Cardiopulmonary bypass in a patient with classic paroxysmal nocturnal hemoglobinuria during treatment with eculizumab

INTRODUCTION
Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease characterized by chronic intravascular hemolysis and a highly increased risk for thrombosis. A mutation of the PIG-A gene in a hematopoietic stem cell results in deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins at the cell membrane of all its progeny. Without protective GPI-anchored proteins these cells are vulnerable to complement-mediated lysis. Surgery, and particularly open heart surgery, has a high risk of complications in patients with PNH. First, major complement activation by both the surgical procedure itself and cardiopulmonary bypass (CPB) can elicit a hemolytic crisis. Second, CPB causes excessive thrombin generation and further increases thrombotic risk. Lastly, patients with PNH frequently have bone marrow failure, increasing the risk of infections and bleeding.

ECULIZUMAB
Eculizumab, a monoclonal antibody to complement factor C5, effectively blocks intravascular hemolysis and reduces the risk of PNH-related thrombosis. Eculizumab at levels above 35 ug/ml prevents hemolysis, but dosages required to maintain adequate levels during excessive complement activation as in surgery are unknown. Moreover, complement activation, bleeding, and hemodilution may easily render peroperative eculizumab levels insufficient. This implies a risk of massive lysis of the increased number of GPI-deficient erythrocytes during treatment with eculizumab. Therefore, strategies to minimize additional complement activation and to maintain adequate complement blockade are extremely important in eculizumab-treated patients with PNH requiring surgery and CPB. Strategies minimizing the risk of hemolysis include leukocyte-depleted red blood cell (RBC) transfusions to reduce the percentage of GPI-deficient erythrocytes, and avoiding complement-containing blood products, such as fresh frozen plasma and albumin.

CASE REPORT
Here, we report on a seventy-yr-old PNH patient undergoing aortic valve replacement surgery during maintenance treatment with eculizumab. PNH granulocyte and erythrocyte clone sizes at that time were 95% and 70%, respectively. Medical history included hypertension, diabetes mellitus type II, moderate renal insufficiency, secondary hemochromatosis, and stable minimal angina pectoris. After an earlier cholecystectomy for acute cholecystitis, patient suffered from recurrent episodes of enterococcal bacteriaemia. Cardiac ultrasound showed aortic valve lesions suggestive of endocarditis aortic valve insufficiency (grade II) and stenosis (peak gradient 70 mmHg, valve area 0.9 cm²). Intravenous antibiotic treatment was initiated, and aortic valve replacement surgery was performed. Surgery was scheduled 1 day after his regular eculizumab infusion. Two units of RBC were given to dilute the number of GPI-deficient erythrocytes. To reduce complement activation by blood–air contact, a minimized physio-coated (Sorin, Milano, Italy) CPB circuit was assembled. Priming of the extracorporeal circuit included 2500 IU of heparin, 500 mg tranexamic acid, 40 mg dexamethasone; 1500 mg cefuroxime antibiotic prophylaxis, 10 mg dexamethasone and 1000 mg tranexamic acid, followed by 400 mg/h to prevent fibrinolysis, were ad-
ministered. The coated minimized CPB circuit allowed reduction of the amount of heparin to 30% prior to cannulation. Thereby, we aimed to restore coagulation by metabolization of heparin without using protamine, which causes classical pathway complement activation upon complex formation with heparin.

Four units of RBC were given peroperatively to compensate for blood loss. An aortic valve bioprosthesis (Perimount; Carpentier-Edwards, Irvine, CA, USA) was placed. Additionally, half a dose of eculizumab was infused after closure of the heart. Despite sufficient decrease in the activated clotting time 1 h after closure, prolonged bleeding necessitated multiple RBC and thromocyte transfusions. Bleeding finally ceased upon prothrombin complex (80 mL) administration, which was initially avoided because of potential contamination with complement proteins. Subsequently, the bioprosthesis turned out to obstruct an aberrantly localized right coronary artery (RCA) ostium, urging RCA bypass grafting that was performed on a beating heart. Heparin was given, which, after the bypass procedure, was antagonized with protamine, as most GPI-deficient erythrocytes were believed to be replaced by the RBC transfusions. As expected, complement was clearly activated during surgery, but undetectable terminal complement complex levels confirmed complete C5 blockade by eculizumab peri-operatively. Intravascular hemolysis was not significant, as LDH and bilirubin levels remained unchanged. To measure coagulation activation, levels of D-dimer and procoagulant microparticles were determined at various time points peri-operatively.

Table 1. Laboratory parameters before, during and after open heart surgery. Various parameters during the surgical procedures. AoX=crossclamp time, CPB=cardiopulmonary bypass time, ACT=Activated Clotting Time (sec), Ht=Patient hematocrit (%), Glu=blood glucose level (mmol), pH=blood pH, Lac=blood lactate level (mmol).

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<td>4.4</td>
<td>5.4</td>
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Figure 1. Various parameters during the surgical procedures. AoX=crossclamp time, CPB=cardiopulmonary bypass time, ACT=Activated Clotting Time (sec), Ht=Patient hematocrit (%), Glu=blood glucose level (mmol), pH=blood pH, Lac=blood lactate level (mmol).
though microparticle concentration rose slightly after initiating CPB, low D-dimer levels peri-operatively were not indicative for major coagulation activation. Serum eculizumab levels preoperatively and 2 day postoperatively proved adequate (234 and 76 µg/mL, respectively). The normal dosing regimen for this patient (1200 mg biweekly) was resumed 2 day postoperatively. He was discharged after 12 day and had an uneventful recovery without hemoglobinuria or thrombosis.

To avoid using protamine with subsequent complement activation we considered alternative methods for anticoagulation than heparinization. However, heparin was chosen over other anticoagulants because of its short half life. Other anticoagulants have longer half lives and cannot be antagonized. The coated minimal extracorporeal circuit allowed reduction of the amount of heparin to 30% prior to cannulation, lowering the time needed to restore coagulation. Heparin levels decreased through metabolization, nonetheless resulting in prolonged bleeding following aortic valve replacement, and necessitated administration of blood products and eventually prothrombin complex. Protamine has been used previously without causing excessive hemolysis in cases of CPB in untreated PNH patients\(^5,6\). However, in these patients PNH granulocyte and erythrocyte clone size was smaller. In retrospect, the blood products administered to our patient may have activated complement more. Nonetheless, this case demonstrates that adequate complement blockade by perioperative eculizumab administration and the strategies applied for minimizing procedure-related complement activation contributed to a successful outcome.

REFERENCES