Severe breakthrough hemolysis during compassionate use of Pegcetacoplan in paroxysmal nocturnal hemoglobinuria: managing an emergency

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INTRODUCTION

Pegcetacoplan is a pegylated pentadecapeptide-binding activated complement component 3b (C3b) which controls C3b-mediated extravascular hemolysis and terminal complement-mediated intravascular hemolysis[1]. In Italy, Pegcetacoplan was approved in October 2022 for patients affected by paroxysmal nocturnal hemoglobinuria (PNH) with persistent anemia after at least three months of C5 inhibitor treatment. A consistent gain in hemoglobin level has been reported with the use of Pegcetacoplan as compared with Eculizumab, together with a better FACIT fatigue score[2]. However, breakthrough hemolysis (BTH) of the large PNH red cell population is of concern for patients, due to the potential severity of hemolysis in PNH patients treated with proximal inhibitors[3-5]. Recently, Griffin and colleagues[6] reported 7 cases of breakthrough hemolysis in 3 patients treated with Pegcetacoplan for compassionate use. All but one patient needed single or multiple doses of Eculizumab to resolve BTH.

CASE REPORT

Here we report the case of a 32-year old woman diagnosed with PNH in October 2018 in a small hospital in the Region of Lazio, Central Italy. Eculizumab was started in January 2019, and complete hemolysis control was achieved; however, after a few months, a progressive trilinear cytopenia with transfusion requirement was documented. In July 2019, a diagnosis of severe aplastic anemia (SAA) in PNH was made. In the absence of a suitable donor, the patient was successfully treated with Cyclosporine-A, rabbit anti-thymocyte globulin, and Eltrombopag. In September 2021, the patient showed a flare of intravascular hemolysis due to PNH red cells (hemoglobin [Hb] 8.5 g/dL, lactate dehydrogenase [LDH] 600 Ul/L [n.v.<200], bilirubin 2.1 mg/dL), and Eculizumab treatment was restarted. After this, Eculizumab 900 mg every 14 days was consistently unable to control hemolysis, and, despite reticulocytosis, the patient gradually needed transfusion support and intervals between drug administration had to be reduced (900 mg every 12 days). In February 2022, the patient was referred to our center for alternative treatment.

Laboratory tests were as follows: 98.8% of PNH granulocytes and 67% of PNH red cells (PNH red cell count is to be considered underestimated because of recent transfusion), white blood count (WBC) 1.19×10^9/L, Hb 7.5 g/dL, MCV 114.8 fL, reticulocytes 319×10^9/L, platelets 130×10^9/L, LDH 1184 Ul/L (n.v. <250), haptoglobin 7 mg/dL (n.v. 45-320), negative direct antiglobulin test. The patient reported symptoms of asthenia and abdominal pain. C3-inhibitor Pegcetacoplan was requested and obtained under the terms of dedicated compassionate use in force in Italy. In the meantime, the patient was vaccinated

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against pneumococcus (13- and 23-strains), *Haemophilus* influenza B, and meningococcus (ACWY and B strains). Anti-thrombotic prophylaxis with low molecular weight heparin was also added. In May 2022, subcutaneous Pegcetacoplan was started at the dose of 1,080 mg twice a week, while Eculizumab was maintained for the first 4 weeks. One month later, laboratory tests notably improved: Hb 13.9 g/dL, MCV 107.9 fL, reticulocytes 48×10⁹/L, LDH 222 Ul/L, haptoglobin 84.9 mg/dL. The patient was taught to self-administer Pegcetacoplan and she was able to continue treatment at home within two months. The patient had rapidly obtained an increase of more than 6 g in Hb levels, with complete hemolysis control, and no drug-related side effects.

At the beginning of September 2022, the patient developed nausea and vomiting; values at the last check up had been Hb 13.3 g/dL, LDH 240 UI/L. At first access to the nearest Emergency Department, she was managed only for her symptoms and was discharged without laboratory testing. Twenty-four hours later, the patient went back to the Emergency Department for abdominal cramps, and persistent vomiting and diarrhea. Computed tomography with contrast showed a thickening of the cecum wall with edema of peri-cecal adipose tissues. Laboratory tests showed severe hemolysis with Hb 7 g/dL, LDH 2,552 UI/L, creatinine 8 mg/dL (n.v. <1.2), and negative direct antiglobulin test. The patient was promptly transferred to our department for severe (BTH) management. On admission, the patient had diarrhea, pain in her left inferior abdominal quadrant, and oliguria without fever or neutrophil leukocytosis. Metronidazole and ceftriaxone were added together with heparin calcium. The administration schedule for Pegcetacoplan was modified to 1,080 mg every 3 days, with transfusion support as required. Urine, blood and stool culture were negative. The patient rapidly became anuric, needing daily hemodialysis and fluid restriction. Ultrasound examination revealed enlarged kidneys with inhomogeneous echostructure, hypoechoic appearance of pyramids, and increased cortical echogenicity. The study of intraparenchymal tracers documented a slight increase in resistance, especially on the left side. The patient required two weeks of hemodialysis before recovering spontaneous renal function. Similarly, hemolysis control was regained with an increase in hemoglobin level (**Figure 1**). Four days later, a sudden flare of hemolysis occurred, and it was considered useful to add anti-C5 inhibitor Eculizumab at the dose of 900 mg, obtaining a partial response. The most probable cause of BTH was an inflammatory cecum colitis. The resolution of the abdominal trigger was confirmed with magnetic resonance imaging. A second dose of Eculizumab was administered after 14 days, resulting in a further

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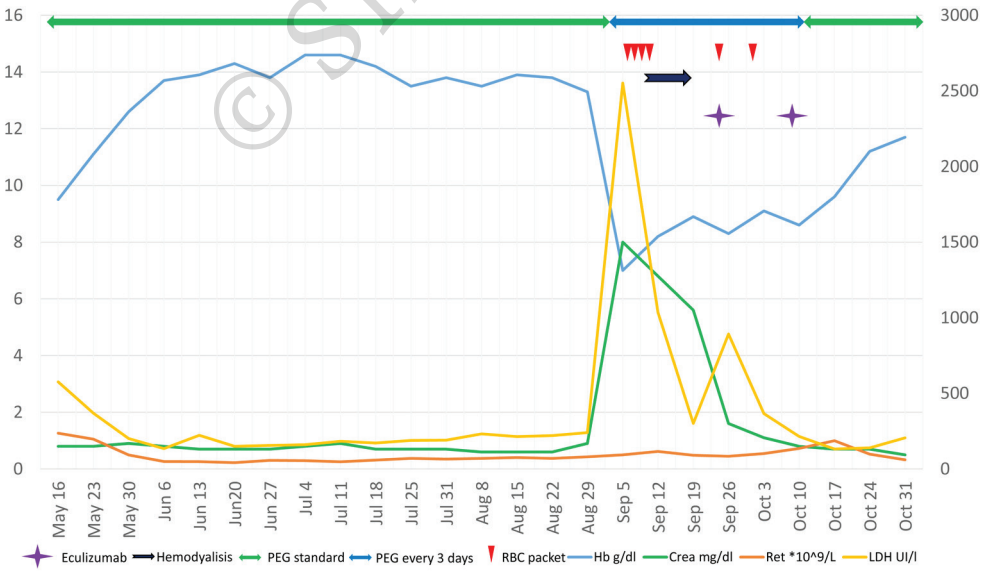


Figure 1 - Trend of laboratory examinations since the start of Pegcetacoplan and through breakthrough hemolysis
PEG: pegcetacoplan; RBC: red blood cell count; Hb: hemoglobin; Crea: creatinine; Ret: reticulocytes; LDH: lactate dehydrogenase.

slight reduction in Hb level. The patient was subsequently discharged and returned to the standard schedule of Pegcetacoplan. The patient achieved stable hemolysis control, with an increase in Hb over 11 g/dL. Laboratory values and treatment lines are summarised in **Figure 1**.

DISCUSSION

There has been an increase in the use of proximal complement inhibitors in PNH in patients with suboptimal response to Eculizumab. In the pivotal Pegasus trial, a randomized comparison of Pegcetacoplan to Eculizumab in PNH patients with Hb <10.5 g/dL, the primary endpoint of a change in mean Hb from baseline to week 16 was met[4]. One of the major drawbacks with proximal complement inhibitors is related to the enlarged PNH red cell population increasing vulnerability and amplifying BTH intensity, as elegantly reported in the recent paper from Notaro *et al.*[5], and related complications including kidney failure and/or thrombosis. Notaro *et al.*[5] described why BTH occurring during proximal inhibitor treatment might be more severe and life-threatening than BTH occurring during terminal inhibitor treatment. While in the former case each molecule of C5 convertase derived from incomplete C3 inhibition will result in several molecules of C5, and consequently many copies of MAC, in the latter case, each molecule of C5 that escapes inhibition will form one copy of MAC. Therefore, an enlarged PNH red cell population together with amplified enzymatic cascade could be responsible for more severe BTH during C3-inhibitor therapy.

Managing patients with BTH on proximal complement inhibitors is challenging and requires strict follow up, particularly if these drugs are self-administered. No guidelines on the treatment of BTH in such patients are currently available. However, from the experience of Griffin *et al.*[6], both shortening the interval between doses or intravenous administration of Pegcetacoplan and Eculizumab pulses if life-threatening conditions are present should be promptly adopted, as in our case. In conclusion, severe BTH on proximal complement inhibitors requires prompt diagnosis and treatment to avoid potentially life-threatening events.

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ETHICAL CONSIDERATION

The study was conducted according to the principles of the Declaration of Helsinki for medical research involving human subjects and was approved by the Ethics Committee of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome (Protocol number 0045489/21). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from the patient for study participation and data publication.

AUTHORS' CONTRIBUTIONS

EM and SS performed the research. SS and PC designed the research study. EM, SS, MAL, AC, LP, PC and SG managed patients during different phases of treatment. EM and SS managed patients before and during cell therapy treatment. SB provide laboratory assays for PNH diagnosis and follow-up. EM and SS analyzed the data. EM and SS wrote the paper. All Authors revised and approved the final version of this manuscript.

DISCLOSURE OF CONFLICTS OF INTEREST

EM and SS received congress support, honoraria for presentation and speakers fees, and participated on Advisory Boards sponsored by Sobi and Alexion. The remaining Authors have no competing financial interests to disclose.

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