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Case Report

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Successful Management of Severe Hyperhaemolysis with Combined Tocilizumab and Rituximab in Non-Transfusion-Dependent Thalassaemia: A Case Report

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Abstract

Introduction: This is the fourth case reporting the administration of tocilizumab to control hyperhaemolysis. It was administered with rituximab to stop hyperhaemolysis refractory to frontline therapy. Hyperhaemolysis is a rare life-threatening subtype of delayed haemolytic transfusion reaction. Refractory cases pose a clinical challenge with no standard of care to date. ***Case Presentation:*** A 29-year-old lady with non-transfusion-dependent thalassaemia presented with refractory hyperhaemolysis necessitating the administration of rituximab. This was complicated with anaemic heart failure and altered sensorium exacerbated with further transfusions. A nadir haemoglobin of 2.1 g/dL was reached after the initiation of rituximab, and her condition was too critical to wait for the slow expected improvement. Hence, tocilizumab was given as a bridging therapy to block haemolysis till the delayed onset of radical treatment. ***Conclusion:*** Tocilizumab can be effectively combined with rituximab to stop hyperhaemolytic episode refractory to first-line treatment when a prompt response is needed.

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Introduction

Hyperhaemolysis syndrome (HHS) is a rare post-transfusion reaction typically occurring within 2 weeks of transfusion. It is characterized by lower haemoglobin values than pre-transfusion levels, reticulocytopenia, and markedly elevated lactate dehydrogenase (LDH) [1]. Bystander haemolysis is partially incriminated with the destruction of both donor red blood cells (RBCs), which expresses the culprit alloantigen, and the autologous RBCs [2].

The pathophysiology of HHS remains elusive; however, complement-mediated lysis of erythrocytes, halted erythropoiesis, hyperactive macrophages, and erythrocytophagocytosis all were proposed mechanisms implicated in the aetiopathogenesis [3]. It has two recognized forms according to the temporal relationship to the index transfusion [4]. The acute form, taking place within 7 days of transfusion, and the delayed one taking place after that timeframe.

Management includes the avoidance of further transfusions [2], glucocorticoids [5], IVIG [6], and high doses of erythropoietin [7], with suggested doses from 250 to 800 units/kg/dose given thrice-weekly [2] or once-weekly dosing of 40,000–60,000 units of recombinant human erythropoietin [8]. Nonetheless, recurrent and refractory HHS represents a challenge to the clinician with many lines of therapy evaluated including eculizumab [9, 10], rituximab [11, 12], and plasma to RBC exchange [13].

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Tocilizumab is a well-known effective therapy in some autoimmune disorders including macrophage activation syndrome and cytokine release syndrome complicating chimeric antigen receptor T (CAR T)-cell therapy. It was tried as a potential therapeutic option in refractory HHS in three prior cases given its anti-macrophage properties [3, 4].

Our case represents the fourth case illustrating the successful use of tocilizumab in the management of refractory hyperhaemolysis. Tocilizumab was given as a combination therapy with anti-CD20 monoclonal antibody, rituximab, to aid in achieving rapid control over the haemolytic process till the effective depletion of B-lymphocytes is capable of abrogating haemolysis.

Case Report/Case Presentation

A 29-year-old female patient was diagnosed as non-transfusion-dependent beta thalassemia with no previous transfusion history (her baseline haemoglobin was 9–10 g/dL). Her family history is notable for her mother having life-long anaemia that was never investigated. An informed written consent was obtained from the patient to publish her clinical and laboratory data.

Our case presented at the Ain Shams University Specialized Hospital, Cairo, Egypt, about 2 weeks after having an infectious mononucleosis episode complicated with accentuated anaemia necessitating transfusion of three units of ABO- and Rh-matched packed RBCs.

Twelve days after the first blood transfusion, she suffered a bout of high-grade fever (39°C), severe bony aches, headaches, dark Coca-Cola-coloured urine, and acute drop of haemoglobin (HB 4.8 g/dL) that was well below the pre-transfusion level (7.8 g/dL). Her platelet counts reached 88 × 10^9/L with normal white cell count and differential. Her laboratories showed corrected retics 0.6%, negative direct and indirect anti-globulin tests, consumed haptoglobin, elevated bilirubin (total 9 mg/dL and direct 4 mg/dL), LDH >2,000 IU/dL, and consumed complement C3 at 83 mg/dL. Moreover, elevated ferritin (>2,000 ng/mL), triglycerides (273 mg/dL), and soluble CD25 (>30,000 U/L), along with deranged coagulation profile with markedly prolonged PT at 21.8 s, aPTT 41 s, D-dimer 1.6 mg/L, and consumed fibrinogen 0.9 g/L were all observable. Her ISTH-DIC score was 6 with probable DIC [14]. Brain MRI revealed rim of subdural haematoma capping both cerebral hemispheres.

Polymerase chain reaction for Epstein-Barr Virus deoxyribonucleic acid (EBV DNA)s was positive at 250 copies/mL, whereas other viruses like Cytomegalovirus and severe acute respiratory syndrome Coronavirus 2 were ruled out using PCR. Her abdominopelvic sonography demonstrated significantly increasing hepatosplenomegaly (liver 19.5 cm and spleen 21 cm), and positron emission tomography and computed tomography effectively ruled out the possibility of lymphoproliferative neoplasm given the low fluorodeoxyglucose avidity shown in lymph nodes and the hugely enlarged spleen compatible with her background history of congenital haemolytic anaemia. A bone marrow aspirate was moderately hypercellular with an inverted myeloid to erythroid ratio, it demonstrated megaloblastoid dyserythropoietic changes and some macrophages, yet none showed features of haemophagocytosis. A calculated H score was 204 points with ~88–93% probability of haemophagocytic lymphohistiocytosis (HLH) diagnosis [15].

Repeated extended RBC phenotyping and cross-matching showed the presence of anti-Jka, anti-E, and anti-S antibodies in the blood. Given the above-mentioned results, patient was labelled as having EBV-associated HLH complicated with DIC and hyperhaemolysis episode with the presence of multiple alloantibodies.

We decided to avoid transfusion whenever possible and to give her a 5-day course of IVIG 0.4 g/kg/day and pulsed methylprednisolone 1 g/day followed by prednisone 1 mg/kg/day slowly tapered to withdrawal over the period of 6 weeks, darbepoetin alfa at an initial dose of 200 μg that was up-titrated to 4.5 μg/kg; the maximum therapeutic dose for 11 weekly doses as an off-label indication [8], and haematinics including oral iron, vitamin B12, and folic acid. Her bleeding DIC was conservatively managed with intravenous vitamin K, fresh frozen plasma, and cryoprecipitate infusions with good control of her subdural haemorrhage. HLH management with HLH-2004 [16] was not feasible given the severe life-threatening anaemia she had by that time. Furthermore, her EBV positivity made rituximab an appealing therapeutic option, with dual effect on both EBV-associated HLH as well as hyperhaemolysis.

As her haemoglobin failed to improve and continued further drop despite the aforementioned lines of therapy, we decided to give her rituximab 375 mg/m^2 on weekly basis for 4 weeks starting from day 12 of hospitalization. The patient's condition was complicated with anaemic heart failure with bouts of severe brain hypoxia manifested by lapse of consciousness and haemoglobin drop down to 3.2 g/dL necessitating further transfusion. Extended phenotyped blood negative for Jka, E, and S alloantigens was administered to the patient. However, she developed severe intravascular haemolysis with haemoglobinuria after receiving only 50 mL of that blood precluding further transfusion. Her haemoglobin showed precipitous drop down to 2.8 g/dL on day 17 of hospitalization, and she was transferred to intermediate care unit for better monitoring of her critical condition. Another dose of IVIG 1 g/kg/day for 2 days and re-institution of pulsed methylprednisolone was done starting from day 12 with haemolysis failing to stop and HB reaching a nadir of 2.1 g/dL. That is why a trial of IL-6 blockade and antagonizing phagocytosis by macrophages was done using tocilizumab. Tocilizumab was given on days 16 and 17 of hospital admission at a dose of 8 mg/kg/day. On day 18, a partial improvement was observed with haemoglobin creeping up to 3.7 g/dL. Limitation of iatrogenic blood loss was done by limiting laboratory investigations to twice weekly and relying more upon the clinical findings like her vital signs and conscious level. Her haemoglobin after 6 days of tocilizumab administration was 3.5 g/dL, LDH 1,115 U/L, and reticulocyte percentage of 2%.

She stayed hospitalized for 62 days with very slow recovery of her haemoglobin. Her hospital stay was complicated by fever that was ascribed to central venous catheter infection with multidrug-resistant Klebsiella pneumonia. This explained the protracted course of her haemoglobin increase due to the infection-induced myelosuppression blunting the medullary response. After the achievement of adequate control of the infection with broad-spectrum antimicrobial therapy, haemoglobin response was steadier and steeper from day 62 onwards. Figure 1 illustrates her haemoglobin levels throughout her clinical course and highlights the timeline of the principal interventions. During her hospitalization, she completed her 4-week course of weekly rituximab, she was maintained on maximal dose of darbepoetin alfa, oral iron therapy, vitamin B12, folate, danazol, and multivitamins. She was discharged from hospital on day 62 with a haemoglobin level of 4.7 g/dL, LDH 346 IU/dL, and ferritin 1,546 ng/mL. Her haemoglobin reached 9.6 g/dL and ferritin was 960 ng/mL by day 98.

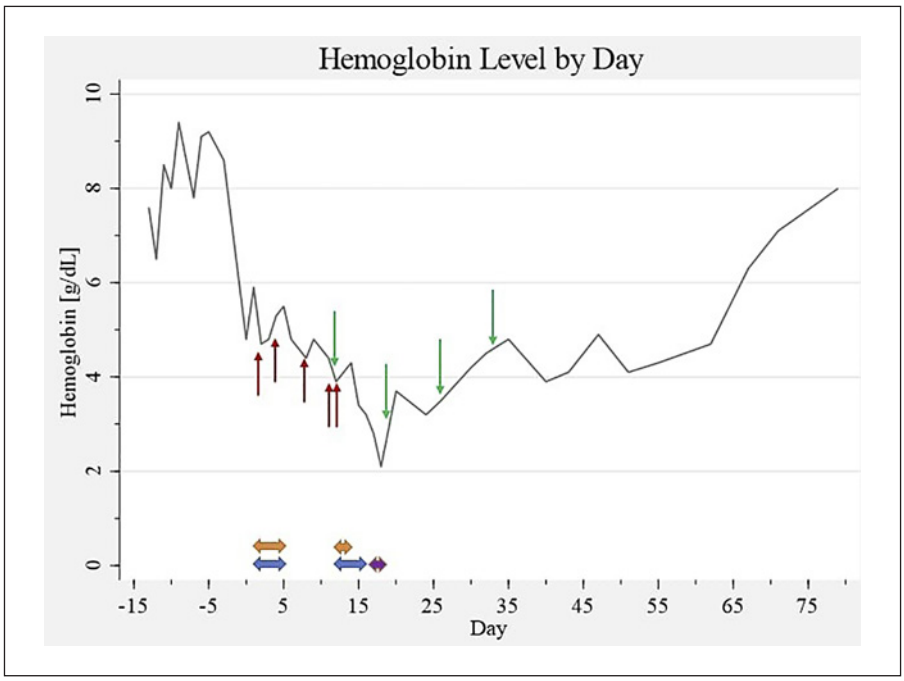

Fig. 1. Haemoglobin levels of the case throughout the course of the disease.

Discussion/Conclusion

HHS is a type of delayed haemolytic transfusion reaction characterized by brisk intravascular haemolysis. Complement activation may be incriminated via the activation of the classic pathway by the alloantibodies and the alternative pathway by free heme leading to endothelial dysfunction. This in turn plays an important role in the evolution of multi-organ dysfunction syndrome [10]. However, suppressed erythropoiesis as evidenced by concomitant reticulocytopenia and macrophage activation as demonstrated by hyperferritinaemia were all key players contributing to the disease process [3].

Tocilizumab is an interleukin-6 receptor monoclonal antibody that has the capacity to reduce IL-6 pro-inflammatory response and to reduce the macrophage activation. There are three previous reports of using tocilizumab in managing HHS [3, 4]. The first has used a 4-day regimen in reference to the dose used to combat the cytokine release syndrome after the administration of CAR T-cell therapy [4], whereas the second one used 2 days of tocilizumab 8 mg/kg/day [3]. The third case used only a single infusion of tocilizumab 8 mg/kg [17].

Given the success of the second 2-day regimen [3], to control the disease, and that our patient has been receiving rituximab, with heightened concerns about intense immunosuppression and infection risk, and the fact that our patient presented before the publishing of the third case confirming the efficiency of a single day regimen, we opt to the dose adopted by Sivapalaratnam et al. [3].

There are prior reports of the use of eculizumab with rituximab in managing HHS [18]. Our case is the second case examining the combination of tocilizumab with rituximab in such a clinical scenario. However, we examined the efficiency of combined rituximab and tocilizumab, whereas Hair et al. [17] combined tocilizumab with eculizumab and rituximab in a way that makes it difficult to conclude whether response is attributable to eculizumab or tocilizumab or their synergy.

The safety of combined rituximab and tocilizumab was tested before in a cohort of 79 autoimmune encephalitis patients dissected into three subgroups. The third subgroup, given IVIG combined with rituximab and tocilizumab, exhibited better clinical efficacy outcome without safety concerns as compared to other two subgroups [19].

The patient tolerated tocilizumab well with no discernible infusion reactions. Though her haemoglobin has been creeping up very slowly over a 2-month period, she manifested stabilization of her haemoglobin level after the administration of tocilizumab. Part of her slow response was attributable to central venous catheter infection complicating her hospital stay which delayed her haemoglobin recovery. Once the infection got under control, she experienced a rapid rise in her haemoglobin from day 62 onwards.

Unlike the case of Lee et al. [4], that received both tocilizumab with haemoglobin glutamer, an RBC substitute, who suffered mild transient thrombocytopenia [20], our case had mild to moderate thrombocytopenia before the administration of tocilizumab attributable to dissem-

inated intravascular coagulopathy. It progressed from day 7 to day 21 following tocilizumab use followed by recovery. We cannot consider tocilizumab as the incriminated agent in the evolution of thrombocytopenia as it has a multifactorial aetiology. Our case corroborates the low-grade evidence obtained by the three prior cases published by Lee et al. [4], Sivapalaratnam et al. [3], and Hair et al. [17]. Tocilizumab should be considered as a plausible therapeutic option that can bring about comparable results to eculizumab. Eculizumab has been mentioned as a conditional recommendation to manage sickle cell anaemia patients suffering HHS by the American Society of Haematology. It is also issued in the British Clinical Commissioning policy to manage HHS [21]. However, there are major concerns about its availability, safety, and clinical staff expertise, especially in developing world. That is why tocilizumab may represent a less expensive option, readily available medication with wider experience among clinicians, especially in resource-limited settings.

Statement of Ethics

At our institution, ethical committee approval is not required for case reports. An informed written consent was obtained from the patient to display her clinical and laboratory data.

Conflict of Interest Statement

Authors have no personal or financial conflicts of interest to disclose.

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Nil.

Author Contributions

Amal M. El-Afifi supervised and advised the medical treatment, advised the investigations, and revised the manuscript. Alia M. Saeed shared in treatment decisions, following the treatment plans, collecting and processing data, and wrote the final version of the manuscript. Gehad H. Fekry advised the follow-up plans and shared in following up the progress of the clinical condition and in collecting data. Mariam A. Mostafa was one of the treating frontline physicians, drafted the primary manuscript, shared in collecting and processing data. Reham A. Elmetwally, Inas M. Hamed, Aliaa N. Hussein, and Gomaa M. Hasanien were the treating physicians who implemented the treatment and followed-up the patient on the front line along the course of admission. Moreover, they shared in collecting data.

Data Availability Statement

Data are available upon request. They are not openly available on a repository for confidentiality as they pertain to a certain patient and not to a study.

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