Clinical Obstetrics, Gynecology and Reproductive Medicine

Case Report

Prepartum Eculizumab for prevention of atypical hemolytic uremic syndrome: A case report

Gianluigi ARDISSINO[1*], Giulia Maria BAFFERO[2], Manuela Wally OSSOLA[2], Benedetta Maria AGNOLI[2], Francesca TEL[1], Michela PERRONE[1], Stefania SALARDI[3], Martina SGARBANTI[3] and Silvana TEDESCHI[3]

[1]Center for HUS Control, Prevention and Management, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, via Commenda 9, Milan, Italy

[2]Obstetrics and Gynaecology Department, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Ospedale Maggiore Policlinico, via Commenda 12, Milan, Italy

[3]Laboratory of Medical Genetics, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Ospedale Maggiore Policlinico, via Commenda 12, Milan, Italy

Abstract

Background: Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) often caused by complement disregulation for which pregnancy and delivery are common triggers. The disease is associated with a poor prognosis both for the mother and the fetus.

Case: A 30-year-old women with a membrane cofactor protein (MCP) gene mutation and two previous aHUS episodes, presented at 23 weeks of pregnancy with no signs of active TMA. Pregnancy proceeded uneventfully and a single dose of Eculizumab was given 24 hours prior to delivery. The patient gave birth to a healthy baby, did not develop TMA and had no side effects.

Conclusion: A single prepartum Eculizumab dose may be a cost-effective and safe strategy to face the high risk of relapse in pregnancy-associated aHUS.

Introduction

Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) often caused by mutations in genes encoding complement regulatory proteins, that leads to uncontrolled activation of the alternative complement pathway and deposition of the membrane-attack complex (C5b-9) on the endothelial cell surface. This process finally causes endothelial damage, mechanical, non-immune mediated hemolytic anemia, platelet consumption and renal and multiorgan impairment. The incidence in the general population is not well known and, until few years ago, it was associated with a severe prognosis, with the majority of patients reaching end-stage renal disease (ESRD) few years after disease onset [1].

The most common genetic abnormalities in patient with aHUS are those involving complement factor H (CFH), factor I (CFI), membrane cofactor proteins (MCP), C3 or, less commonly, factor B, while at least 30% of the cases remained unexplained [2]. Pregnancy is an important factor known to trigger disease expression in patients with a specific pathogenetic mutation. Fakouri and co-workers analysed 100 women with aHUS and reported that in 21 of them the disease occurred during pregnancy and the postpartum period (n=4 and n=15 respectively, while for the other 2 women it was not specified when aHUS exactly presented). The prognosis was poor both for mother and fetus with 62% of patient in ESRD within one month after disease onset and with higher risk of pregnancy complications such as preeclampsia and fetal death [3].

Since 2009 Eculizumab (a humanised recombinant monoclonal antibody targeting C5 and thus preventing the generation of the C5b-9 membrane-attack complex), has been successfully used in patients with aHUS [4] and its efficacy has been demonstrated to be greater than plasma exchange (PEX) which has little or transient effect on disease remission [5]. In 2011 the drug has received approval for the treatment of aHUS in the United States and Europe, thus becoming the frontline treatment for this syndrome.

In recent years Eculizumab has been used during pregnancy in women with ongoing aHUS [6,7] but the best management for pregnant women at risk for aHUS, especially those carrying specific pathogenetic mutations and with previous episodes of disease expression, is still unclear. Herein, we report a case of a pregnant woman with MCP mutation and previous aHUS manifestations treated with a single prepartum Eculizumab dose to prevent disease expression in the most critical period.

Case

A 30-year-old Caucasian woman presented to our hospital at 23 weeks' gestation of her second pregnancy. She was diagnosed as having aHUS at 8 years of age and has already had a relapse at 28 years. The first event (in 1993) subsided spontaneously while the second required dialysis and several PEX sessions but her renal function fully recovered and molecular biology for complement regulatory genes performed at this point identified a mutation on MCP gene (c.565T>G, p.Tyr189Asp). Her family history was unremarkable and she already

Correspondence to: Gianluigi ARDISSINO, Center for HUS Control, Prevention and Management, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Via Commenda 9, 20122 Milano, Italy, Phone: +39 0255032300; Fax: +39 0255032451; E-mail: ardissino@italkid.org

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had one previous uncomplicated pregnancy at 26 years.

At presentation, laboratory findings showed a normal renal function (serum creatinine 0.56 mg/dl), normal platelets count (193.000/mm^3), normal complement function (C3 119 mg/dl, C4 31 mg/dl, CH 50 103% and AP50 76%) and no signs of active TMA. Pregnancy proceeded without any complications both for the mother and the fetus: laboratory relevant for TMA remained normal and there were neither signs of complement activation nor of disease relapse until delivery. Given the high risk of aHUS at delivery or during the postpartum period [3], the documented pathogenetic mutation, the personal medical history and the successful experience with Eculizumab treatment during pregnancy [6,7], it was decided to administer a single dose of Eculizumab (900 mg intravenously) the day before delivery. Antibiotic prophylaxis for Neisseria meningitides was immediately started with Amoxicillin 1gr tid given that the patient was not vaccinated and that complement inhibition exposes to a high risk of infections with capsulated bacteria. Twenty-four hours after Eculizumab infusion global complement activity was completely suppressed (alternative and classical pathway activity respectively AP50 and CH50: 0%) and the woman underwent a scheduled cesarean section (as she already had a caesarean section in her previuos pregnancy). An appropriate for gestational age (AGA) alive and healthy girl of 3140 gr. (Apgar scores 9 at 1 and 10 at 5 minutes) was delivered. The drug was well tolerated and no side effect was recorded. The postpartum period proceeded uneventfully and the complement function recovered within the subsequent 3 weeks and therefore antibiotic treatment was discontinued 21 days after delivery.

The baby's complement function was also investigated and her global complement activity was almost completely suppressed with an AP50 of 6%; given this level of inhibition (although not unusual also in healthy newborns) and the very particular situation, the baby was addressed to antibiotic prophylaxis for 10 days. Later, molecular biology showed that the baby did not carry the MCP mutation.

Discussion

TMAs are rare conditions during pregnancy (approximately 1 in 25.000) but they can have devastating consequences both for the mother and the baby. Only a small proportion of cases exhibit complement disregulations specific for aHUS but those patients are at high, although not well known, risk of relapse during pregnancy, particularly if they have previously had one ore more TMA event. Fakouri and colleagues analysed 21 patients with pregnancy-related aHUS and reported that more than two third presented in the postpartum period and that the outcome was very poor with 81% requiring dialysis during the acute disease and 61% remaining in ESRD [3].

Since 2009 Eculizumab is available for the treatment of aHUS and the drug has proven to be highly effective to induce disease remission and to prevent relapses. The use of the same drug was also reported in women with aHUS during pregnancy obtaining remission without side effects [6,7].

When a patient with a known pathogenetic mutation becomes pregnant (or plans a pregnacy) the physician faces a dilemma regarding how to best manage the risk of aHUS relapse. Two options are available: to carefully monitor the patient and start Eculizumab treatment in case of disease reactivation or to provide Eculizumab treatment prophylactically. The latter option will then open up new dilemma: when is the most appropriate time to start Eculizumab in order to reduce the exposure (and the very high costs) but also maximize the preventive benefits.

The present case report describes our choice: to protect with Eculizumab the period at higher risk for relapse: the peripartum period. Actually, the patient was offered the use of Eculizumab throughout the III trimester but since she was reluctant to be exposed (and to expose the baby) to an i.v. monoclonal antibody for several weeks, she was offered the opportunity of a limited yet concentrated coverage during the period of maximal risk.

Based on our limited experience, the issue of safety for the fetus and the newborn deserves a comment. Very recently, Hallensten and colleagues measured complement activity and Eculizumab-complement complexes in serum of normal babies and of babies born to patients treated with Eculizumab during pregnancy. The investigations lead the authors to conclude that Eculizumab had not affected the complement system of the newborns even if they found low level of the drug in the blood [8].

One important issue that deserved a comment, is the economic impact of the proposed strategy: the approach herein proposed requires less than 12,000 US dollars per pregnancy while a preventive schedule to cover the entire third trimester of pregnancy would require more than 100,000 US dollars.

In conclusion, in patients with previous aHUS events and well defined gene mutations responsible for complement disregulation, a single prepartum Eculizumab dose (900 mg) may be a cost-effective and safe strategy to prevent the high risk of pregnancy-associated disease relapse. The proposed strategy requires investigation on large series to be confirmed and to detail the best procedures for drug administration including timing and patient's selection for treatment.

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Competing interest

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