Received: 12 April 2022 | Revised: 11 July 2022 | Accepted: 12 July 2022

DOI: 10.1111/ejh.13830

CASE REPORT

European Journal of Haematology

WILEY

Urgent use of voxelotor in sickle cell disease when immediate transfusion is not safe

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Funding information
Global Blood Therapeutics

Abstract

The use of blood transfusions to improve anemia resulting from sickle cell disease (SCD) is often limited by alloimmunization, which occurs due to exposure to incompatible antigen present on donor red blood cells (RBCs). This complication occasionally manifests as delayed hemolytic transfusion reactions (DHTRs) that cause hemolysis of the recipient's own RBCs and can lead to fatal anemia. In this case study, we report a patient with SCD who experienced a DHTR following chronic transfusion and was successfully treated with voxelotor, an orally administered sickle hemoglobin (HbS) polymerization inhibitor for the treatment of SCD. Laboratory tests following admission indicated pan-reactivity in antigens, and a rare donor registry was used to locate acceptable units. The patient experienced the DHTR 3 days after admission, which limited laboratory tests due to profound hemolysis. Alternative treatments were limited, and phenotypically matched units were incompatible, so voxelotor was selected as a last-resort treatment. Following initiation of voxelotor 1500 mg, the patient's hemoglobin levels returned to baseline (6 g/dl) within 10 days, with clinical improvements. This report provides evidence regarding the use of voxelotor in the treatment of profound anemia where other treatments could be unsafe or unavailable.

KEYWORDS
anemia, delayed hemolytic transfusion reaction, hyperhemolysis, sickle cell disease, voxelotor

Sickle cell disease (SCD) comprises a set of genetic hematologic abnormalities primarily affecting patients of Sub-Saharan African descent.[1] Transfusion to reduce the amount of sickle hemoglobin (HbS) is a standard of care for SCD.[2] However, chronic transfusion is often limited by alloimmunization arising from the recipient's exposure to donor red blood cells (RBCs) with different surface antigens. Recipients' macrophages may eliminate new foreign RBCs carrying the same antigens as those from a prior transfusion, which can lead to delayed hemolytic transfusion reactions (DHTRs).[1,2] A difficult-to-manage form of DHTR, hyperhemolysis, occurs in the absence of newly identified alloantibodies and can destroy both transfused RBCs and the recipient's RBCs through a mechanism known as bystander hemolysis, leading to fatal anemia. Typically, in DHTRs, no new antibodies are found, and the direct antiglobulin test (DAT) is negative.[3]

Voxelotor is a first-in-class oral HbS-polymerization inhibitor shown to increase hemoglobin (Hb) and reduce incidences of anemia and hemolysis in patients with SCD.[4] Here, we report a patient with SCD whose anemia was successfully treated with voxelotor following a severe DHTR, which possibly occurred due to hyperhemolysis.

The patient is a 59-year-old African American female with the HbSS SCD genotype who presented with ankle pain that was unrelenting for 3–4 days despite improved ankle edema. Her baseline Hb was 6–6.5 g/dl on monthly simple transfusions for chronic ankle ulcers and chronic hypoxia due to pulmonary fibrosis. Her last

transfusion was of 2 phenotypically matched, crossmatch-compatible units 17 days before admission. The DAT at transfusion was negative. After the transfusions, she reported abdominal and lower-extremity edema, along with pain and weight gain. She reported clinical improvement but incomplete resolution of weight gain and edema with previous furosemide treatment. Because this patient was receiving transfusions, she was not eligible for the Phase 3 HOPE trial, which assessed the safety and efficacy of voxelotor in patients with SCD.

Upon admission, her vital signs were stable, with oxygen saturation at 95%. Laboratory evaluation revealed leukocytosis of 20.1 K/μl, Hb at 4.1 g/dl, and total bilirubin at 2.9 mg/dl (unconjugated 2.2 mg/dl). Imaging revealed cardiomegaly and a pulmonary infiltrate. She received RBCs, antibiotics, and intravenous opioids. The blood bank workup showed O+ blood type, and the antibody screen was pan-reactive. She had previously identified RBC alloantibodies against the antigens C, D, Fy^a, Js^a, M, V, and a warm antibody of undetermined specificity. The DAT was weakly positive for C3d and negative for IgG. Due to the pan-reactivity in all antibody-identification panels, no additional antibodies were identified, which did not preclude the possibility of an additional antibody. The next day, laboratory studies showed continued leukocytosis of 18.4 K/μl and Hb of 3.3 g/dl. Due to the broad reactivity of all the blood bank serologic testing, we searched the rare donor registry for phenotypically matched RBCs that lacked E, K, S, and Fy^a antigens.

On Day 3 of admission, the patient developed severe respiratory distress, tachycardia to 160 bpm, and hypoxia to a partial pressure of oxygen of 80 mmHg despite oxygen supplementation. She reported dyspnea, anxiety, flushing and increased pain. Pain and anxiety were treated pharmacologically, and oxygen supplementation was increased to high flow. Laboratory studies reported pH 7.26 and lactate at 5.2 mmol/L, consistent with extreme lactic acidosis. Blood bank testing showed the same pan-reactivity, with a negative DAT and no new antibodies. The patient requested a transition to comfort care. The transfusion medicine team suspected that the patient was having a DHTR and associated hyperhemolysis secondary to the prior transfusion, supported by broad reactivity in the antibody workup.

Multiple specialists evaluated the potential use of high-dose steroids, intravenous immunoglobulin, and other medications for treating her hyperhemolysis but determined that the time it would take to effectively reverse hemolysis and stimulate red cell production would be too lengthy and that the response could be limited in the case of renal dysfunction. We also discussed the role of erythropoietin but felt that it would not be beneficial given the urgency of raising the patient's Hb and the presence of a pulmonary infiltrate, which was concerning for pulmonary embolism. Due to the patient's unstable condition, pulmonary embolism could not be ruled out, and because requesting additional tests to measure renal function and other indications of multiple organ failure could not be justified for a patient with undetectable Hb, the specialists would not recommend or approve other treatment options, as they required lab studies to justify safety. Additionally, we felt that the patient's condition would deteriorate too rapidly for any of the usual interventions to be effective. We accepted 2 available phenotypically matched units that would still require additional compatibility testing.

The patient's condition remained critical the next day. She required high-flow oxygen to maintain oxygen saturation above 85%, and tachycardia to 140 bpm persisted. At her request for comfort care, no further laboratory studies were done. Her caregivers weighed the risks and benefits of voxelotor as a last attempt at preserving life. After learning that the 2 units of RBCs from

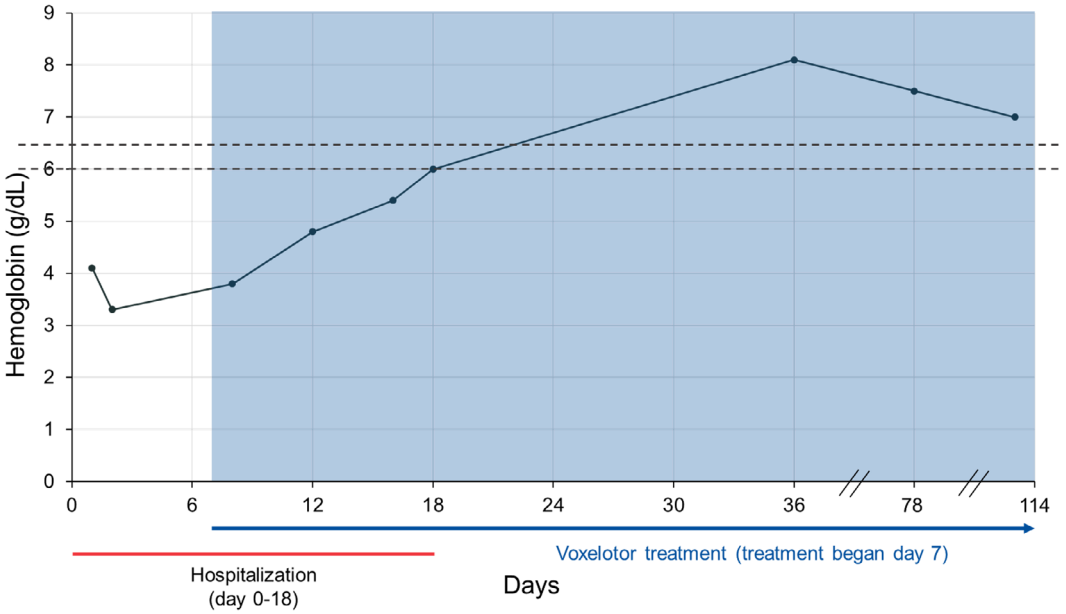

FIGURE 1 Changes in hemoglobin after hospitalization. The patient was admitted after a blood transfusion and DHTR/hyperhemolysis. Hemoglobin levels were critically low at the start of hospitalization (4.1 g/dl), and severe injury and death were concerns. Hemoglobin levels did not improve from Days 1–5. The patient was administered voxelotor on Day 7.5 and was monitored from Day 8 onward, including after discharge. DHTR, delayed hemolytic transfusion reaction.

TABLE 1 Change in vital signs in the patient since admission

Admission, day	1	2	3	4	7	8	12	16	18[a]	36	78	113
Voxelotor, day					1[b]	2	6	10	12	30	72	107
Heart rate, bpm	160	140	~140	~140	~120	~110	~110	~110	~110	79	79	69
Oxygen saturation, %	100 on HFNC 65% and 50 LPM	100 on HFNC 65% and 50 LPM	100 on HFNC 65% and 50 LPM	100 on HFNC 65% and 50 LPM	100 on HFNC 50% and 35 LPM	>95 4 LPM NC	>95 4 LPM NC	>95 4 LPM NC	98 on 2 LPM NC	>95 on 2 LPM NC	>95 on 2 LPM NC	>95 on 2 LPM NC
Hb, g/dl	4.1	3.3	–	–	–	3.8	4.8	5.4	6.0	8.1	7.5	7.0
WBC, K/μl	20.1	18.4				18.1	9.3	8.7	7.7	5.5	9.7	7.8
Total bilirubin, mg/dl	2.9					1.1			1.1			1.1
Indirect bilirubin, mg/dl						0.6			0.6			0.6

Note: Blue shading indicates duration of voxelotor treatment.
Abbreviations: Hb, hemoglobin; HFNC, high-flow nasal cannula; LPM, liters per minute; NC, nasal cannula; WBC, white blood cell.
[a]Patient was discharged.
[b]Voxelotor treatment began in the evening.

Nevada were incompatible, the team decided to turn to the use of voxelotor, the only medication for which specialty approval was not needed and additional laboratory testing for renal injury was not required.

With the patient's consent, voxelotor 1500 mg was administered on Day 7.5 of admission. Another blood sample revealed Hb of 3.8 g/dl the next morning. The patient reported no side effects, and daily oral dosing continued thereafter. After 4 days, her Hb was 4.8 g/dl. The patient reported improvement in her pain such that intravenous analgesia could be reduced. Her Hb was 6 g/dl after 10 days of voxelotor treatment and 8.1 g/dl after 27 days (Figure 1 and Table 1). The patient was discharged to low-level rehabilitation 18 days after presentation.

Emergency use of medication for acute improvement or stabilization of Hb as a response to transfusion-related hemolysis has not been studied. In this case study, there was strong clinical evidence suggesting DHTR/hyperhemolysis that could have been exacerbated by additional RBC transfusions. Voxelotor, which was cleared for accelerated approval by the US FDA to treat anemia due to SCD,[4] was trialed as a final effort to reduce hemolysis. Voxelotor was previously used to treat anemia in a patient with SCD and COVID-19 who received RBCs but did not have increased Hb and had no other treatment options due to hyperhemolysis concerns. That patient's Hb increased from 6.5 to 8.0 g/dl within 2 days of starting treatment and was 10.3 g/dl by Day 10,[5] which is the same rapid response time to recover from life-threatening anemia that was observed in the patient in this case study. A similar rapid increase in Hb was observed in the Phase 3 HOPE trial; although change in Hb was not measured within days of treatment initiation, the increase in Hb among patients treated with voxelotor 1500 mg was measured at 2 weeks after treatment initiation and was similarly rapid, with a mean increase from baseline of approximately 1.4 g/dl.[4] However, it is important to note that in our patient, Hb levels had partially started to recover just before the initiation of voxelotor, which may have contributed to the rapid increase in Hb noted within days of treatment.

Based on the rapid onset time observed in the clinical trial and patient case reports, voxelotor has shown the potential to be lifesaving for patients who need to increase Hb quickly and to avoid adverse effects, such as DHTR. It may be useful when other modes of replenishing oxygen, such as transfusions, have been exhausted.

ACKNOWLEDGMENT

Medical writing and editorial assistance were provided by Dylan Mori, PhD (Healthcare Consultancy Group, funded by Global Blood Therapeutics).

CONFLICT OF INTERESTS

MF: Speaker: Global Blood Therapeutics. TL: Nothing to disclose. SDR: Nothing to disclose. WS: Consultant: Global Blood Therapeutics, Novartis, Pfizer, GlycoMimetics, Ironwood, Novo Nordisk, Emmaus Pharmaceuticals. Research funding: Global Blood Therapeutics, NHLBI, PCORI, HRSA, Novartis, Imara, and Shire.

DATA AVAILABILITY STATEMENT

Health Insurance Portability and Accountability Act (HIPAA) prevents sharing these data from an individual patient file, beyond what is published.

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How to cite this article: Ferlis M, Lipato T, Roseff SD, Smith WR. Urgent use of voxelotor in sickle cell disease when immediate transfusion is not safe. *Eur J Haematol*. 2022; 109(5):586-589. doi:10.1111/ejh.13830