Efficacy and safety of Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (PNH) after 15 years steroids treatment: A case report description

Endri Mauro ∗,1 and Filippo Gherlinzoni ∗

Department of Internal Medicine, Division of Hematology, Hospital of Treviso, Treviso, Italy.

ABSTRACT Background: Paroxysmal Nocturnal Hemoglobinuria (PNH) pathogenesis is due to acquired lack of glycosylphosphatidylinositol-anchored protein complement regulatory proteins (CD55 and CD59) and intra-extravascular hemolysis. Eculizumab is a monoclonal antibody binding complement protein 5 (C5 receptor CD59), blocking complement upstream and reducing hemolysis. Case Summary: In 1999, we diagnosed PNH in a male 54-year-old. Therapy with prednisone and blood transfusions started. After 13 years (2012) of continuative steroid, we started eculizumab every 14 days. Clinical and laboratory improvement has been reported, and the prednisone therapy has been tapered; no further hemolytic crises reappeared. However, mild anaemia, high reticulocytes count, high LDH serum levels are still reported. Actually, despite to suboptimal response, the patient shows a good quality of life. Conclusion: Here we report a case of PNH with a fully documented medical history of long-term steroid therapy confirming efficacy and safety of eculizumab. However “C3 tick over” effect may induce suboptimal clinical results with residual hemolytic activity also on heavy steroid-treated patients.

KEYWORDS Paroxysmal Nocturnal Hemoglobinuria, eculizumab, steroids

Introduction

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a clonal hematopoietic stem cell disorder due to acquired lack of glycosylphosphatidylinositol-anchored protein complement regulatory proteins (CD55 and CD59) [1]. Therefore PNH red blood cells are more exposed to complement upstream, in particular to membrane attack complex (MAC), resulting in chronic intra-extravascular hemolysis with exacerbations [1]. The consequent haemoglobin release leads anaemia, thrombosis, dysphagia, abdominal pain, pulmonary hypertension and renal impairment [2,3]. Until recent years, the treatment was only based on immune suppressors (steroids) and transfusions to manage hemolytic crises. During long term of corticosteroids therapy adverse events have to be considered as such as Cushing’s syndrome, diabetes mellitus, osteoporosis, thrombosis and infections. On other hand bone marrow transplantation is associated with high risk of morbidities and mortality [3]. From 2007 Eculizumab, a humanized monoclonal antibody that blocks terminal complement binding to C5 has been approved for PNH [4] changing the clinical course of these patients dramatically. Although the efficacy and safety of eculizumab have been reported [5], few data are available in heavily treated patients with steroids and transfusions [6,7]. Here we discuss a case report of PNH treated with eculizumab after long-term steroid therapy and supportive care.

Case report

In November 1999 a 54-year-old male came to our attention because of anaemia, leucopenia, dark coloured urine (just reported in medical history from one year), jaundice. Physical examination findings were unremarkable, abdominal ultrasound was normal. Main laboratory tests showed White Blood Cells
Table 1: Changes in Haemoglobin, White Blood Cells and Lactate Dehydrogenase during therapy. Legend: HGB haemoglobin, WBC White Blood Cells, LDH Lactate Dehydrogenase (normal range 100-204 U/L), *start eculizumab every ten days, **end eculizumab every ten days, SC serum creatinine.

<table>
<thead>
<tr>
<th>Start therapy (May 2012)</th>
<th>Month</th>
<th>Months</th>
<th>Months</th>
<th>Months</th>
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<tr>
<td>HGB (g/dL)</td>
<td>107</td>
<td>99</td>
<td>113</td>
<td>121</td>
<td>124</td>
<td>124</td>
<td>124</td>
<td>124</td>
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<td>LDH (U/L)</td>
<td>217</td>
<td>335</td>
<td>237</td>
<td>237</td>
<td>237</td>
<td>284</td>
<td>277</td>
<td>150</td>
<td>200</td>
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<tr>
<td>WBC (10^9/L)</td>
<td>3.85</td>
<td>2.01</td>
<td>4.16</td>
<td>2.56</td>
<td>2.51</td>
<td>2.59</td>
<td>2.53</td>
<td>2.78</td>
<td>2.65</td>
<td>2.12</td>
<td>2.36</td>
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<tr>
<td>SC (mg/dL)</td>
<td>1</td>
<td>0.6</td>
<td>0.4</td>
<td>0.89</td>
<td>0.62</td>
<td>0.45</td>
<td>0.78</td>
<td>0.87</td>
<td>0.97</td>
<td>0.80</td>
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</table>

4.25x10^9/L, Hemoglobin 8.4 g/dL, Platelets 226x10^9/L, lactate dehydrogenase (LDH) 935 U/L, Coombs tests negatives, Haptoglobin 7 mg/dL, total bilirubin 2.6 mg/dL, transaminases in normal range. Diagnosis of PNH was confirmed by Ham test and bone marrow trephine. Immediately after diagnosis, the patient started steroid (prednisone) with dosage adjustment during hemolytic crises and received intermittent treatment with blood transfusions. During the period from 1999 to 2012 the patient experienced multiple severe hemolytic crises, thrombosis of portal and splenic veins, diabetes mellitus, infectious episodes and sepsis, blood transfusions were required intermittently for symptoms of anaemia and fatigue. In May 2012, after 13 years of continuous modulated treatment with steroids (we calculated a total of 72845 mg of administered prednisone), we started eculizumab according to dose and prevaccinations as per manufacturer’s instructions. The laboratory data just before eculizumab therapy showed White Blood Cells 3.95x10^9/L (Neutrophils 2.04x10^9/L), Hemoglobin 10.7 g/dL (in transfusion regimen), reticulocytes 109.7x10^9/L (2.6%), platelets 132x10^9/L, LDH 917 U/L, total bilirubin 1.9 mg/dL, haptoglobin 7 mg/dL, ferritin 15 ng/mL (see table 1); bone marrow flow-cytometry revealed PNH clone size 97% in neutrophils, 97% in monocytes and 50% in erythrocytes. Soon after starting treatment with eculizumab, dramatic clinical and laboratory improvement has been reported; the prednisone therapy has been tapered; no further hemolytic crises reappeared with stable haemoglobin levels. However, mild anaemia, elevated reticulocytes count, fluctuating LDH serum levels have been still reported (table 1). After three years of treatment with eculizumab, in May 2015 flow-cytometry in bone marrow aspirate showed a PNH-clone size 94% in neutrophils, 90% in monocytes, 45% in erythrocytes, bone marrow trephine did not show malignant cells or myelodysplasia, karyotype was normal. To get optimal response and to contrast the mild anaemia and high serum levels LDH, the range time between doses has been reduced from 14 to 10 days without a considerable improvement of laboratory data (table 1). The patient returned to eculizumab therapy every two weeks showing a good quality of life.

Discussion
PNH pathogenesis is featured by the acquired lack of glycosylphosphatidylinositol-anchored protein complement regulatory proteins (CD55 and CD59) resulting in intravascular hemolysis [8]. Eculizumab is a humanized monoclonal antibody that binds to complement protein 5 (C5), whose receptor is CD59, blocking complement cascade and reducing intravascular hemolysis [5]. In the pre-eculizumab era, the treatment was based on steroids, danazol and supportive care such as blood transfusions [9] but many side effects limited this therapeutic approach in particular Cushing’s syndrome, osteoporosis, infections, diabetes mellitus and secondary hemochromatosis. Today Eculizumab is considered the backbone of treatment not only in patients with new diagnosis but also in previously treated cases with supportive care in long-standing PNH [3-5]. However, in literature, only two cases with fully documented medical history of long term steroid therapy are reported [6, 7]. Therefore the efficacy and safety of eculizumab in this particular set of patients are not well assessed. Röth and colleagues [6] showed a case of 56-year-old male with long-standing PNH...
with steroid therapy for approximately 15 years before treatment with eculizumab; the patient achieved a complete cessation of hemolytic episodes with Hemoglobin increasing and LDH normalization.

On the other hand, Ueda and coworkers [7] reported a case of 27 years old woman treated from October 2002 until August 2011 with steroids (approximately 9 yrs); after treatment with eculizumab the patient achieved the remission of fatigue and the transfusion independence, but hemolytic findings remained. Similarly, our patient is featured by long medical history (17 yrs) and by previous heavy steroid treatment; our patient achieved the transfusion independence but not the complete laboratory remission of hemolysis; in particular LDH levels remained fluctuating up the upper normal level (figure 1), Haptoglobin always low, mild anemia, high levels of reticulocytes. In 2015 Peffault de Latour and co-workers described ex vivo measurements of complement activity in PNH on eculizumab treatment [10]. Briefly, the routine 50% hemolytic complement (CH50) tests the functional activity of the classical and terminal complement pathways. In particular CH50 is related to both LDH serum levels (intravascular hemolysis) and circulating free eculizumab serum levels. Therefore CH50 may be used to track pharmacologic efficacy of complement inhibition. The authors conclude that CH50 would be useful not only in monitoring of complement blockade but also in evaluating the therapeutic effectiveness of eculizumab, consequently modulating the dosage.

In our institution CH50 assay is not available; however persistent high levels of LDH, reticulocytes, the mild anemia induced us to reduce from 14 to 10 days the range time of therapy without a definite improvement of laboratory data. According to literature [3, 11], we think that mild residual anaemia and fluctuating LDH (marker of persistent hemolysis) are related to bad compensation of CD55/CD59 deficiency. In particular the continuous C3d deposition on the PNH red cells is not blocked by eculizumab, perpetuating a mild-moderate intra and extravascular hemolysis with anaemia and elevated reticulocyte count (know as tick over) [3]. To solving this problem, antibody-based anti-C3 strategies are becoming a new therapeutic approach [12]. However efficacy of these new drugs has to be assessed, in particular on residual complement activity resulting from upstream complement components.

Moreover other studies are needed to evaluate safety given that C3 pathway’s inhibition could be associated with a risk of developing severe infection and autoimmune diseases. Recently a phase 3, multicenter open-label study reported the non-inferiority of ravulizumab (a new complement C5 inhibitor administered every eight weeks) to eculizumab in the percentage of patients achieving LDH normalization [13]. Moreover no patient in ravulizumab experienced breakthrough hemolysis compared with 5 patients in the eculizumab group. Considering the administration schedule every 8 weeks, efficacy and safety, ravulizumab could become the more suitable therapy for these patients [13].

Conclusion
To our knowledge, here we described the third case report of PNH with a fully documented medical history of long-term steroid therapy (6, 7). Our data show that tick over effect could induce suboptimal clinical results with residual hemolytic activity on heavy steroid-treated patients. Further studies are warranted to evaluate efficacy and safety of antibodies-based anti-C3 and the new complement C5 inhibitors in patients with suboptimal clinical response.

Conflict of Interest
There are no conflicts of interest to declare by any of the authors of this study.

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