

# Eculizumab for paroxysmal nocturnal hemoglobinuria

*First-in-class complement inhibitor enables patients with a rare hemolytic anemia to avoid transfusions*

## What's new, what's important

Eculizumab (Soliris) is the only agent approved by the US Food and Drug Administration (FDA) for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). It is a humanized monoclonal antibody targeting and preventing cleavage of the terminal complement protein C5.

The FDA-approved dose is 600 mg, given as an IV infusion over 30 minutes every 7 days for the first 4 weeks, followed by 900 mg for the fifth dose and then 900 mg every 2 weeks. Improvements in transfusion requirements, the risk of thrombosis, and quality of life were clearly seen in patients who were treated with eculizumab in clinical trials.

Eculizumab can increase the risk of meningococcal infection. Therefore, all patients should receive meningococcal vaccination 2 weeks prior to the administration of eculizumab. In general, it is well tolerated.

Future studies will define the exact role of eculizumab, but at present it represents a promising therapeutic option for patients with PNH.

— Jame Abraham, MD  
Section Editor

**E**culizumab (Soliris) is a humanized monoclonal antibody that targets and prevents cleavage of the terminal complement protein C5.<sup>1</sup> C5 is the first protein of terminal complement assembly and is the juncture at which complement activation pathways converge. Prevention of cleavage of C5 results in inhibition of later complement components and inhibits serum hemolytic activity, whereas earlier components involved in the clearance of microorganisms and immune complexes remain active.

Eculizumab was approved by the US Food and Drug Administration in March 2007 to reduce hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH). PNH is characterized by clonal expansion of red blood cells (RBCs) that lack the ability to inhibit complement-mediated hemolysis, resulting in RBC de-

struction, anemia, and thrombosis.

## Efficacy studies

In an early-phase investigation, 11 patients with PNH received eculizumab for an initial 12 weeks followed by an additional 52-week extension period.<sup>2</sup> Treatment with intravenous (IV) eculizumab at a dose of 900 mg every 12–14 days consistently and completely blocked complement activity in all patients, resulting in a dramatic reduction in hemolysis, as indicated by a dramatic decrease in lactate dehydrogenase (LDH) levels. Benefits included significant reductions in transfusion requirements and the number of days with gross evidence of hemoglobinuria, accompanied by a significant improvement in quality of life.

In a subsequent phase III trial,<sup>3</sup> 87 patients with PNH were randomized to receive placebo or eculizumab, 600

mg IV per week for 4 weeks, 900 mg 1 week later, and then 900 mg every 2 weeks, for a total of 26 weeks of treatment. The primary endpoints of the trial were stabilization of patients' hemoglobin levels and RBC transfusion requirements.

To be eligible for the study, patients had to require a transfusion of RBCs during a pretreatment observation period, the criteria for transfusion being a hemoglobin level < 9 g/dL with symptoms or a hemoglobin level < 7 g/dL with or without symptoms. Hemoglobin level at this time defined the hemoglobin set point that had to be maintained or exceeded to meet the study endpoint of hemoglobin stabilization. Baseline characteristics of the study patients are given in Table 1.

Summary by Matt Stenger, MS; reviewed by Minoo Battiwalla, MD, MS, Roswell Park Cancer Institute, Buffalo, NY.

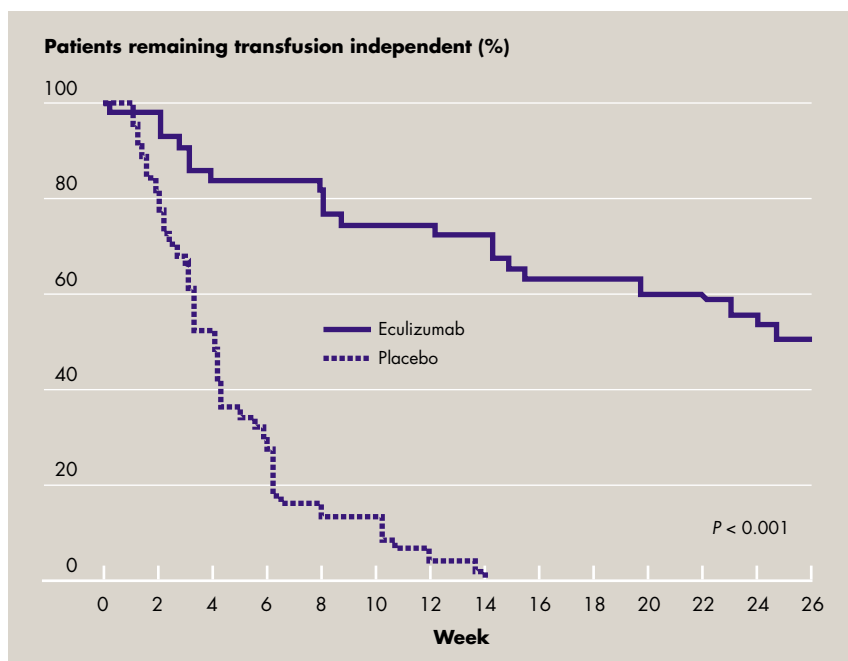
**TABLE 1**

Baseline patient characteristics

	Placebo (n = 44)	Eculizumab (n = 43)
Female/male ratio	29/15	23/20
Median age (range), years	35 (18–78)	41 (20–85)
Median duration of PNH (range), years	9.2 (0.5–38.5)	4.3 (0.9–29.8)
Median reticulocyte count (range), $\mu\text{L}^{-1}$	204,400 (45,400–556,200)	206,600 (40,200–570,400)
History, n (%)		
Aplastic anemia	12 (27)	6 (14)
Myelodysplastic syndrome	0	2 (5)
Thrombosis	8 (18) (11 events)	9 (21) (16 events)
Erythropoietin	0	3 (7)
Cyclosporine	1 (2)	1 (2)
Anticoagulants	11 (25)	21 (49)
Corticosteroid/androgenic steroid use	12 (27)	12 (28)

PNH = paroxysmal nocturnal hemoglobinuria

Adapted from Hillmen et al<sup>3</sup>



**FIGURE 1** Kaplan-Meier estimates of time to first transfusion of packed red blood cells in patients receiving eculizumab versus placebo. Adapted, with permission, from Hillmen et al.<sup>3</sup>

In 42 of 43 patients receiving eculizumab, serum hemolytic activity was completely blocked (as measured by a presensitized erythrocyte hemolytic assay); therapeutic trough levels of the drug were not maintained in the remaining patient.

LDH levels were reduced from a mean of 2,199.7 U/L to 327.3 U/L in the eculizumab group, compared with maintenance of elevated levels in the placebo group (2,258.0 U/L at baseline and 2,418.9 U/L at the end of the study; *P* < 0.001 for

comparison between groups). Patients receiving eculizumab showed an early reduction in LDH levels that was maintained throughout the study.

The reduction in hemolysis with eculizumab was reflected in an increase in the mean level of PNH type III erythrocytes from 28.1% to 56.9%, compared with an absence of change with placebo (35.7% initially to 35.5% at study end; *P* < 0.001). Overall, 21 (49%) of 43 eculizumab-treated patients, versus 0 of the 44 placebo-treated patients, had stable hemoglobin levels (*P* < 0.001; Table 2). Baseline and final mean hemoglobin levels were 10.0 and 10.1 g/dL, respectively, in the eculizumab group and 9.7 and 8.9 g/dL, respectively, in the placebo group (*P* < 0.001). The median numbers of units of packed RBCs transfused per patient during treatment were 0 in the eculizumab group versus 10 in the placebo group (*P* < 0.001). A comparison between the two groups in time to first transfusion is shown in Figure 1.

Quality of life was assessed by the Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue instrument and the 30-item European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30).

During the course of treatment, the eculizumab group had a mean increase (indicating improvement) in the FACIT–Fatigue score of 6.4 points, compared with a decrease of 4.0 points in the placebo group (a change of  $\geq 3$  points is considered clinically significant). Eculizumab-treated patients also showed significant improvements in most items on the EORTC QLQ-C30 (Table 3).

These beneficial effects occurred in the absence of complete resolution of anemia, substantiating the observation that hemolysis itself contributes to reduced quality of life in PNH patients.

**TABLE 2**

## Stabilization of hemoglobin and RBC transfusion requirements

	Before treatment		During treatment	
	Placebo	Eculizumab	Placebo	Eculizumab
Patients with a stabilized hemoglobin level, %	–	–	0	49*
RBC transfusion, units/patient†				
Median	8.5	9.0	10	0*
Interquartile range	7–12.5	6–12	6–16	0–6
Mean	9.7	9.6	11.0	3.0
Total units transfused	417	413	482	131

RBC = red blood cell

\*  $P < 0.001$ 

† Pretreatment values normalized to 6-month equivalents

**TABLE 3**

## EORTC QLQ-C30 outcomes

	Mean change in score		
	Placebo	Eculizumab	P value
Global health status scale (positive change indicates improvement)	–8.5	10.9	< 0.001
Functioning scales (positive change indicates improvement)			
Role	–6.9	17.9	< 0.001
Social	2.0	16.7	0.003
Cognitive	–6.1	7.9	0.002
Physical	–3.5	9.4	< 0.001
Emotional	–3.7	7.5	0.008
Symptom scales (negative change indicates improvement)			
Fatigue	10.0	–16.9	< 0.001
Pain	5.3	–12.3	0.002
Nausea	2.8	–0.4	0.06
Single-item measures (negative change indicates improvement)			
Dyspnea	8.9	–7.9	< 0.001
Loss of appetite	3.3	–10.3	< 0.001
Insomnia	4.9	–7.9	0.01
Financial difficulties	0.0	–10.3	0.19
Constipation	0.0	–6.3	0.20
Diarrhea	5.7	4.8	0.15

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire  
Adapted from Hillmen et al<sup>3</sup>**Safety and tolerability**

No patients died during the study. One patient in the placebo group had a thrombotic event. Eculizumab treatment was generally well toler-

ated. Serious adverse events occurred in four eculizumab-treated patients (there was one case each of exacerbation of PNH, renal colic, lumbar or sacral disk prolapse, and  $\alpha$ -hemolyt-

**TABLE 4**

## Most frequent adverse events

Adverse event	Number (%) of patients	
	Placebo (n = 44)	Eculizumab (n = 43)
Headache	12 (27)	19 (44)
Nasopharyngitis	8 (18)	10 (23)
Upper respiratory tract infection	10 (23)	6 (14)
Back pain	4 (9)	8 (19)
Nausea	5 (11)	7 (16)
Cough	4 (9)	5 (12)
Diarrhea	5 (11)	4 (9)
Arthralgia	5 (11)	3 (7)
Abdominal pain	5 (11)	2 (5)
Dizziness	5 (11)	2 (5)
Vomiting	5 (11)	2 (5)
Fatigue	1 (2)	5 (12)
Viral infection	5 (11)	1 (2)

Adapted from Hillmen et al<sup>3</sup>

ic streptococcal bacteremia) and nine patients receiving placebo (including exacerbation of PNH in three cases and one case each of central-line and urinary tract infection, upper respiratory tract infection, probable viral infection, neutropenia, cellulitis/folliculitis/neutropenia, and anemia/pyrexia). None of these adverse events was considered treatment-related, and all resolved.

The most common adverse events seen in the eculizumab group are shown in Table 4. All 85 patients completing the study elected to receive eculizumab in an open-label extension of the trial.

**References**

1. Thomas TC, Rollins SA, Rother RP, et al. Inhibition of complement activity by humanized anti-C5 antibody and single chain Fv. *Mol Immunol* 1996;33:1389–1401.
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*From the Community Oncologist's Perspective*

## Novel alternative for treating paroxysmal nocturnal hemoglobinuria in selected patients

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**P**aroxysmal nocturnal hemoglobinuria (PNH) is a rare hematologic stem-cell disorder caused by acquired mutations in the *PIGA* gene on the X chromosome that encodes glycosylphosphatidylinositol, a structural anchor for several cell-surface proteins. One of these cell-surface proteins is decay accelerating factor (CD55), which prevents hemolysis by impairing assembly of the complement cascade on the erythrocyte membrane. Red blood cells (RBCs) with the PNH phenotype are susceptible to complement-mediated lysis, the basis of the classic Ham's diagnostic test. Nowadays, PNH is diagnosed by flow cytometry of peripheral blood, which also permits quantification of the size of the PNH clone.

### Clinical presentation

PNH has diverse presentations, including intravascular hemolysis, bone marrow failure, and thrombophilia. Classic PNH presents with episodes of intravascular hemolysis, often accompanied by hemoglobinuria. Hypoplastic PNH is typically associated with a smaller clone size (< 20%) against a background of bone marrow failure. The degree of hemolysis ranges from well compensated to severe. Complicating the picture is a poorly understood tendency to thrombosis, the likelihood approaching 50% for patients with active hemolysis. Thrombosis may catastrophically involve unusual areas, such

as the cerebrovascular, hepatic, or mesenteric circulations. In addition to the symptoms related to hemolysis, thrombosis, or bone marrow failure is a constellation of symptoms related to nitric oxide scavenging by free hemoglobin in the circulation. These symptoms, including esophageal spasm and erectile dysfunction, may significantly impair quality of life.

The intravascular hemolysis in PNH has traditionally been managed with iron and folate supplementation. Transfused RBCs are not deficient in *PIGA* and, therefore, not vulnerable to complement lysis. About 50% of patients respond to corticosteroids. The management of thrombophilia is less clear; clone size and ethnic/geographic factors influence the risk, and there is no consensus on prophylactic anticoagulation. Allogeneic blood or marrow transplant from a matched donor, the only cure, is indicated for patients with PNH who have thrombosis.

### Enter eculizumab

Eculizumab (Soliris), a monoclonal antibody directed against C5, was developed as a terminal complement inhibitor and has been found to reduce hemolysis in PNH patients. Associated benefits have been an improvement in the quality of life and a marked reduction in the frequency of thrombotic events. Eculizumab is the only Food and Drug Administration-approved therapy for PNH and is broadly indicated for patients with

ongoing hemolysis.

Although eculizumab prevents hemolysis, it does not reduce the size of the PNH cell population, and, in fact, the PNH RBC clone is likely to expand. Meningococcal vaccination, though protective against some strains, does not entirely eliminate the possibility of meningococcemia, and, consequently, unexplained fevers in PNH patients should always prompt evaluation. Long-term administration of eculizumab is well tolerated, with no diminution of response due to the development of enhanced immune clearance.

A critical question is identifying which PNH patients should be treated with eculizumab, an orphan drug with significant cost considerations. Although most patients with PNH have some degree of ongoing hemolysis, not all patients are transfusion dependent or even anemic. Selection of patients should be guided by the degree of hemolysis and the risk of thrombosis.

### References

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