Management of a pregnant woman with common variable immunodeficiency and previous reactions to intravenous IgG administration

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SUMMARY

Common variable immunodeficiency is the most common symptomatic primary immunodeficiency in adulthood. Pregnant women with common variable immunodeficiency have different needs from other patients with the same disease. Because of immature state of the fetal and neonatal immune system, transplacental transfer of immunoglobulin G (IgG) has a relevant role in protecting the infant. We here report on a high-risk pregnant woman with common variable immunodeficiency with adverse reactions to intravenous immunoglobulin that was successfully rescued with a new Ig human intravenous, 10% liquid preparation. The treatment was tailored to the health status and characteristics of the patient. The new product was safe and well tolerated. The mother did not report any infections during pregnancy and the baby had a healthy course with 'protective' serum IgG levels. Our case is a further demonstration that intravenous immunoglobulin tolerability in patients with immunodeficiency could be linked to a product's characteristics.

(normal values 90–450 mg/dl), IgM 30 mg/dl (normal values 50–180 mg/dl), by nephelometry. The diagnosis of CVID was confirmed by the absence of isohemagglutinins and the impaired response to a booster of tetanus vaccination. She was treated with IVIg at the dose of 0.4 g/kg every 28 days. With IVIg treatment, the rate and severity of respiratory infections declined. In January 2011, she had a spontaneous miscarriage at 8 weeks. A month later, the day after the periodic administration of IVIg, she complained of a reaction with vomit, dizziness and stiff neck treated with metoclopramide and hydration with resolution in the following day. Despite premedication, a second infusion was followed by a similar reaction. The IVIg treatment was withdrawn and the patient remained out of her treatment for the following months.

On May 2011, the woman was pregnant again. She refused to start the IV or SC Ig administration, until 18 weeks of pregnancy (September 2011), when her serum levels of IgG dropped to 340 mg/dl.

BACKGROUND

Common variable immunodeficiency (CVID) is a low-prevalence (1 : 25 000–1 : 50 000) condition characterised by low immunoglobulin levels (IgG, IgA and/or IgM) and scant antibodies production.¹ Patients suffering from CVID show recurrent infections, granulomatous and/or autoimmune diseases. The diagnosis is usually made during adulthood, between the ages of 20 and 40 years, with an average delay of time between the onset of symptoms and diagnosis of 6–8 years.¹ Patients with humoral immunodeficiency are dependent on the exogenous administration of immunoglobulin G (IgG) to prevent recurrent infections and improve morbidity and mortality. IgG replacement therapy may be administered via intravenous infusions (IVIg) or subcutaneous (SC) injections (SCIg), depending on several factors, including patients' perception.

CASE PRESENTATION

Our patient is a 42-year-old Caucasian woman. Her medical history was unremarkable, except for an autoimmune thyroid disease in 2007, subsequently treated with L-thyroxine. Thyroid peroxidase antibodies were present. At that time, hypogammaglobulinaemia was present, but it was not further investigated. For the long-term recurrence of upper respiratory infections, she came to our attention in 2008, when diagnosis of CVID was made. Laboratory examinations showed IgG 434 g/l (normal values 700–1600 mg/dl), IgA 32 mg/dl

TREATMENT

We decided to adopt a new preparation, Privigen (human immunoglobulin 100mg/ml, 10%, CSL Behring GmbH, Marburg, Germany). Before each IVIg infusion, the patient received a premedication with oral chlorphenamine and paracetamol, and intravenous hydrocortisone. During the first infusions, the 10% liquid Ig preparation was diluted 1 : 2 in saline and it was infused at 0.3 ml/kg/h, thereafter, slowly increased at 2.5 ml/kg/h. This new product was well tolerated and subsequently it was infused at the dose of 10 g/weekly (0.6 g/kg/monthly).

OUTCOME AND FOLLOW-UP

During the pregnancy, she did not present any infectious problem and her IgG levels, monitored every 2 weeks, increased to 1068 mg/dl, the last detection (23 January) before childbirth.

On 1 February 2012, at 40 weeks of gestation, she gave birth to a normal, healthy male child by spontaneous vaginal childbirth. After delivery, the mother continued IVIg infusion every 3 weeks at the dose of 0.4 g/kg. She decided to breastfeed the baby. One month after birth, baby's IgG levels were 622 mg/dl and those of the mother 876 mg/dl. She had a regular *puerperium*. Baby grew normally without significant problems.

DISCUSSION

CVID comprises a range of disorders with hypogammaglobulinaemia, resulting mostly in antibody

To cite: Danieli MG, Moretti R, Pettinari L, et al. *BMJ Case Reports* Published online: 17 December 2012
doi:10.1136/bcr-2012-007594

deficiency and recurrent infections. The clinical heterogeneity reflects the different genetic immune defects with complex inheritance patterns, thus only in a minority of cases a genetic defect has been recognised. In 7–10% CVID patients, mutations in the gene encoding the transmembrane activator and calcium-modulating cyclophilin ligand interactor have been identified as the cause of the disorder (rev.in²). Treatment with IV or SC IgG has been demonstrated to prevent infections, increase the patient's life expectancy and improve quality of life.¹ However, despite rare, adverse events (AEs) to IVIg treatment are reported. These include acute renal failure, stroke, myocardial infarction, venous thromboembolism, anaphylaxis, aseptic meningitis and haemolysis.³ The per infusion rates of mild-to-moderate AEs range from 5% to 15%.^{3, 4} The mechanisms triggering AEs are still unknown. Some authors draw attention to the presence of anti-IgA antibodies as a risk factor for AEs; however, only in a minority of patients, these antibodies could be detected. Therefore, other factors could be responsible for the occurrence of AEs in patients with CVID receiving Ig replacement therapy.^{3, 4} According to the literature, patients at risk for AEs are those with newly diagnosed CVID never treated with IVIg; those who are switching from one IVIg product to another; those who have had a dose interruption; and those with a chronic underlying infection, such as bronchitis or sinusitis.³ The risk of AEs may be reduced by eliminating aggregates, by administering the product at a slower infusion rate and by premedicating the patient with corticosteroids, antihistamines and/or antipyretics.³ Only rarely, the severity of AEs leads to treatment withdrawal.⁴

Our patient presented with a high-risk pregnancy, due to multiple factors: her age, the previous miscarriage, CVID and the adverse reactions to the IVIg treatment.

Pregnant CVID patients have different needs from other CVID patients.^{5, 6} Even if pregnancy does not hold an increased risk of infection for the mother, CVID women carry an increased risk of fetal loss.⁷ As for the baby, the immune system is physiologically immature at birth and during the first months of life. The active transplacental IgG transport, which occurs mainly after 32 weeks, plays a central role in protecting the infant from infections.⁸ Another protective factor is breastfeeding, since in vitro analyses of the colostrum and milk from women with CVID documented a strong inhibition of enteropathogenic *Escherichia coli* adhesion.⁹ During the intrauterine life, the maternal IgG primes the fetus by the means of the idiotype–anti-idiotype network.¹⁰ It has been proposed that this priming may exert long-life immunoregulatory functions and it may be involved in the recognition of allergens in the newborn.¹¹

Regular replacement therapy is thus crucial, during pregnancy and *puerperium*, for the mother's health and for providing immunological protection for the infant. Since stable protective IgG levels (≥ 500 mg/dl) are achieved only after 3–6 months of replacement therapy, IgG treatment should be started in the early stages of pregnancy to ensure stable IgG serum levels in both the mother and the infant.^{7, 8} This issue is particularly relevant in the cases, not rare, of fetal intrauterine growth retardation or preterm babies from CVID mothers.

Because of haemodilution naturally occurring during pregnancy, which leads to fluctuation of maternal serum IgG levels, the IgG dose should be adjusted to higher dosage than the one employed in non-pregnant CVID patients. In pregnancy, the usual dosage is 0.4–0.6 g/kg at monthly intervals.^{5–9} It is also important to modify the IVIg dose according to modifications in the weight of the mother, as pregnancy advances.^{7, 8}

In CVID, women treated with replacement IgG therapy, stable serum IgG levels in the mother correlates with equal or

even higher cord blood levels in term babies,⁷ thus avoiding the necessity to infuse IgG in the infant.

Pregnant CVID women can be treated by IV or SC route, this latter being better tolerated in patients with previous adverse reactions to IVIg administration.^{3, 12} Despite the advantages of home treatment, some patients (as our patient) still prefer IV to SC IgG administration, probably because they fear to manage self-infusions and eventual AEs at home.

We thus decided to treat our patient with a new product, a ready-to-use, sterile, 10% protein liquid preparation of polyvalent human IgG for IV administration. This preparation has a purity of at least 98% IgG, consisting primarily of monomers and it can be stored over 36 months, with improved convenience for patients and pharmacies.¹³ The usual infusion rate is 8 mg/kg/min; even though Sleasman *et al*¹⁴ documented that selected patients can tolerate it at a higher infusion rate (12 mg/kg/min).

Clinically, the 10% liquid Ig preparation is approved for the treatment of primary immunodeficiencies (PID) with insufficient antibody production; some defined secondary immunodeficiencies, Kawasaki disease, Guillain-Barré syndrome and chronic immune thrombocytopenic purpura (ITP).

In patients with PID and ITP, the 10% liquid Ig preparation showed good tolerability and safety profile, being the majority of AEs reported as mild and their frequencies slightly lower than that reported for other IVIg treatment.^{15, 16} The low rate of AEs seems to be linked to the stabilisation with L-proline that limits the excessive formation of idiotype–anti-idiotype dimers which can precipitate AEs. Moreover, a formulation based on low sodium, no sugar, low IgA contents (≤ 25 mcg/ml) and low volume load also contribute to ameliorate the tolerability profile. Other advantages of the 10% liquid Ig preparation are related to well-tolerated high-infusion rates and convenience of use owing to room-temperature storage.

In our patient, we started with a very low IVIg dose at the lowest infusion speed that was gradually increased, reaching thereafter the dosage of 10 g/week (0.6 g/kg/month). Premedication with chlorphenamine, paracetamol and hydrocortisone was used before the first infusions and then stopped. The product was well tolerated and allowed to achieve safe IgG serum levels in the mother and in the infant. The new product was safe and well tolerated without any infectious episodes during pregnancy. The newborn was also protected with good IgG levels. Unfortunately, we could not detect cord blood IgG levels, as we have already programmed. Our case documented the effectiveness and the safety of 10% liquid Ig preparation in a high-risk pregnant woman with CVID and a history of adverse reactions to IVIG replacement therapy.

Learning points

- ▶ The immature state of the fetal and neonatal immune system makes replacement immunoglobulin G (IgG) treatment crucial in pregnant women with common variable immunodeficiency (CVID).
- ▶ Because of haemodilution naturally occurring during pregnancy, higher dosage of IgG should be used in pregnant CVID patients (usually 0.4–0.6 g/kg intravenously, monthly).
- ▶ In intravenous infusions (IVIg)-treated patients, the per-infusion rates of mild-to-moderate adverse events range from 5% to 15%.
- ▶ The Ig human intravenous, 10% liquid preparation was safe and well tolerated in a high-risk pregnant woman with CVID and a history of adverse reactions to IVIG replacement therapy.

Competing interests None.

Patient consent Obtained.

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