

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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## Eculizumab for the Treatment of Paroxysmal Nocturnal Hemoglobinuria

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**H&O** Can you give a short background on the standard of care for paroxysmal nocturnal hemoglobinuria before the advent of eculizumab?

**AH** Until recently, the treatment for paroxysmal nocturnal hemoglobinuria (PNH) was predominantly supportive. Red blood cell (RBC) transfusions were administered when appropriate, and warfarin or other anticoagulation therapy was given following a thrombosis. In the UK we practice primary prophylaxis with anticoagulant therapy depending on the neutrophil PNH clone size. Other therapies, such as corticosteroids or androgen therapy, have also been used, but less commonly and with efficacy in only a few patients; the mechanism of action behind these treatments is unclear. Stem cell transplantation has also been used in the past, but of course this approach is associated with serious complications. It has been difficult to develop an evidence base for treatment because of the heterogeneous nature and rarity of this disease. Before eculizumab (Alexion), treatment for PNH was limited to alleviating symptoms and improving patient quality of life. Eculizumab is a monoclonal antibody that blocks the complement system at protein C5.

**H&O** What is the rationale for the development of eculizumab for the treatment of PNH?

**AH** We know the hemolysis in PNH is complement-mediated, thus this drug should be effective in preventing hemolysis. The pathogenesis of PNH is known to be due to complement sensitivity of RBCs against complement attack. RBCs in PNH have lost their protective proteins

(eg, CD55 and CD59) that would normally prevent complement-mediated lysis. It was hypothesized that if the complement attack on the RBCs could be blocked, the hemolysis in PNH and its associated symptoms could be prevented. Based on patients who have inherited complement deficiencies, it appears that patients with deficiencies in complement proteins C5–C9 suffer few clinical consequences compared to those with deficiencies in the complement proteins before C5. Therefore, C5 seemed to be a logical target for blocking the complement cascade. Eculizumab was developed for the purpose of blocking the complement system safely and without severe complications.

**H&O** Eculizumab has been evaluated for the treatment of rheumatoid arthritis, systemic lupus erythematosus, and other autoimmune conditions. Is there a similarity between these conditions and PNH that spurred investigators to evaluate eculizumab in PNH?

**AH** The research strategy has been to develop therapeutic approaches that block complement activity, which contributes to a variety of disorders. There is some evidence that some components of autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus are complement-mediated. In PNH, however, almost all of the clinical symptoms are due to the uncontrolled activity of complement. Therefore, whereas there are many possible disorders in which complement blockade might have some efficacy, PNH is the disorder in which we had little doubt that eculizumab would be effective.

**H&O** What were some of the initial findings with eculizumab in PNH?

**AH** In May 2002, we began the pilot study of eculizumab in PNH. Patients enrolled had been having regular transfusions, and most exhibited dark urine (a sign of intravascular hemolysis) and severe symptoms of PNH such as difficulty swallowing (dysphagia) and abdominal pain. Men complained of erectile dysfunction. Additionally, they had biochemical parameters indicative of active, ongoing intravascular hemolysis. We found that just 1 infusion of the drug caused a resolution of the

dark urine by the next morning. Other symptoms, such as abdominal pain and difficulty in swallowing, resolved quickly. Of the 6 male patients who had experienced erectile dysfunction, 5 experienced complete resolution of this symptom. The patients felt better quickly and, in terms of biochemical parameters, we found quick improvements in lactate dehydrogenase levels as well.

**H&O** What were the next steps after this initial study?

**AH** The pilot study was initially planned to be 12 weeks in duration, but at the end of the 12 weeks, all patients wanted to continue with eculizumab therapy. The extension phase of the trial commenced and is still continuing with 10 of the 11 patients. Patients have experienced a dramatic improvement in their quality of life and generally prefer 2 weekly infusions of eculizumab rather than their previous treatment, which might have been, for example, 4 weekly blood transfusions. Some patients have become transfusion-independent.

**H&O** What side effects are associated with eculizumab?

**AH** The side effects associated with eculizumab have been very minimal. One patient in the pilot study had a reaction to the initial infusion, consisting of shivering and fever. She required observation only and has tolerated every infusion after that extremely well with no further reactions; she is still on the drug more than 3 years later. No other patients experienced any infusion-related reactions. The only minor side effect has been headache after the first or second infusions in some of the patients, but otherwise toxicity has not been a problem. There is a theoretical risk of meningitis, but this has not been a major issue to date.

**H&O** Is there any sense about whether eculizumab treats all patients equally or are there variations between patients that might change the efficacy of the agent?

**AH** We found that patients who have the classic purely hemolytic PNH respond better to the drug than those who have a hypoplastic bone marrow. The reason for this difference is simply that marrow failure can sometimes contribute more significantly than hemolysis to anemia, in which case, although the hemolysis will be blocked

by eculizumab, marrow failure will most likely still lead to anemia and therefore continuing transfusions will be required. Certainly any patient with classical PNH who is hemolyzing frequently is a good candidate for eculizumab therapy. This agent would also be appropriate for patients with biochemical and clinical evidence of hemolysis because their quality of life can be improved.

**H&O** What is the clinical trial status of eculizumab?

**AH** Two phase III trials opened worldwide in the last year: TRIUMPH and SHEPHERD. The first opened about a year ago and the second opened earlier this year. The trials are now closed to recruitment, and we are eagerly awaiting the results. If the results of this trial are positive, I would expect that applications for product licenses would be made relatively quickly.

**H&O** Does eculizumab appear to have any effect on thrombosis, the most significant morbidity associated with PNH?

**AH** Although at the moment we have no evidence that eculizumab will prevent thrombosis, it is reasonable to hypothesize that thrombosis may be prevented by this terminal complement blockade through its mechanism of action. Theories for the causes of thrombosis in PNH include activation of PNH platelets by complement attack and nitric oxide depletion through free hemoglobin scavenging. Eculizumab should prevent both consequences. This possibility will be very interesting to examine in the future. In the pilot study there was no evidence of thromboses in any of the patients.

**Suggested Reading**

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