Received: 24 February 2023 | Accepted: 25 February 2023

DOI: 10.1111/bjh.18741

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

LETTER TO THE EDITOR

Successful outcome of pregnancy post-allogeneic stem cell transplant despite severe RH1 alloimmunization: A case report

Rhesus D antigen (RH1)-negative women, when exposed to RH1-positive red blood cells (RBC), are at risk of developing anti-RH1 antibodies. If their offspring are RH1-positive, there is a risk of haemolytic disease of the fetus and newborn (HDFN). Prevention of RH1-mediated HDFN is achieved with (i) RH/KEL compatible transfusion in women of childbearing age, and (ii) administration of anti-RH1 immunoglobulin prophylaxis.[1–3] Once RH1 alloimmunization is established, its management in pregnancy is challenging and relies mainly on intra-uterine transfusions (IUTs).[3] Intravenous immunoglobulin (IVIG), with or without therapeutic plasma exchange (TPE), may be used as a bridge to IUT.[4–10] Blockade of the fetal/neonatal Fc receptor (FcRn) to reduce transplacental IgG transfer is a promising therapy currently under investigation.[11] Disparate therapeutic approaches are utilized clinically due to a lack of clear evidence supporting specific protocols, and significant fetal morbi-mortality persists despite 'optimal therapy'. Here, we present a case of RH1 immunization post-allogeneic stem cell transplant (HSCT), which was successfully managed during pregnancy with IVIG and PE, allowing for a late-preterm birth of a transfusion-independent neonate. Regular antibody level monitoring allowed us to tailor therapy for this challenging case.

The patient was diagnosed with chronic myeloid leukaemia (CML) at the age of 26. Despite treatment with tyrosine kinase inhibitors, the disease evolved to accelerated-phase CML with an additional genetic mutation of dismal prognosis, prompting HSCT. Fertility preservation prior to conditioning chemotherapy resulted in the cryopreservation of nine embryos, as previously described.[12] The patient developed post-transplantation amenorrhoea with premature ovarian insufficiency. HSCT from a donor with blood group O, RH: −1, −2, −3, 4, 5 to a B, RH: 1, 2, 3, 4, 5 recipient induced RBC alloimmunization, with anti-RH1, anti-RH2, and anti-RH3 antibodies detected 6 months post-transplantation.

The patient successfully conceived following transfer of the couple's last blastocyst at 41 years of age, resulting in their only pregnancy. Initial antibody screening at eight weeks gestation (WG) identified a critical titre of anti-RH1 antibodies (1/2048, Figure 1A) and a low titre for anti-RH3 (1/1) and anti-RH2 (detectable solely by enzymatic techniques). Anti-RH1 quantification by continuous flow analysis (CFA)[13] at 12 WG, prior to treatment initiation, was 9.2 IU/mL (≈2 μg/mL, Figure 1B), confirming the presence of a high anti-RH1 titre. The father was identified to have a *RH1* heterozygous genotype. Non-invasive fetal genotyping at 12 WG, was uninterpretable due to maternal origin cell-free DNA contamination (data not shown). Reanalysis of a cryopreserved pre-HSCT bone marrow sample demonstrated a homozygous *RH1* genotype in the mother. Consequently, the fetus was considered RH1-positive and no invasive testing was performed.

International guidelines remain elusive for the optimal management of pregnancies at high risk of HDFN.[1,3] Considering the high anti-RH1 antibody titre, the absence of remaining embryos, and the couple's wishes, we initiated weekly IVIG therapy at 1 g/kg starting at 12 WG and TPE 3×/week starting at 15 WG after determination of the fetal RH1-positive status. Therapy was well tolerated. A decline of the anti-RH1 antibody titre assessed by indirect antiglobulin test (IAT) (Figure 1A) and CFA (Figure 1B) demonstrated effectiveness. IVIG monotherapy reduced the anti-RH1 antibody concentration from approximately 2 to about 1 μg/mL; the addition of TPE further reduced anti-RH1 antibody concentration below the critical threshold (Figure 1B).[14,15] Between 17 and 23 WG, the anti-RH1 antibody concentration remained at 1 μg/mL or less. After 25 WG, anti-RH1 antibody titres raised exponentially (Figure 1B), suggesting that TPE could no longer counterbalance the anti-RH1 antibody production and was discontinued. IVIG was maintained as monotherapy.

The fetus was followed by weekly ultrasonography including Doppler studies,[16] never meeting criteria for IUT (Figure 1C), and from 32 WG, non-stress tests. The pregnancy remained uneventful and induction of labour at 36 WG resulted in the birth of a late-preterm male neonate [weight 2520 g (10–25th percentile)] with adequate neonatal transition. The placenta was underweight (5th percentile) with histological signs of fetal vascular hypoperfusion. Cord blood analysis showed severe, yet compensated, haemolysis [Hb 129 g/L, haematocrit 42%, reticulocytes 401 10^9/l, total bilirubin 116 μmol/l, lactate dehydrogenase (LDH) 1175 iu/L]. Neonatal blood group was B RH1-positive with a highly positive direct antiglobulin test (>1/1024). Elution confirmed the presence of anti-RH1, anti-RH2, and anti-RH3 antibodies

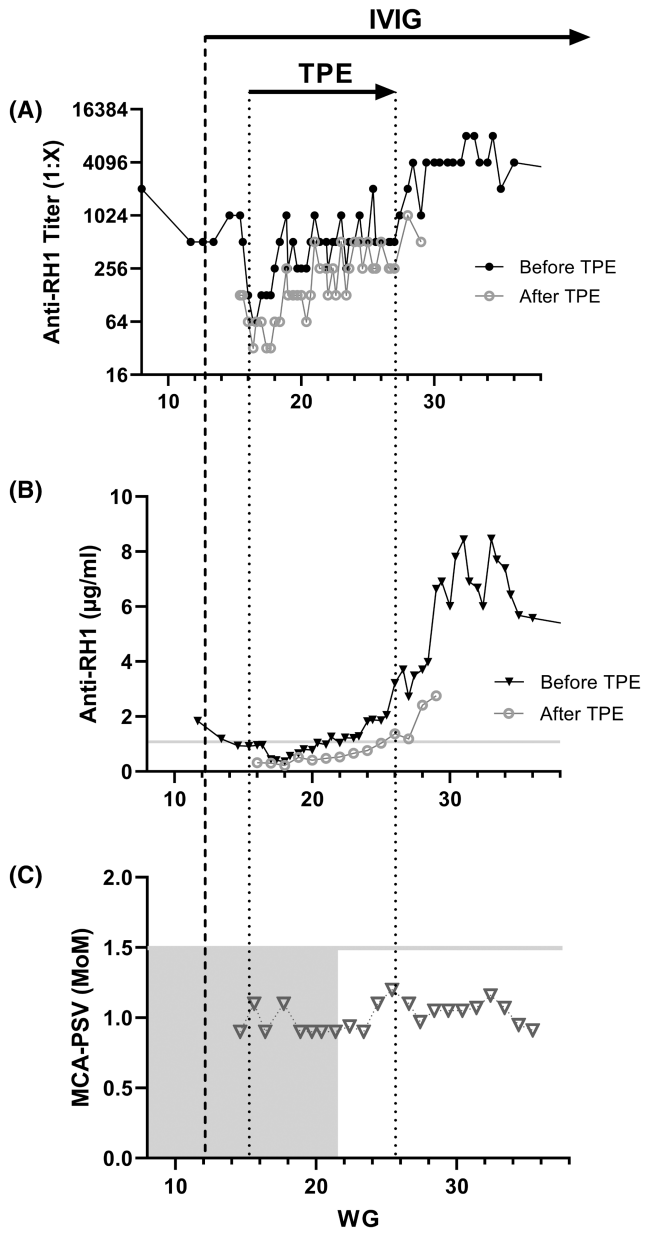

FIGURE 1 Clinical course during pregnancy. (A) Changes in anti-RH1 antibody titres (1:X) as assessed by indirect antiglobulin test (IAT) in our laboratory. (B) Anti-RH1 antibody quantification (µg/mL) by continuous flow analysis (CFA), as performed at the CNRHP (Paris; France). Maternal serum anti-RH1 antibody concentration, IgG1 subtype, was measured with an autoanalyser calibrated against anti-RH1 antibody standard, as described.[7] (C) Foetal anaemia surveillance by means of MCA-PSV. IVIG, intravenous immunoglobulin; MCA-PSV, middle cerebral artery peak systolic velocity; MoM, multiple of the median; PE, plasma exchange; RH1, Rhesus D antigen; WG, weeks gestation.

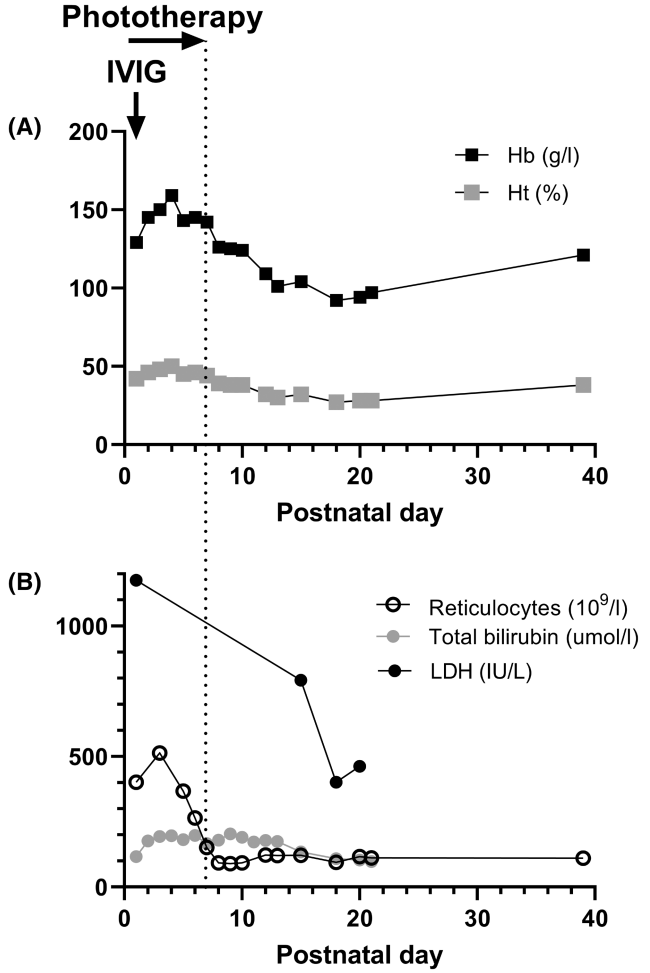

FIGURE 2 Clinical course of the neonate. (A) Postnatal evolution of haemoglobin (g/L) and haematocrit (%). (B) Postnatal evolution of the haemolysis parameters reticulocytes (g/L); total bilirubin (µmol/L); and lactate dehydrogenase (LDH) (IU/L). IVIG, Intravenous immunoglobulin.

on neonatal erythrocytes. The baby received a single 1 g/kg dose of IVIG on day 1 and intensive phototherapy (total 133 h, days 1–7), with favourable clinical and biological evolution (Figure 2A,B). The neonate was discharged home on day 34 of life and is currently one year of age with no health concerns.

The mainstay of therapy for HDFN is IUT[3] with unclear benefit of additional IVIG and TPE.[5–10] At present, large studies are lacking, and meta-analysis is hampered by the heterogeneity of treatment protocols. Our tailored ('tiered') approach, guided by the anti-RH1 antibody concentration, partly circumvents this issue. IVIG has a demonstrated effect on postponing the first IUT,[5] especially if initiated before 13 WG.[6] We therefore utilized IVIG as a 'first-tier therapy'.

By the time the fetal genotype was determined, the impact of IVIG on anti-RH1 antibody levels had plateaued at the critical threshold. We therefore added intensive TPE (3×/week) as our 'second-tier therapy', which resulted in an additional reduction of the anti-RH1 antibody concentration. By physically removing the harmful antibody, TPE, unlike any other therapy, is able to remove several mg of anti-RH1 antibodies (depending on the antibody concentration and the plasma volume treated). However, TPE cannot control antibody production, and could potentially aggravate it.[17] Antibody synthesis is triggered by continued antigen exposure and progresses with increasing gestational age (Figure 1). As the majority of IgG (55%–65%) are located in the extravascular compartment,[17] the post-procedure 're-distribution effect' led to rapid restauration of the plasma

concentration (Figure 1). Finally, TPE is a well-tolerated procedure but not completely devoid of risk. Primary concerns include hypofibrinogenaemia and its associated bleeding risk, deterioration of venous capital, and allergic reaction to fresh frozen plasma (FFP) during TPE. Fetal safety data are scarce. During TPE, the blood is anticoagulated with a citrate-based anticoagulant solution acting through calcium chelation. Placental examination in this case revealed perivillous fibrin depositions with calcifications. A previous case of severe anti-RH1 alloimmunisation with fetal demise at 34 WG due to umbilical cord thrombosis during IUT in spite of intensive TPE and IVIG therapy revealed similar placental and intracerebral calcifications on fetal autopsy (Giorgia Canellini and Nathalie Rufer, pers. commun.) suggesting that caution regarding a balance of the risks and benefits of continued TPE in pregnancy is needed. Furthermore, TPE clears IVIG, shortening its circulating half-life, which is typically 4–5 weeks. As IVIG immunomodulatory effects are manifold,[11] including blockade of the FcRn-dependent IgG transplacental transport, its benefit persists independently of maternal anti-RH1 antibody levels. We thus concluded that TPE was no longer beneficial and reverted to IVIG monotherapy until induced delivery at 36 WG.

In our view, optimal pregnancy management should not only aim to bridge to the minimum gestational age for IUT (16–18 WG), but should also attempt to limit the need for IUT altogether. The risk of fetal mortality is 1%–3% for each IUT and is cumulative.[18] Furthermore, even with IUT, the fetus may be anaemic, and major organs hypo-oxygenated, for prolonged periods of fetal development, causing neurodevelopmental delays and motor defects in some infants.[19] In addition, active haemolysis constitutes a prothrombotic factor[20]; repetitive thrombosis may have accounted for the placenta hypoperfusion and low weight in the present case.

The incidence of RBC alloimmunization after HSCT is low, observed in less than 0.2% to 0.5% of patients,[14] and HSCT is most often associated with secondary infertility in women.[15] Nevertheless, for women going through fertility preservation, the risk of alloimmunization and HDFN should be considered during HSC donor selection.

This case is unique as it presents a successful pregnancy outcome in spite of hemato-oncological disease, post-HSCT infertility, and severe RH1 alloimmunization. To the best of our knowledge, this is the first report of such a case. We discussed the expected benefits and potential risks of the most common established therapeutic options (IUT, IVIG, and TPE). We suggest utilization of a 'tiered approach' combining therapeutic interventions in a stepwise manner and highlighted the importance of withdrawing therapeutic measures once their benefits appear exhausted. Regular antibody level monitoring is key in guiding therapeutic decisions. We hope this case report may contribute towards personalized care plans for these complex patients.

AUTHOR CONTRIBUTIONS

Mathilde Gavillet and Nathalie Rufer collected and analysed the data and wrote the manuscript. Francesco Grandoni, Mattia Rizzi, Nicolas Vulliemoz, David Baud and Lorenzo Alberio contributed to the data collection and analysis in their area of expertise and critically revised the whole manuscript. Giorgia Canellini and Hélène Legardeur supervised the data analysis, and critically revised the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

As the proverb says 'It takes a village to raise a child', an entire community of people must provide for and interact positively for children to grow in a safe and healthy environment. The authors are deeply thankful to Dr Anne Rosselet, MSci Ana Batista, and Christelle Chirlias, Virginie Morin, Isabelle Weigand, and the whole nursing team of apheresis centre (Biopole), Christel Corisello, Denise Hubert and the whole team of local immunoatology technicians (UMT) as well as in the reference lab in Paris (CNRHP), the immunoology and HLA-lab at the HUG in Geneva, the fertility team in the CHUV, the desk coordination of the central lab in CHUV and many, many more. We are especially thankful to the parents for their continued trust and strength through this medical journey and wish this family a bright future. Open access funding provided by Universite de Lausanne.

CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Mathilde Gavillet[1,2]
Nathalie Rufer[2]
Francesco Grandoni[1]
Mattia Rizzi[3]
Nicolas Vulliemoz[4]
David Baud[5]
Lorenzo Alberio[1]
Giorgia Canellini[2]
Hélène Legardeur[5]

[1]*Service and Central Laboratory of Haematology, Department of Oncology and Department of Laboratories and Pathology, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland*
[2]*Interregional Blood Transfusion SRC, Epalinges, Switzerland*
[3]*Pediatric Hematology-Oncology Unit, Division of Pediatrics, Department "Woman-Mother-Child", Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland*
[4]*Centre de Procréation Médicalement Assistée, Lausanne, Switzerland*

[5]*Materno-fetal and Obstetrics Research Unit, Department of Obstetrics and Gynecology, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland*

Correspondence
Mathilde Gavillet, Service and Central Laboratory of Haematology, Department of Oncology and Department of Laboratories and Pathology, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland.
Email: mathilde.gavillet@chuv.ch

ORCID

Mathilde Gavillet https://orcid.org/0000-0002-2485-8197
Nathalie Rufer https://orcid.org/0000-0002-9871-6271
Francesco Grandoni https://orcid.org/0000-0003-2208-2070
Mattia Rizzi https://orcid.org/0000-0001-6987-0678
David Baud https://orcid.org/0000-0001-9914-6496
Lorenzo Alberio https://orcid.org/0000-0001-9686-9920
Hélène Legardeur https://orcid.org/0000-0002-1124-847X

REFERENCES

1. ACOG practice bulletin no. 192: management of alloimmunization during pregnancy. Obstet Gynecol. 2018;131(3):e82–90.
2. Qureshi H, Massey E, Kirwan D, Davies T, Robson S, White J, et al. BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. Transfus Med. 2014;24(1):8–20.
3. Society for Maternal-Fetal Medicine (SMFM), Mari G, Norton ME, Stone J, Berghella V, Sciscione AC, et al. Society for Maternal-Fetal Medicine (SMFM) clinical guideline #8: the fetus at risk for anemia--diagnosis and management. Am J Obstet Gynecol. 2015;212(6):697–710.
4. Moise KJ Jr, Argoti PS. Management and prevention of red cell alloimmunization in pregnancy: a systematic review. Obstet Gynecol. 2012;120(5):1132–9.
5. Maisonneuve E, Dugas A, Friszer S, Toly-Ndour C, Cariot L, Dhombres F, et al. Effect of intravenous immunoglobulins to postpone the gestational age of first intrauterine transfusion in very severe red blood cell alloimmunization: a case-control study. J Gynecol Obstet Hum Reprod. 2021;50(7):102119.
6. Zwiers C, van der Bom JG, van Kamp IL, van Geloven N, Lopriore E, Smoleniec J, et al. Postponing early intrauterine transfusion with intravenous immunoglobulin treatment; the PETIT study on severe hemolytic disease of the fetus and newborn. Am J Obstet Gynecol. 2018;219(3):291 e1–9.
7. Houston BL, Govia R, Abou-Setta AM, Reid GJ, Hadfield M, Menard C, et al. Severe Rh alloimmunization and hemolytic disease of the fetus managed with plasmapheresis, intravenous immunoglobulin and intrauterine transfusion: a case report. Transfus Apher Sci. 2015;53(3):399–402.
8. Nwogu LC, Moise KJ Jr, Klein KL, Tint H, Castillo B, Bai Y. Successful management of severe red blood cell alloimmunization in pregnancy with a combination of therapeutic plasma exchange, intravenous immune globulin, and intrauterine transfusion. Transfusion. 2018;58(3):677–84.
9. Wind M, Gaasbeek AGA, Oosten LEM, Rabelink TJ, van Lith JMM, Sueters M, et al. Therapeutic plasma exchange in pregnancy: a literature review. Eur J Obstet Gynecol Reprod Biol. 2021;260:29–36.
10. Ruma MS, Moise KJ Jr, Kim E, Murtha AP, Prutsman WJ, Hassan SS, et al. Combined plasmapheresis and intravenous immune globulin for the treatment of severe maternal red cell alloimmunization. Am J Obstet Gynecol. 2007;196(2):138.e1–6.
11. Castleman JS, Moise KJ Jr, Kilby MD. Medical therapy to attenuate fetal anaemia in severe maternal red cell alloimmunisation. Br J Haematol. 2021;192(3):425–32.
12. Gazdaru S, Perey L, Rosselet A, Mathevet P, Chalandon Y, Vulliemoz N. Successful ovarian stimulation for fertility preservation in a patient with chronic myeloid leukemia: switch from Nilotinib to interferon-alpha. Oncologist. 2018;23(6):719–21.
13. Toly-Ndour C, Mourtada H, Huguet-Jacquot S, Maisonneuve E, Friszer S, Pernot F, et al. Clinical input of anti-D quantitation by continuous-flow analysis on autoanalyzer in the management of high-titer anti-D maternal alloimmunization. Transfusion. 2018;58(2):294–305.
14. Worel N. ABO-mismatched allogeneic hematopoietic stem cell transplantation. Transfus Med Hemother. 2016;43(1):3–12.
15. Noetzli J, Voruz S, Wunder D, Primi MP, Spertini O, Blum S. Ten-year single-Centre experience in fertility preservation of 459 patients suffering from acute leukaemia. Br J Haematol. 2019;184(6):969–73.
16. Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ Jr, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the blood velocity in anemic fetuses. N Engl J Med. 2000;342(1):9–14.
17. Kaplan AA. Therapeutic plasma exchange: core curriculum 2008. Am J Kidney Dis. 2008;52(6):1180–96.
18. Zwiers C, Lindenburg ITM, Klumper FJ, de Haas M, Oepkes D, van Kamp IL. Complications of intrauterine intravascular blood transfusion: lessons learned after 1678 procedures. Ultrasound Obstet Gynecol. 2017;50(2):180–6.
19. Lindenburg IT, Smits-Wintjens VE, van Klink JM, Verduin E, van Kamp IL, Walther FJ, et al. Long-term neurodevelopmental outcome after intrauterine transfusion for hemolytic disease of the fetus/newborn: the LOTUS study. Am J Obstet Gynecol. 2012;206(2):141 e1-8.
20. Fattizzo B, Bortolotti M, Giannotta JA, Zaninoni A, Consonni D, Barcellini W. Intravascular hemolysis and multitreatment predict thrombosis in patients with autoimmune hemolytic anemia. J Thromb Haemost. 2022;20:1852–8.