bjh short report

The management of pregnancy in paroxysmal nocturnal haemoglobinuria on long term eculizumab

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Summary

In Paroxysmal nocturnal haemoglobinuria (PNH), pregnancy is associated with increased maternal and foetal complications to such an extent that the condition has been considered relatively contra-indicated in PNH. Eculizumab has revolutionized the treatment of PNH. We evaluate its use in pregnancy to date. We report on seven patients exposed to eculizumab at different stages of pregnancy including the first two patients to receive the drug from conception to delivery. There was no evidence of complement blockade from cord blood samples taken at delivery. Eculizumab appears safe to use in this setting and is likely to prevent many of the complications usually observed.

Keywords: Paroxysmal Nocturnal Haemoglobinuria (PNH), pregnancy, eculizumab.

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Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disorder of haemopoietic stem cells resulting in the expansion of a haemopoietic clone of cells with a mutated *PIGA* gene (Takeda *et al*, 1993). This mutation disrupts glycophosphatidylinositol (GPI) biosynthesis, leading to reduced or absent expression of GPI-linked cell surface proteins (Kinoshita *et al*, 1997). Affected individuals have intravascular haemolysis as their erythrocytes are more susceptible to attack from complement. Clinical manifestations of the disease include anaemia, dysphagia, erectile dysfunction, haemoglobinuria, pulmonary hypertension, renal impairment and thromboembolism. Thrombosis is the main cause of mortality in PNH, accounting for 40–67% of PNH-related deaths (Hillmen *et al*, 2007). There is an increased risk of venous and arterial thrombosis with pulmonary, lower limb, hepatic and cerebral veins being the commonest sites affected (Hillmen *et al*, 1995; de Latour *et al*, 2008).

Historically, the management of PNH patients during pregnancy has been challenging and pregnancy itself has generally been discouraged (Bais *et al*, 1994; Bjorge *et al*, 2003; Fieni *et al*, 2006). Intravascular haemolysis and anaemia are frequently more severe than in the non-pregnant state with increased transfusion requirements throughout pregnancy (Spencer, 1980; Ray *et al*, 2000; Tichelli *et al*, 2002). Thrombocytopenia is also more common and platelet counts typically fall to $<50 \times 10^9$/l (Ray *et al*, 2000). Maternal and foetal morbidity and mortality are increased in PNH both during the pregnancy and, for the mother, during the post-partum period (Ray *et al*, 2000; Tichelli *et al*, 2002; Fieni *et al*, 2006). Maternal mortality rates of 12–21% have been reported, with the main risks being thromboembolism and infection (Ray *et al*, 2000; Fieni *et al*, 2006). An increase in foetal mortality relates to premature births with only half of pregnancies progressing to term and mortality rates reported of 7–9% (Ray *et al*, 2000; Fieni *et al*, 2006).

Eculizumab is a humanized monoclonal antibody that binds to the complement protein C5, preventing its cleavage, and thereby blocking the formation of the terminal components of the complement cascade whilst keeping the proximal components intact (Thomas *et al*, 1996). It is given initially as a weekly intravenous infusion at a dose of 600 mg for 4 weeks, followed by 900 mg every 14 days (Hillmen *et al*, 2004, 2006; Brodsky *et al*, 2008). Clinical trials in PNH patients have shown that eculizumab reduces haemolysis and subsequently stabilizes haemoglobin levels, reduces transfusion requirements and improves quality of life (Hillmen *et al*, 2004, 2006; Brodsky *et al*, 2008). Eculizumab has dramatically altered the treatment of PNH. Young women on treatment feel symptomatically better, so the question of eculizumab use during pregnancy is increasingly likely. Here we present our experience in the use of eculizumab in pregnancy.

Methods

Information was collected on seven patients on eculizumab: five who became pregnant during the clinical trials and a further two patients who became pregnant after the clinical trials. Pregnancy was an exclusion criterion in the eculizumab clinical studies therefore only very limited data exists regarding its use during pregnancy. Three of these patients received eculizumab treatment either during the last trimester (starting eculizumab at week 27) or throughout gestation to term. Maternal blood, cord blood and breast milk samples were analysed to assess the distribution of eculizumab in these patients as IgG antibodies can cross the placental barrier. Patient characteristics are shown in Table I.

Results

There were five reported pregnancies from 106 female patients during the clinical trials of eculizumab in PNH (Hillmen *et al*, 2004, 2006; Brodsky *et al*, 2008). The trial protocols specified withdrawal of patients from the trial and cessation of eculizumab for patients who became pregnant during the study.

Patients during eculizumab clinical trials

Patient 1 elected to terminate her pregnancy and continued eculizumab.

Patients 2, 3 and 4 discontinued eculizumab treatment at 5, 14 and 4 weeks gestation, respectively. These patients delivered healthy newborn babies without any adverse effects from the eculizumab given during the early stages of their pregnancies. Patient 3 developed hyperpyrexia and hypertension shortly after delivery. She was diagnosed with pyrexia of unknown origin, treated and subsequently discharged. There were no other reported postpartum complications.

Patient 5 conceived having been on eculizumab for 5 years. She withdrew from the extension study and continued eculizumab off trial throughout her pregnancy. Prior to conceiving she needed occasional transfusions, around 3–4/year. During her pregnancy her transfusion requirement increased to every 2–4 weeks. Her platelet count was normal before the pregnancy and remained within the normal range whilst she was pregnant. She had no prior history of thrombosis but is heterozygous for the *F2* 20201A mutation. Anticoagulation with low molecular weight heparin (LMWH) is routine practice during pregnancy in PNH and at week 8 of gestation, LMWH was commenced (Tichelli *et al*, 2002). During week 26 of her pregnancy she became unwell with haemoglobinuria 3 or 4 days prior to her eculizumab treatment suggestive of breakthrough haemolysis. Daily serum and urine samples were obtained for the week leading up to her next eculizumab infusion. She again became unwell with breakthrough haemolysis 12 days after her last infusion. During this episode her lactate dehydrogenase (LDH) level became elevated and serum eculizumab level was subtheraputic confirming breakthrough haemolysis. The interval between eculizumab infusions was reduced to 12 days for the remainder of the pregnancy without further evidence of

Table I. Summary of patient characteristics.

Patient	Age (years)	Granulocyte clone size (%)	LDH At Baseline (i/u per l)	Eculizumab use in pregnancy	Last LDH During Pregnancy (i/u per l)	Maternal eculizumab levels (μg/ml)	Cord eculizumab levels (μg/ml)	Complications in pregnancy	Outcome	Anticoagulation	
										Before pregnancy	During pregnancy
1	24	69·6	1336	Up to 5 weeks gestation	200*	NA	zNM	No	Elective termination	Not known	No
2	25	92·9	2376	Up to 5 weeks gestation	269*	NM	NM	No	Healthy baby	Warfarin	Theraputic LMWH
3	22	95·8	2014	Up to 14 weeks gestation	261*	NM	NM	Postpartum PUO	Healthy baby	Not known	Not known
4	26	87·5	1263	Up to 4 weeks gestation	272*	NM	NM	No	Healthy baby	Not known	Therapeutic LMWH
5	27	99·7	10 300	All pregnancy & postpartum	703	116·1	Undetected	Breakthrough haemolysis	Healthy term baby	No	Prophylactic LMWH
6	35	97·6	1616	From week 27 & postpartum	387	80·5	Twin 1 19·2 Twin 2 14·4	Postpartum haemorrhage	Healthy twins at 35 weeks	No	Theraputic LMWH
7	28	98·1	2642	All pregnancy & postpartum	414	63·2	Undetected	Pre-eclampsia	Healthy baby at 28 weeks	Warfarin	Theraputic LMWH

LDH, Lactate dehydrogenase; PUO, pyrexia of unknown origin; NM, not measured.
*These LDH values were taken at the beginning of the pregnancy before eculizumab treatment was stopped.

intravascular haemolysis. She had a normal vaginal delivery at term with a healthy 4 kg baby. Serum samples at delivery showed therapeutic levels of eculizumab in the mother with no eculizumab detected in the cord blood. Breast milk was analysed at days 1, 2, 3, 9 and 10 after delivery with no eculizumab detected.

Patients treated with eculizumab after the clinical trials

Patient 6 was diagnosed with PNH during *in vitro* fertilization and embryo storage for fallopian tube disease. She was treated with eculizumab for 2 years prior to stopping the drug for embryo implantation. She started therapeutic LMWH in the first trimester and recommenced eculizumab at week 27 of her twin pregnancy with the standard induction regime. She continued to have evidence of intravascular haemolysis with haemoglobinuria and a raised LDH, and so received eculizumab 900 mg weekly until an elective caesarean section was performed at 35 weeks gestation. Two healthy babies were born weighing 2·4 and 2 kg. She developed a post-partum haemorrhage whilst on warfarin, requiring treatment with prothrombin complex concentrate (PCC) and uterine artery embolization. Her condition was further complicated by a portal vein thrombosis thought to have been precipitated by the reversal of her anticoagulation with PCC. Serum samples at delivery showed therapeutic levels of eculizumab in the mother and low levels in the cords of both twins that were within the background levels for the assay and insufficient to block complement.

Patient 7 was diagnosed with PNH following treatment for aplastic anaemia 2 years previously at which time she developed hypertension. She conceived after being on eculizumab for 6 years and at week 5 gestation her warfarin was changed to LMWH. She remained well throughout her pregnancy until week 28 of gestation when she developed pre-eclampsia. She did not require transfusions during the pregnancy and her platelet count remained within the normal range before, during and after the pregnancy. A caesarean section was performed, delivering a 900 g baby. The baby was found to have meconium plug syndrome, which is a functional immaturity of the colon associated with prematurity. Serum samples at delivery showed therapeutic levels of eculizumab in the mother with no eculizumab detected in the cord blood. Both mother and baby remain well.

Conclusions

Based on our observations eculizumab may be safe to use in treating pregnant patients with PNH. However this conclusion is based solely on data from three patients treated and this report does not prove either the safety or efficacy of eculizumab in pregnancy. Many more patients need to be treated with eculizumab during pregnancy to determine its safety in this setting. Patient 7 did develop pre-eclampsia and her foetus had meconium plug syndrome despite eculizumab treatment. Eculizumab does not appear to cross the placenta or be excreted in breast milk but this needs to be confirmed in further patients. We report no long-term adverse effects in the children born who now vary from the youngest at 4 months old to the eldest at 16 months old. We observed no maternal morbidity that was attributable to PNH.

The dose of eculizumab required to block complement during the latter stages of pregnancy appeared to be greater than in the non-pregnant state, but again this needs to be confirmed in other pregnancies. Break-through from complement blockade manifests itself with patients experiencing haemoglobinuria prior to their next dose of eculizumab even in patients who had been well controlled on the standard dose for years prior to becoming pregnant.

All pregnant patients with PNH should be closely monitored during pregnancy by both haematology and obstetric specialists. In view of the risks associated with pregnancy in PNH the use of low molecular weight heparin should be considered as soon as pregnancy is confirmed. It appears that eculizumab can be safely used throughout pregnancy and theoretically it would be expected to reduce the complications of PNH frequently seen during pregnancy. This initial report of the use of eculizumab throughout pregnancy is encouraging, however more evidence on its use in this setting is needed.

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Disclosure of conflicts of interest

E.C. has received honoraria from Alexion Pharmaceuticals. R.K., A.H., S.R. and R.N. have received honoraria and have sat on advisory boards for Alexion Pharmaceuticals. J.S., A.R. and P.H. have received honoraria, research funding and have sat on advisory boards for Alexion Pharmaceuticals. J.B., G.K. and R.R. are employed by and have equity ownership in Alexion Pharmaceuticals.

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