

## Improvement in the symptoms of smooth muscle dystonia during eculizumab therapy in paroxysmal nocturnal hemoglobinuria

**Aberrant smooth muscle dystonia during hemolytic episodes in paroxysmal nocturnal hemoglobinuria (PNH) is implicated in the symptoms of abdominal pain, dysphagia and erectile dysfunction. Here we report two PNH patients treated with the complement inhibitor, eculizumab. Complement inhibition has been sustained for over 2 years and results in resolution of intravascular hemolysis and amelioration of symptoms associated with smooth muscle contractions.**

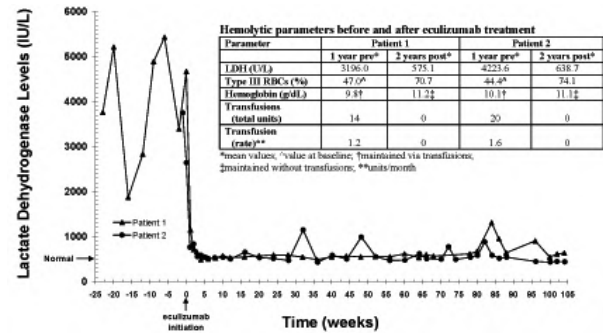
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Paroxysmal nocturnal hemoglobinuria (PNH) is a hematopoietic stem cell disorder that renders affected red blood cells sensitive to complement-mediated lysis resulting in the release of hemoglobin. During severe bouts of hemolysis (paroxysms), hemoglobin (Hb) can saturate biochemical systems in place to remove it, resulting in hemoglobinuria. Hemolysis has more recently been linked to smooth muscle dystonia including abdominal pain, dysphagia and erectile dysfunction (Rother *et al*, 2005). Gastrointestinal dystonia including abdominal pain and dysphagia are experienced by approximately 25-35% of PNH patients during a paroxysm and episodes generally resolve when the paroxysm abates. In addition, erectile dysfunction (ED) occurs in PNH males at a frequency of at least 35% and is also closely linked to paroxysms (Moyo *et al*, 2004), although ED can persist past the paroxysm and may become permanent. Abdominal pain, dysphagia and ED occur almost exclusively in patients with large PNH clone sizes and therefore high hemolytic rates (Moyo *et al*, 2004; Rosse, 2000). It has been proposed that these symptoms are associated with the excessive release of hemoglobin from the red blood cells (Rother *et al*, 2005).

Recently, we reported the results of a clinical study designed to investigate the effects of eculizumab, a functionally blocking monoclonal antibody targeting the complement component C5, on hemolysis and transfusion requirement in PNH patients (Hillmen *et al*, 2004). This study demonstrated a dramatic and sustained reduction in the biochemical and clinical parameters of hemolysis with a concomitant reduction in transfusion requirement. Here we describe the effect of controlling intravascular hemolysis on symptoms of smooth muscle dystonia in two PNH patients (patients 010-003 and 010-007 from Table 1, Hillmen *et al*, 2004). Both patients suffered with abdominal pain and severe dysphagia during paroxysms, and one patient reported persistent ED prior to eculizumab treatment.

### Case Reports

Patient 1 (female, 27 years) was diagnosed with aplastic anemia in 1995 and treated with anti-lymphocyte globulin (ALG) and ciclosporin until 1996, at which time she developed renal toxicity and therapy was discontinued. The diagnosis of PNH was made in 1998 and the patient has been transfusion-dependent since that time, receiving approximately 1-2 units/month. Prophylactic warfarin therapy to prevent thrombosis was initiated in 1999. During the one year period prior to eculizumab treatment, hematological parameters were as follows: mean LDH 3196.0 IU/L (range, 2642-3750 IU/L), 47.0%



**Figure 1.** Levels of LDH and other hemolytic parameters before and after eculizumab treatment. Curves show levels of LDH in two PNH patients up to 25 weeks before and two years after eculizumab therapy. Initiation of eculizumab is indicated at time 0. The upper limit of the LDH normal range is identified on the y-axis (Normal). Mean values of various hemolytic parameters (LDH, PNH type III redcells (RBCs), hemoglobin and transfusion requirement) during the 1 year period before and 2 year period during eculizumab are depicted in the table inset.

type III PNH RBCs (at baseline), Hb 9.8 g/dL (range, 7.18-11.95 g/dL; level maintained by transfusions), and a total of 14 units of packed red blood cells (PRBC) were given (Figure 1 inset). The frequency of paroxysms with hemolysis related symptoms during the one year period prior to therapy were severe hemoglobinuria (black urine) at least once per month lasting 3-7 days, dysphagia (to solids only) during paroxysms and intermittent occurrences of abdominal pain. The abdominal pain was not clearly associated with paroxysms. The patient also reported extreme fatigue and lethargy during paroxysms and was only able to work for up to 2 weeks following each monthly transfusion.

After starting eculizumab therapy in July 2002, hemolysis rapidly decreased as mean LDH levels fell to 575.1 IU/L (normal range 150-480) (Figure 1), the proportion of PNH type III RBCs increased to 70.7%, the patient immediately became transfusion-independent and the Hb values stabilized at a mean of 11.2 g/dL in absence of transfusions. No episodes of hemoglobinuria, dysphagia or abdominal pain have occurred since starting therapy and the patient has reported feeling *extremely well*. She has now resumed a normal work schedule.

Patient 2 (male, 61 years) was diagnosed with aplastic anemia in 1984 and was transfusion-dependent at that time. He was treated with oxymethalone, danazol and ALG and became transfusion-independent following 1 dose of ALG. In 1987 the patient presented with dark urine and was diagnosed with PNH. He again became transfusion-dependent in 1989, receiving approximately 1-2 units of PRBC per month since that time. The patient was initially treated unsuccessfully with steroids and started prophylactic warfarin therapy in 1990. The 1 year pre-eculizumab hematological parameters were as follows: mean LDH 4223.6 IU/L (range, 1872-6030 IU/L), 44.4% type III PNH RBCs (at baseline), Hb 10.1 g/dL (range, 8.8-11.4g/dL; level maintained by transfusions), and a total of 20 units of PRBC were given (Figure 1 inset). The patient was experiencing paroxysms of hemoglobinuria every month with episodes lasting 3-7 days and severe dysphagia (to solids and liquids) and abdominal pain during the paroxysms. The abdominal pain was reported to be so severe that it prevented the patient from bending down. Extreme lethargy reported by the patient correlated with Hb levels below 10 g/dL. The patient also reported persistent erectile dysfunction,

which worsened during paroxysms, over the past 10 years which was only partially responsive to sildenafil therapy at times. Sildenafil was not administered during eculizumab therapy.

Ecuzumab therapy was initiated in this patient in May 2002, and hemolytic parameters rapidly improved; mean LDH levels fell to 638.7 IU/L, PNH type III RBCs increased to 74.1%, the patient became transfusion-independent, and Hb levels stabilized at 11.1 g/dL in the absence of transfusions. No episodes of paroxysms, dysphagia, abdominal pain or erectile dysfunction have been reported by the patient after starting ecuzumab therapy and he has not received any further transfusions. The patient reports that the change to his life has been dramatic and that he has *not felt this well for 15 years*.

### Discussion

We have previously reported a significant improvement in quality of life (QoL) in PNH patients treated with the terminal complement inhibitor ecuzumab using the EORTC-QLQC30 instrument (Hillmen *et al*, 2004). Improvements were demonstrated in several QoL parameters including global health, physical functioning, emotional functioning, cognitive functioning, fatigue, dyspnea and insomnia. Interestingly, these improvements occurred despite the observation that total hemoglobin levels were unchanged during treatment, most likely due to a reduction in hemolytic rate and transfusion requirements. In the present case report of two PNH patients, we have extended these observations to include clinical improvements in symptoms attributed specifically to hemolysis including hemoglobinuria, abdominal pain, dysphagia and erectile dysfunction. Other patients in the 11 patient ecuzumab trial that reported one or more of these symptoms prior to treatment all responded with dramatic improvements in clinical signs and symptoms (Table 1, Hill *et al*, 2004).

**Table 1. Symptoms pre- and 2 years post-ecuzumab in 11 PNH patients.**

Patient	Pre-Ecuzumab			Post-Ecuzumab		
	Abdominal Pain	Dysphagia	Erectile Dysfunction	Abdominal Pain	Dysphagia	Erectile Dysfunction
010-001	Every 4 - 8 weeks	Every 4 - 8 weeks	Every 4 - 8 weeks	None	None	None
010-002	None	None	--	None	None	--
010-003	Every week	Every week	Every week	None	None	None
010-004	Every 4 - 6 weeks	None	--	None	None	--
010-006	None	None	None	None	None	None
010-007	None	At least every 4 weeks	--	None	None	--
010-008	None	Every 10 weeks	Every 10 weeks	None	Intermittent	
010-009	None	None	None	None	None	None
010-010	Every 4 weeks	Every 4 weeks	None	None	2 episodes * in 2 years	None
011-001	None	None	--	None	None	--
011-003	None	None	--	None	None	--

\*This patient experienced a transient breakthrough in complement blockade with a return of hemolysis and symptoms. Increasing the dosing frequency to 12 days

re-established complete complement blockade and prevented further occurrence of symptoms.

A potential association between excess free plasma hemoglobin and smooth muscle dystonia is supported by clinical studies involving the administration of exogenous hemoglobin. Administration of hemoglobin preparations to normal human subjects results in dose-dependent occurrences of gastrointestinal symptoms including abdominal pain, esophageal spasms and dysphagia (Carmichael *et al*, 2000; Murray *et al*, 1995; Przybelski *et al*, 1996; Savitsky *et al*, 1978; Viele *et al*, 1997). The occurrence of these symptoms may be mediated by the systemic depletion of nitric oxide (NO) by plasma free hemoglobin. Indeed, NO inhibition in healthy human volunteers causes an increase in esophageal peristaltic amplitude and velocity (spasms), and clinical benefit has resulted from the enhancement of NO via inhibition of phosphodiesterase type 5 (PDE5) with sildenafil in patients with esophageal motor disorders (Bortolotti *et al*, 2002; Eherer *et al*, 2002).

Hemoglobin-mediated NO depletion and subsequent smooth muscle contractility have also been implicated in ED associated with PNH (Moyo *et al*, 2004; Rosse, 2000). It has been well established that local NO deficiency is one of the major factors responsible for ED, and drugs such as PDE5 inhibitors that promote the accumulation of NO-induced cGMP have provided dramatic benefit to patients (Corbin *et al*, 2002). Benefit from PDE5 inhibitors in PNH patients is reported by patients to be substantially reduced when macroscopic hemoglobinuria is present. Although it is possible that the stabilization of hemoglobin levels during ecuzumab therapy may contribute to the improvement in ED described in this study, this mechanism has not been previously observed. Therefore the improvement in ED for patients on ecuzumab is most likely due to reduced hemolysis with subsequent reduced NO absorption.

In addition to its role in smooth muscle relaxation, NO has also been shown to be a critical regulator of platelet thrombus formation through inhibition of platelet activation, and NO scavenging by hemoglobin results in platelet aggregation (Olsen *et al*, 1996; Schafer *et al*, 2004). Whether resolution of hemolysis in PNH patients with ecuzumab will prevent this life-threatening complication remains to be determined.

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