

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

## Update on Eculizumab for the Treatment of Paroxysmal Nocturnal Hemoglobinuria

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**H&O** What is known about the mechanism of action of disease in paroxysmal nocturnal hemoglobinuria?

**AH** Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by complement-induced hemolytic anemia, chronic hemolysis, and thrombosis, and is associated with bone marrow failure. The clinical manifestations are attributed to the inability to regulate terminal complement on the surface of cells, particularly red blood cells and platelets. Blood cells in PNH have lost protective proteins, CD55 and CD59, which normally prevent complement-mediated lysis. Previous methods of treatment were simply supportive, including red blood cell transfusions when appropriate. It had been hypothesized that if complement attack of red blood cells could be blocked, then complement-mediated red cell lysis could be prevented. Platelets in PNH also lack CD59 and are therefore activated by complement. If the complement system were blocked, then PNH platelets should also be protected from activation. Eculizumab (Soliris, Alexion), a monoclonal antibody, was developed for this purpose. Eculizumab works by blocking the complement cascade by preventing activation of terminal complement through binding to complement protein C5.

**H&O** What other effects result from blocking activation of terminal complement?

**AH** The human body uses the complement system to destroy foreign organisms, particularly bacteria and some

viral proteins. Although eculizumab prevents terminal complement activation, infections to many pathogens should not be increased because most infections are actually cleared by complement proteins before C5, particularly C3. Eculizumab will therefore not affect the clearance of most bacteria and viruses; however, there is one group of infections that, as a result of eculizumab treatment, can occur more frequently. We know this from patients who have inherited deficiencies of terminal complement proteins C5 through C9, as they have an increased risk of *Neisserial* infection, mainly *Neisseria meningitidis*. Because of this increased, although still small, risk, patients need to be aware and contact their physicians if they develop any symptoms. Vaccination against meningococcal infections is also required.

**H&O** What were the initial findings that led to the introduction of eculizumab for treatment of PNH?

**AH** The initial study, the pilot study, that was conducted in 2002, found that treatment with eculizumab (600 mg/week  $\times$  4 weeks, then 900 mg in the fifth week followed by 900 mg every 2 weeks thereafter) resulted in an immediate reduction in markers of intravascular hemolysis, in particular serum lactate dehydrogenase. The enrolled patients who presented with dark urine found that a single infusion of the drug led to resolution of the dark urine. It was also found that patients who were transfusion-dependent became transfusion-independent, or at the very least had a very significant reduction in the number of transfusions needed. There was also a significant improvement in quality of life and fatigue and a resolution of PNH-associated symptoms, such as dysphagia, abdominal pain, and erectile dysfunction.

**H&O** Were there any side effects associated with eculizumab?

**AH** There were no side effects that would be a cause of major concern. It was noted that some patients experi-

enced headache after their first or second infusion, probably due to the vasodilatation caused by an increase in nitric oxide levels; however, this toxicity was controlled by simple analgesics and resolved with subsequent infusions.

### **H&O** What were the findings of the phase III trials that subsequently evaluated eculizumab?

**AH** The results of the pilot study led to two phase III studies, TRIUMPH and SHEPHERD. Both of the studies recruited hemolytic PNH patients. TRIUMPH was a double-blind, placebo-controlled, randomized study. The study's duration was 6 months, and enrollment criteria included patients who were transfusion-dependent and had a platelet count above  $100 \times 10^9/L$ . This study validated the findings from the pilot study. SHEPHERD, in contrast, was an open-label safety study. The entry criteria were broadened to increase patient enrollment; patients had to have received only a single transfusion in the previous 2 years, with a platelet count above  $30 \times 10^9/L$ . The results of this study confirmed the findings from the pilot and TRIUMPH studies, with reduction in transfusion requirements and in markers of intravascular hemolysis, as well as improvement in quality of life seen across all studies. The improvement in quality of life was a particularly impressive finding, in my opinion. Patients who had received only a single transfusion in the previous 2 years chose to continue in the extension study, receiving drug infusions every 2 weeks, rather than go back to their previous life of only very occasional transfusions, reflecting the significant positive improvement in their quality of life on treatment. Some patients were even able to return to work on a full-time basis.

A prospective evaluation of the risk of thrombosis in all three studies was also performed. Patients were assessed before they started eculizumab and again during treatment. Eculizumab reduced thrombosis risk significantly for patients with PNH. This finding was noteworthy because thrombosis is the major cause of morbidity and mortality in PNH. This reduction in thrombosis rate was found in the overall analysis and also in subgroup analyses looking at patients who were anticoagulated and those who had had a previous thrombosis.

### **H&O** Is there any further research ongoing with eculizumab in the setting of PNH?

**AH** I believe the clinical effectiveness of this drug is well established. Researchers are now trying to assess whether

eculizumab can prevent any of the other complications that are seen in PNH. It remains to be determined definitively whether PNH symptoms are related to nitric oxide consumption, as postulated, and if eculizumab can thus prevent them. These initial studies suggest strongly that this is the case. There is also ongoing research into the ability of eculizumab to prevent and reverse renal impairment in PNH. Additionally, researchers continue to focus on the effectiveness of eculizumab in subgroups of PNH.

### **H&O** Are there any other antibodies that could be researched in this setting?

**AH** At the moment there does not appear to be a need for further therapies in PNH. Unless we see any major problems or complications from this drug in the long term, I do not think there will be any future development of other therapies. Previously, researchers, including ourselves, were studying a compound that replaces CD59, which is missing in PNH, making cells susceptible to complement attack; however, the compound never progressed to human studies.

### **H&O** Is eculizumab's mechanism of action similar in other settings in which it has been evaluated?

**AH** Because eculizumab blocks the complement system, any disease that has clinical manifestations related to complement attack could potentially benefit from eculizumab therapy. Therefore, with this complement attack, eculizumab can possibly help patients with other hematologic diseases, such as atypical hemolytic uremic syndrome and catastrophic antiphospholipid syndrome, as well as rheumatologic disorders, neurologic disorders, and transplant rejection.

### **Suggested Readings**

- Hill A. Eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. *Clin Adv Hematol Oncol*. 2005;3:849-850.
- Schubert J, Hillmen P, Röth A, et al. Eculizumab, a terminal complement inhibitor, improves anaemia in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2008. [E-pub ahead of print]
- Brodsky RA, Young NS, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2008;111:1840-1847.
- Hillmen P, Muus P, Dührsen U, et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2007;110:4123-4128.
- Hill A, Richards SJ, Hillmen P. Recent developments in the understanding and management of paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2007;137:181-192.