Erythropoietin treatment during complement inhibition with eculizumab in a patient with paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by intravascular hemolysis leading to anemia and other clinical manifestations. Transfusions are often required to support hemoglobin at tolerable levels. A PNH patient with aplastic anemia was treated with the complement inhibitor eculizumab, followed by concurrent treatment with recombinant human erythropoietin (rHuEpo). Eculizumab alone reduced hemolysis, increased PNH red blood cell (RBC) mass, and decreased transfusions. Addition of rHuEpo during eculizumab therapy, enhanced erythropoiesis, further increased PNH RBC mass and hemoglobin levels, and rendered the patient transfusion independent for more than two years. These data show that driving erythropoiesis during eculizumab treatment provided further benefit to a patient with PNH and underlying bone marrow failure.

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Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired genetic disorder resulting from clonal expansion of a hematopoietic stem cell containing a somatic mutation of the PIG-A gene, which results in a deficiency of glycosylphosphatidylinositol (GPI) anchored proteins from the surface of red blood cells (RBCs).[1] Absence of the GPI-anchored terminal complement inhibitor CD59 on RBCs results in an increase in complement-mediated RBC lysis leading to anemia and other clinical manifestations of the disease.[2-5] Currently, no approved therapies effectively reduce intravascular hemolysis in PNH, and patients are often dependent on transfusions to artificially support hemoglobin levels.[2]

Eculizumab is a novel humanized monoclonal antibody directed against the complement protein C5.[6] Eculizumab was previously shown to safely and effectively reduce intravascular hemolysis and transfusion requirements in patients with PNH.[7-9] Herein, we report a case study of a PNH patient with evidence of underlying aplastic anemia who was treated with eculizumab and thereafter received recombinant human erythropoietin (rHuEpo) in an effort to increase PNH RBC production during complement inhibition and thereby further reduce transfusion requirements.

Case report

A 48-year old transfusion-dependent male was diagnosed with aplastic anemia in May 1988 and with PNH in September 1993. He has been transfusion-dependent due to PNH starting in September 1993, requiring transfusions of packed red blood cells (PRBCs) every 4 to 6 weeks. He received eculizumab infusions starting May 22, 2002 and is currently dosed at 900 mg every other week. On November 6, 2002, after 6 months of receiving eculizumab, rHuEpo (NeoRecormon®) therapy was initiated at the following doses: 450 IU/kg/week in 3 divided doses during the first 2 months; 900 IU/kg/week in 3 divided doses during the next 15 months; and 750 IU/kg/week in 3 divided doses until May 3, 2006. At that time he was switched to Aranesp® at a dose of 300 mcg every 2 weeks. The dose was increased to 500 mcg every 2 weeks on 28th June 2006.

Intravascular hemolysis was assessed by measuring levels of the enzyme lactate dehydrogenase (LDH). Levels of erythropoiesis were determined by measuring reticulocyte counts. The PNH RBC count was calculated by multiplying the absolute number of RBCs by the proportion of PNH type III RBCs as assessed by flow cytometry.[10] Hemoglobin levels and PRBC transfusion requirements were also monitored. All assessments have been collected to the present date and results are reported through August 2006.

During the year prior to eculizumab therapy, the mean LDH level was 2,075 IU/L (more than 4 times that of the upper limit of the normal range), the mean hemoglobin level was 10.5 g/dL, and the mean reticulocyte count was 77.5×10^9/L (Table 1). The absolute number of PNH type III RBCs was 1.13×10^{12}/L, and the proportion of these cells constituted less than 50% of the total RBC mass. The patient required 1.8 units of PRBCs per month during the pre-treatment period (Table 1), receiving a

Table 1. Hematological parameters before and after eculizumab and rHuEpo therapies.

	Mean ± SD				
Parameter	*Upon Diagnosis of AA (May 1988)*	*Upon Diagnosis of PNH (Sept 1993)*	*Pre-treatment (1 year)*	*Eculizumab alone (0.5 year)*	*Eculizumab + RHuEPO (3.7 years)*
LDH, IU/L (normal range 150-480)	-	-	2075±1590	456 ± 76	679±146
Hemoglobin, g/dL (normal range 13.5-18.0)	7.5	9.3	10.5±1.5	10.2±0.9	11.4±1.1
Reticulocytes, $\times 10^9$/L (normal range 20-80)	-	-	77.5±10.6	96.4±29.5	205.3±43.6
White Blood Cell Count, $\times 10^9$/L	2.9	3.9	4.47±0.53	3.49±0.50	3.84±0.58
Neutrophil Count, $\times 10^9$/L	0.6	2.2	2.83±0.52	2.02±0.28	2.14±0.33
Platelet Count, $\times 10^9$/L	20	140	113.60±14.53	96.88±8.06	114.40±15.62
PNH Neutrophil Proportions (%)	-	-	99.82*	99.84±0.14	99.84±0.10
PNH Red Cell Proportions (%)	-	-	35.10±10.30	65.95±11.68	87.90±9.23
PNH type III RBCs, $\times 10^{12}$/L†	-	-	1.13±0.31	1.93±0.13	2.52±0.27
Units transfused per month	1.6	2.5	1.8	1.0	0.1

**Single reading; †Calculated as (proportion of PNH type III RBCs) x (total number of RBCs) ÷ 100.*

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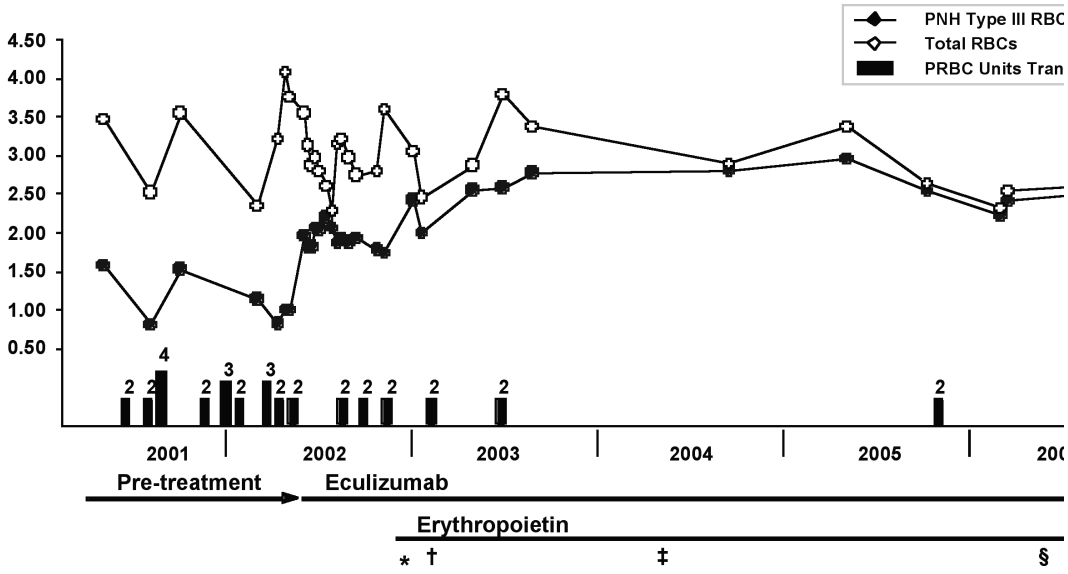

Figure 1. Effect of eculizumab and recombinant human erythropoietin on PNH type III RBC counts and transfusion requirements. The diamonds represent PNH type III RBC counts and solid bars represent the number of PRBC units transfused. The x-axis indicates time in years. Type and dose of erythropoeitin was as follows: *NeoRecormon® at 450 IU/kg/week in 3 divided doses; †NeoRecormon® at 900 IU/kg/week in 3 divided doses; ‡NeoRecormon® at 750 IU/kg/week in 3 divided doses; §Aranesp® at 300 mcg every 2 weeks; ^Aranesp® at 500 mcg every 2 weeks.

total of 9 transfusions and 22 units (Figure 1).

After starting eculizumab treatment, hemolysis was rapidly and consistently reduced as indicated by a 78% decrease in the mean LDH level (Table 1). A concomitant increase (73%) in the PNH type III RBC mass was also demonstrated, supporting enhanced survival of these cells. Further, the average number of transfusions required each month was reduced by 44%. RBC hemoglobin was stable even though transfusion requirement decreased, indicating a net increase in endogenous hemoglobin levels (Table 1).

After 6 months of eculizumab treatment, the patient received concomitant rHuEpo therapy resulting in a mean reticulocyte count increase of 113% (Table 1). This increase in erythropoiesis was associated with an additional 32% increase in the PNH type III RBC mass over that achieved with eculizumab treatment alone. In addition, RBC hemoglobin levels showed an increase from 10.2 g/dL to 11.4 g/dL during the same period. This improvement in anemia resulted in a further decrease in transfusion requirements, eventually leading to transfusion-independence for more than two years (Figure1). This transfusion coincided with a transient decrease in erythropoiesis, as evidenced by a drop in the reticulocyte count (data not shown). There was no evidence of an increase in intravascular hemolysis and LDH levels have remained within the normal range or just above the upper limit of the normal range during the entire treatment period. This patient continues to receive eculizumab and rHuEpo and has received only 1 transfusion in more than 3 years.

In patients with PNH, transfusions are often required to help maintain tolerable RBC hemoglobin. However, the level of hemoglobin in these patients is not only a function of RBC transfusions but also the underlying bone marrow dysfunction and the reduced survival of the complement-sensitive PNH RBC. Attempts to drive erythropoiesis have not generally been successful as a treatment for anemia in PNH patients. Although some patients respond vigorously to erythropoietin administration, this does not translate into a sustainable increase in the endogenous RBC mass as the PNH type III RBC is destroyed by the unopposed activation of terminal complement. In addition, increasing the PNH RBC mass in a setting where these cells are vulnerable to destruction may lead to exacerbation of the disease as intravascular hemolysis is central to the morbidities of PNH.[11]

Eculizumab, a recombinant humanized monoclonal antibody has been shown to reduce chronic intravascular hemolysis, increase PNH RBC survival, improve patient quality of life, and reduce the need for transfusion in patients with PNH.[7-9] In the recent pivotal phase 3 trial, of 43 patients on eculizumab for up to 26 weeks, the reduction in transfusions was sustained in all patients, with 51% maintaining transfusion independence.[7]

We hypothesized that reduction of intravascular hemolysis during eculizumab treatment combined with enhanced erythropoiesis should result in a net increase in PNH RBC mass and higher endogenous hemoglobin levels, thereby further reducing the need for transfusion in patients who were not rendered transfusion independent by eculizumab alone. PNH patients with clear clinical evidence of underlying bone marrow failure, and reticulocyte counts that are either low, normal or only marginally elevated, are likely the best candidates to respond to erythropoietin therapy and therefore benefit in a setting where the PNH RBC is protected. Endogenous serum erythropoietin levels may also be a valuable indicator of those more likely to respond to rHuEpo

therapy although they were not measured in this patient.[12] However, in a meta-analysis by Littlewood *et al*, it was found that 55% of patients with erythropoietin levels >100 mU/mL still responded to rHuEpo by 8 weeks, and even 42% of patients with baseline erythropoietin levels >500 mU/mL ultimately responded;[13] although this study was performed on patients with cancer-associated anemia and may not be directly comparable to patients with AA.

Results of this case study involving a PNH patient with aplastic anemia, demonstrate that control of intravascular hemolysis with eculizumab while driving erythropoiesis further improves anemia by increasing the endogenous PNH RBC mass, thereby reducing and/or eliminating the need for transfusion support.

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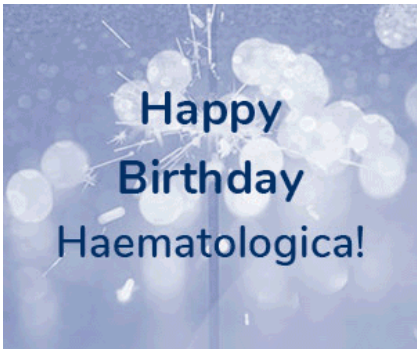

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