase the time interval between doses in those with no issues with drug availability. Long-term follow-up and safety of this approach are not clear yet.

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Compliance with ethical standards

Conflict of interest The authors did not report any potential conflicts of interest.

Ethical standards The present study was performed in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration.

Informed consent Written consent was obtained from the patient discussed and documentation is available for review upon request.

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