To the editor:

Eculizumab salvage therapy for delayed hemolysis transfusion reaction in sickle cell disease patients

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Delayed hemolytic transfusion reaction (DHTR) with hyperhemolysis is a potentially life-threatening complication of sickle cell disease (SCD) occurring 5 to 20 days after transfusion.[1] Patients display symptoms of severe vaso-occlusive crisis (VOC), associated with the destruction of both transfused and autologous red blood cells (RBC).[2-4] DHTR can have disastrous consequences within a few hours, progressing to multiple organ failure and, often, death. In about one-third of DHTR cases, there are no detectable antibodies.[5,6] No optimal treatment of DHTR has yet been defined. One possible approach is to minimize intravascular hemolysis and the side effects of free hemoglobin on the endothelium by inhibiting complement activation. Eculizumab, an anti-C5 monoclonal antibody targeting complement activation, is a potential candidate treatment.

We report data from 3 patients with homozygous SCD hospitalized for severe DHTR and hyperhemolysis, without detectable allo- or autoantibody formation, following transfusion (day 0). Each patient received 2 fixed doses of eculizumab (900 mg) 1 week apart. Plasma samples were collected and then stored frozen to improve the characterization of complement activity. All samples were analyzed at the French Sickle Cell Referral Center. Complement activity before and after treatment is summarized in Table 1.

The patients were included in the SCDTRANSFU trial, which was approved by the local ethics committee. In accordance with French law and the Helsinki Declaration, patients were informed of the risks and the potential benefits of eculizumab therapy, which they were told were only hypothetical. The treatment was administered as a salvage therapy.

Patient 1, a 20-year-old female SCD patient with a homozygous mutation, presented with severe acute VOC 6 days after transfusion with 6 U of cross-matched leukoreduced RBCs. The indication for transfusion was overt stroke with complete neurological recovery. The units were matched for Rh, Kell, Fy, and MNS blood groups because of a known history of anti-S antibody production. DHTR was diagnosed on the basis of decreases in hemoglobin (Hb) and HbA levels associated with an increase in hemolytic parameters (Figure 1A) and dark-colored urine. Screening tests for the detection of newly formed antibody and direct antiglobulin tests (DAT) were negative. Transfusions were discontinued. Given the clinical severity of the condition and the risk of worsening neurological manifestations, eculizumab was administered to the patient, with repeated recombinant erythropoietin injections. Bone pain disappeared and the patient's urine became yellow again on the day after the first eculizumab infusion. Hemolysis decreased (normal haptoglobin and bilirubin levels), and hemoglobin levels gradually increased (Figure 1A). No further complications were observed. The patient was discharged home on day 18.

Patient 2, a 17-year-old female SCD patient with a homozygous mutation, presented with a severe acute chest syndrome, fever, and dark-colored urine 7 days after the transfusion of 2 U RBCs cross-matched for Rh and Kell to treat VOC. The patient had not previously been immunized and the screening test before transfusion was negative. Because of severe anemia (Hb concentration, 28 g/L) and acute kidney injury, a new transfusion of 2 cross-matched RBC units was performed. The patient's clinical condition rapidly deteriorated, with hypotension requiring vasopressive support, dark urine, and acute respiratory, liver (prothrombin time, 20%; factor V, 10%), and kidney failure (requiring renal replacement therapy). Echocardiography revealed severe biventricular dysfunction associated with cor pulmonale. Laboratory tests showed acute hemolysis, a serum-free hemoglobin concentration of 24 g/L, and negative DAT results (Figure 1B). DHTR with hyperhemolysis complicated by multiple organ failure was suspected. Transfusions were stopped and 1 session of plasma exchange was performed, associated with eculizumab treatment (plasma exchange was performed immediately before eculizumab treatment). Repeated recombinant erythropoietin injections were administered, due to reticulopenia. Intravascular hemolysis disappeared and hemoglobin

Table 1. Complement analysis before and after eculizumab infusion

	Day*	C3 level (mg/L)	C4 level (mg/L)	sC5B9 level (mg/L)
Patient 1				
Before eculizumab infusion	0	1080	266	856
First follow-up assessment	2	1030	283	1223
Second follow-up assessment	14	1050	248	1406
Patient 2				
Before eculizumab infusion	0	—	—	—
First follow-up assessment	7	1270	257	1797
Patient 3				
Before eculizumab infusion	0	1070	220	1527
First follow-up assessment	4	313	104	296
Second follow-up assessment	6	359	129	224
Third follow-up assessment	9	928	526	355
Fourth follow-up assessment	13	1210	290	509

C3, C3 complement component (normal range, 660-1250 mg/L); C4, C4 complement component (normal range, 93-380 mg/L); sC5B9, soluble terminal complement complex (normal range, <450 ng/mL).

*Day after first eculizumab injection.

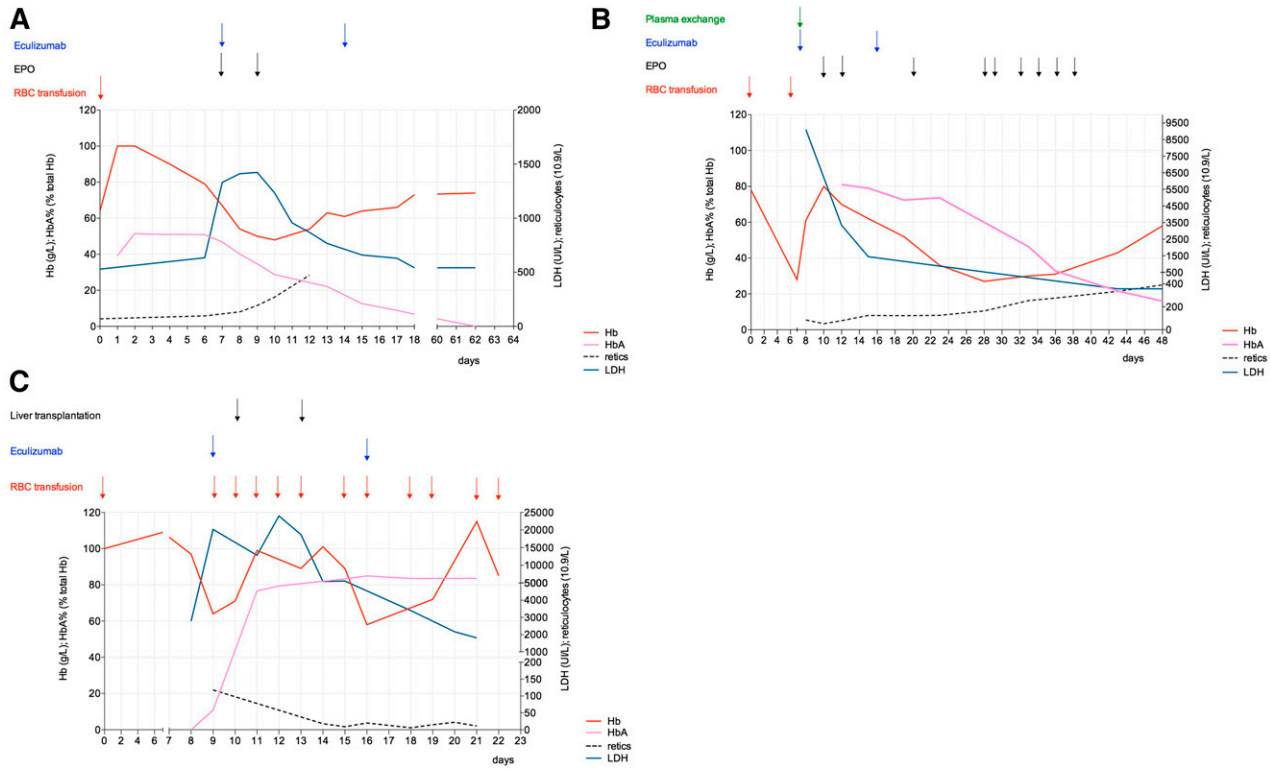

Figure 1. Event history and response to treatment in 3 patients with delayed hemolytic transfusion reaction. Day 0 indicates the day of the transfusion responsible for the hemolytic episode. (A) Timeline history of patient 1. (B) Timeline history of patient 2. (C) Timeline history of patient 3. Blue arrows represent eculizumab infusion. Black arrows indicate recombinant erythropoietin injections (EPO). Red arrows indicate RBC transfusion days; green arrows represent plasma exchange sessions. HbA (indicated as a percentage of total Hb concentration); reticulocytes ([retics] normal range, 20 × 10^9/L-100 × 10^9/L); lactate dehydrogenase ([LDH] normal range, 240-460 U/L).

levels increased on treatment (Figure 1B). Kidney, respiratory, cardiac, and liver abnormalities progressively resolved. The patient was discharged home on day 48.

Patient 3, an 18-year-old male SCD patient with a homozygous mutation, underwent transfusion with 2 cross-matched RBC units. He had previously developed anti-C antibodies because of a partial C antigen; the pretransfusion screening test and DAT were negative. He received D-C-E-Kell–matched RBC units. Seven days after transfusion, he was hospitalized for severe VOC, with fever and dark-colored urine. On day 8, he was confused, but no major deterioration of biological parameters was observed (Figure 1C). On day 9, the patient's condition deteriorated, with shock, acute liver failure, and acute kidney injury. Echocardiography showed acute cor pulmonale. Laboratory findings revealed a drop in hemoglobin levels and an increase in hemolytic parameters (Figure 1C). Initial management involved mechanical ventilation, vasopressor treatment, broad-spectrum antibiotic treatment, and platelet and plasma transfusions. We decided to attempt treatment with eculizumab. Hemolysis and hemostasis stabilized, making it possible to carry out liver transplantation on day 10. Histological examination of the liver revealed intrahepatic VOC and hypoxic hepatitis. Unfortunately, 36 hours after the procedure, the patient developed cardiogenic shock requiring extracorporeal membrane oxygenation and severe acute liver failure. On day 13, liver transplantation was attempted again. Cardiac dysfunction and pulmonary hypertension resolved rapidly, allowing weaning from extracorporeal membrane oxygenation and mechanical ventilation. The patient recovered a normal state of awareness. Postoperative Doppler ultrasound results were normal and liver function stabilized, with normal prothrombin time and factor V levels. Because of the liver transplant and bleeding, transfusions were required, from days 8 to 22, with a total of 59 RBC units matched only for Rh and Kell, because of the large number of units required. Anti-S antibodies appeared 23 days after the first transfusion. At the same time, anti-C antibodies appeared despite the transfusion of C-negative RBCs. Haptoglobin, which was undetectable before transfusion, increased in concentration to 0.42 g/L, reflecting the disappearance of intravascular hemolysis. Unfortunately, the patient died on day 23 from a severe pulmonary infection while on immunosuppressive treatment following liver transplantation, this condition being favored by neutropenia secondary to bone marrow necrosis confirmed on a myelogram.

These reports highlight the potential severity of DHTR with hyperhemolysis in SCD patients, whose natural defense mechanisms, in the form of haptoglobin and hemopexin, are overwhelmed. The catastrophic manifestations of DHTR are due to massive intravascular hemolysis associated with organ damage. Complement activation may be involved in DHTR via the classic pathway when allo- or autoantibodies are detected, or by the alternative pathway.[7-10] Moreover, deleterious effects of free heme on endothelial cells through the alternative complement activation pathway have been demonstrated.[11-13]

None of the patients presented C3 complement component consumption in the acute phase, but the final stage in complement activation was analyzed retrospectively and levels of sC5b9, reflecting membrane attack complex formation, were high in the plasma samples from the patients, suggesting that terminal pathway complement activation had occurred. Patient 3 presented transient alternative pathway consumption, with low C3 and normal C4 complement component levels between days 4 and 9 after the initiation of eculizumab treatment. The lytic pathway of complement may therefore be involved in the intravascular hemolysis and endothelial damage observed, and eculizumab is a promising treatment of these patients. One SCD

patient with HI antibodies was recently treated with eculizumab,[14] but it was difficult to draw any firm conclusions about the efficacy of this treatment because of concomitant treatment with rituximab.

Here, we report a beneficial effect on hemolysis and vasculopathy of eculizumab treatment alone in patients 1 and 2, and in association with immunosuppressants and steroids in patient 3, who underwent liver transplantation.

Eculizumab treatment should probably be started as soon as DHTR appears, but further assessments are required in prospective studies taking into account the cost and possible side effects of this treatment.

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To the editor:

Ibrutinib-induced pneumonitis in patients with chronic lymphocytic leukemia

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Chronic lymphocytic leukemia (CLL) is a B-cell lymphoproliferative disorder partly dependent on the B-cell receptor (BCR) signaling pathway. The novel BCR signal transduction inhibitor ibrutinib has emerged as an effective therapeutic agent for CLL.[1] Ibrutinib covalently binds to and inhibits Bruton tyrosine kinase (BTK), a critical component of BCR signaling thought to be integral to B-cell development, maturation, differentiation, and migration. Ibrutinib is currently approved for the treatment of patients with relapsed CLL or CLL with del(17p), relapsed mantle cell lymphoma, and Waldenström macroglobulinemia.[2-6] Major toxicities of ibrutinib include bleeding, fatigue, arthralgia, infection, and atrial fibrillation.[7,8] One prior case of ibrutinib-associated pneumonitis has been reported.[9] Herein, we report 4 cases of relapsed/refractory CLL patients who developed pneumonitis.

The first case describes a 71-year-old woman with del(17p) del(11q)-positive relapsed CLL who was treated with ibrutinib at 420 mg daily 9 years after initial diagnosis. Prior therapy included fludarabine and rituximab. One month following ibrutinib initiation, she was hospitalized with dyspnea and hypoxia. Infectious workup was negative. A computerized tomography (CT) scan of the chest revealed widespread interstitial ground glass opacities not noted on CT imaging obtained 4 weeks prior to ibrutinib exposure (Figure 1A-B). Transbronchial biopsy and cytology revealed fragments of alveolated lung parenchyma with chronic interstitial inflammation and organization