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Regulatory Issues: FDA

FDA Report: Eculizumab (Soliris®) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria

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Key Words. Eculizumab • Paroxysmal nocturnal hemoglobinuria • PNH • Drug approval

Disclosure: The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors, planners, independent peer reviewers, or staff managers.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the mechanism of action of eculizumab in PNH.
2. Discuss the efficacy findings upon which the approval of eculizumab was based.
3. Manage the safety concerns surrounding the use of eculizumab for the treatment of patients with PNH.

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ABSTRACT

On March 16, 2007, eculizumab (Soliris®; Alexion Pharmaceuticals, Inc. Cheshire, CT), a humanized monoclonal antibody that binds to the human C5 complement protein, received accelerated approval by the U.S. Food and Drug Administration for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis. Eculizumab was studied in a randomized, double-blind, placebo-controlled clinical trial in 87 RBC transfusion–dependent adult PNH patients and in a supportive single-arm study in 96 patients. The eculizumab dose was 600 mg as a 35-minute i.v. infusion administered weekly for the first 4 weeks followed by 900 mg (week 5) then 900 mg every 14 days thereafter. Hemoglobin stabilized in 21 of 43 (48.8%) eculizumab-treated patients, compared with none of 44 placebo-treated patients. Eculizumab-treated patients required significantly fewer RBC transfusions than placebo-treated patients (median, 0 versus 10 units). There was also a significant reduction in the serum lactate dehydrogenase area under the curve with eculizumab compared with placebo treatment. Results of the phase II supportive study were similar to those of the phase III study. The safety database included 196 adult patients with PNH. Significant findings included the development of human anti-human antibody responses in three patients and serious meningococcal infections in three patients. Patients should undergo meningococcal vaccination at least 2 weeks prior to receiving the first eculizumab treatment and have revaccination according to current medical guidelines. Patients must

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ALXN2006
IPR2023-00933

ALXN2006
IPR2019-00740

be monitored and evaluated immediately for early signs of meningococcal infections and treated with antibiotics as indicated. ***The Oncologist*** 2008;13: 993–1000

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an uncommon, life-threatening hemolytic anemia. The disease is characterized by acute exacerbations of chronic intravascular hemolysis, venous thrombosis with predilection for intra-abdominal and cerebral veins, and bone marrow failure [1, 2]. Other common symptoms, likely related to hemoglobin-mediated nitric oxide scavenging, include smooth muscle dystonias of the gastrointestinal tract, manifested as dysphagia, esophageal spasm, and abdominal pain; vascular constriction, possibly causing erectile dysfunction and pulmonary hypertension; endothelial dysfunction, causing hypertension and increased vascular permeability and renal dysfunction with acute or chronic renal failure; and Fanconi syndrome (glycosuria, hyperaminoaciduria, hyperphosphaturia, and bicarbonate and water loss) [3, 4].

The cellular abnormality of PNH is caused by an acquired somatic mutation in the X chromosome of a totipotent hematopoietic stem cell [5]. This mutation leads to a deficiency in phosphatidylinositol glycan class A protein critical for the biosynthesis of glycosylphosphatidylinositol membrane anchoring proteins (GPI-APs). As a result, there is a partial (type II) or complete (type III) deficiency of GPI-APs on the surface of PNH stem cells. Two such deficient proteins are the complement inhibitors CD55 and CD59. Failure of complement regulation by these proteins renders PNH erythrocytes susceptible to complement-mediated lysis.

Diagnosis of PNH can be established by flow cytometric determination of the proportion of GPI-AP–deficient erythrocytes or granulocytes as determined using appropriate monoclonal antibodies and the FLAER assay (GPI-APs are receptors for pro*aer*olycin, a bacterial toxin that can be *fl*uoresceinated). The latter test enhances sensitivity and specificity for the diagnosis of PNH [6].

Small to moderate numbers of PNH clones are found in up to 70% of patients with acquired aplastic anemia, and GPI-AP–deficient cells have also been reported in patients with myelodysplastic syndrome (MDS). Occasionally GPI-AP–deficient cells are found in normal subjects but these are polyclonal and only manifest in committed cells with no self-renewal capability [7].

Prior to the approval of eculizumab, there was no approved therapy for PNH. Therapies commonly used included blood transfusion, erythrocyte-stimulating agent therapy, corticosteroids, anabolic steroids, oral iron therapy for iron deficiency, and bone marrow transplantation. For patients who developed venous thromboembolism, treatment included anticoagulation with low molecular weight heparin followed by chronic warfarin therapy [8].

Eculizumab (Soliris®; Alexion Pharmaceuticals, Inc. Cheshire, CT) is a humanized monoclonal antibody that binds to the human C5 complement protein with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9 (membrane attack complex), responsible for the lysis of PNH RBCs lacking cell surface terminal complement inhibitor CD59 [9].

Biochemically, eculizumab is an IgGκ immunoglobulin comprised of human constant regions and murine complementarity determining regions grafted onto human framework light and heavy chain variable regions. Eculizumab is composed of two 448–amino acid heavy chains and two 214–amino acid light chains and has a molecular weight of approximately 148 kDa. Eculizumab does not inhibit C5 activity in animal sera but does bind to human tissues, including smooth and striated muscle as well as renal proximal epithelium. In animal studies, eculizumab was found to cross the placental barrier and show fetal morbidity and mortality [9].

The metabolism of eculizumab is understood to be via lysosomal enzymes to small peptides and amino acids, as is described for other proteins. In humans, the volume of distribution of eculizumab approximates that of plasma.

Pharmacodynamic assays demonstrate that inhibition of C5 sufficient to prevent hemolysis occurs at eculizumab plasma concentrations in excess of 35 μg/ml. Maximum plasma concentrations of eculizumab with therapeutic doses of the drug are achieved within 1 hour of infusion.

Patients and Methods

Submitted clinical data include a randomized double-blind, placebo-controlled, multicenter study of eculizumab or placebo administered i.v. to patients with PNH (the TRIUMPH study [A Hemoglobin Stabilization in Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab and Paroxysmal Nocturnal Hemoglobinuria Patients]) and a supporting open-label, phase III study (the SHEPHERD study [Safety in Hemolytic Paroxysmal Nocturnal Hemoglobinuria Patients Treated with

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Eculizumab: The Multicenter, Open Label, Research Design Study]) [10–12].

The primary objective of the TRIUMPH trial was to evaluate the safety and efficacy of eculizumab in transfusion-dependent patients with PNH. The trial consisted of a 2-week screening period, an observation period up to 3 months, and a 26-week treatment period. The coprimary efficacy endpoints were hemoglobin stabilization and the number of packed RBC units transfused during the treatment phase of the study. The secondary objectives of this study were transfusion avoidance and hemolysis as measured by lactate dehydrogenase (LDH) area under the curve (AUC) from baseline through week 26. This study also had exploratory endpoints of LDH change from baseline through week 26, health-related quality of life (QoL), as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 from baseline through week 26, as well as measures of thrombosis, platelet activity, nitric oxide, and free hemoglobin.

The primary objective of the SHEPHERD study was to evaluate the safety of eculizumab in patients with transfusion-dependent PNH. The secondary objectives of that study were to analyze hemolysis reduction as measured by LDH AUC and changes in the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) QoL scale. Exploratory endpoints included health-related QoL as measured by the EORTC QLQ-C30 and measures of thrombosis, platelet activity, nitric oxide, and free hemoglobin.

The major inclusion criteria for the TRIUMPH trial were age ≥18 years, RBC transfusion requirement, CD59 cell clone ≥10%, stable doses of erythrocyte-stimulating agents, immunosuppressives, iron, folic acid, corticosteroids, and anticoagulants, and vaccination against *Neisseria meningitides* at least 14 days prior to treatment. In addition, patients were required to have an LDH level ≥1.5 times the upper limit of normal. Patients had to have had RBC transfusions if their hemoglobin was ≤9 g/dl with symptoms or if their hemoglobin was ≤7 g/dl without symptoms, and also within 1.5 g/dl of the mean hemoglobin pretransfusion value for the previous 12 months. A platelet count ≥100,000/μl and an absolute neutrophil count ≥500/μl were also required. Excluded patients included those with a history of bone marrow transplantation or meningococcal disease presence or suspicion of other bacterial infection, known or suspected hereditary complement deficiency, and pregnant or breast-feeding women or women intending to conceive during the course of the study, including the post-treatment phase.

Treatment assignment was stratified based on the number of packed RBC transfusions within 1 year prior to screening (low stratum, 4–14 units; middle stratum, 15–25 units; high stratum, >25 units). Patients randomized to the placebo group received placebo i.v. once a week for five doses then once every 2 weeks for 21 weeks. Patients randomized to the eculizumab group received eculizumab at a dose of 600 mg via a 35-minute i.v. infusion weekly for the first 4 weeks then 900 mg (week 5) then 900 mg every 14 days thereafter for 26 weeks total treatment. Following the 26 weeks of treatment, there was an 8- to 12-week post-treatment follow-up period. The study drug and placebo for the treatment period were supplied by Alexion Pharmaceuticals, Inc., Cheshire, CT.

Patients enrolled in the SHEPHERD study received the same eculizumab dosing regimen as used in the TRIUMPH study. This study had a 12-week enrollment phase followed by a 2-week screening phase followed by a 52-week treatment phase and an 8-week post-treatment phase. The inclusion and exclusion criteria were similar to those of the TRIUMPH study with the exception that patients in the SHEPHERD study were required to have one or more transfusions in 24 months, compared with four or more transfusions in 12 months in the TRIUMPH study, and a platelet count ≥30,000/μl, compared with a platelet count ≥100,000/μl.

For the primary analysis, the hemoglobin set point for each patient was defined as ≤9 g/dl in patients with symptoms and ≤7 g/dl in patients without symptoms. To achieve a designation of hemoglobin stabilization, a patient had to maintain a hemoglobin concentration above the hemoglobin set point and avoid any RBC transfusion for the entire 26-week treatment period. Patients who reached or dropped below their predetermined hemoglobin set point did not achieve hemoglobin stabilization. Those patients who withdrew prematurely from the study or were transfused above their hemoglobin set point during the treatment phase also were treated as not achieving hemoglobin stabilization. A two-sided Fisher's exact test was used for statistical analysis. Each patient's units of packed RBCs transfused after randomization through visit 18 were calculated. For those patients who discontinued the study drug but remained in the study for follow-up, the actual transfusion records were used to calculate the units transfused. For patients who had at least one transfusion but withdrew prematurely from the study prior to 26 weeks, the number of units was prorated by applying the formula (26/number of weeks on study drug) × (number of units transfused while on study drug). For patients who withdrew prematurely from the study prior to having a transfusion, their transfusion data for the 26 weeks previous to their last contact date was used to calculate the number of units of packed RBCs transfused. The primary analysis method was the Wilcoxon rank-sum test.

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Table 1. Demographics and baseline characteristics for patients in the TRIUMPH study

	Eculizumab (n = 43), n (%)	Placebo (n = 44), n (%)
Gender		
Male	20 (46.5)	15 (34.1)
Female	23 (53.5)	29 (65.9)
Age (years)		
Median	41.0	35.0
Range	20.0–85.0	18.0–78.0
Race		
White	37 (86.0)	41 (93.2)
Other	5 (11.6)	2 (4.6)
Not reported	1 (2.3)	1 (2.3)
Transfusion history		
n of units PRBCs transfused in prior 12 months		
Mean (g/dl) (standard deviation)	19.2 (8.41)	19.9 (9.28)
Median	18.0	17.0
Range	7.0–36.0	7.0–44.0
Symptoms associated with transfusion		
Change in mental status	14 (3.2)	20 (4.7)
Severe or worsening shortness of breath	69 (15.8)	63 (14.8)
Severe or worsening fatigue	279 (63.7)	264 (62.0)
Other	76 (17.4)	79 (18.5)
Thrombosis history, n (%)		
Any thrombosis event	9 (20.9)	8 (18.2)
Cerebrovascular accident	1 (2.3)	0 (0.0)
Mesenteric vein thrombosis	0 (0.0)	2 (4.5)
Thrombophlebitis/deep vein thrombosis	4 (9.3)	6 (13.6)
Other[a]	–	0 (0.0)
Concomitant antithrombotic agents, n (%)	24 (55.8)	20 (45.5)
Concomitant systemic corticosteroids, n (%)	13 (30.2)	15 (34.1)
Hemoglobin set value (g/dl), mean (standard deviation)	7.8 (0.79)	7.7 (0.75)
Disease duration (years), median (range)	4.3 (0.93–29.8)	9.3 (0.47–38.5)
Aplastic anemia, n (%)		
Yes	6 (14.0)	12 (27.3%)
No	37 (86.0%)	32 (72.7%)
Myelodysplastic syndrome, n (%)		
Yes	2 (4.7%)	0 (0.0%)
No	41 (95.3%)	44 (100%)
Baseline PNH type III RBCs (%)		
Mean (standard deviation)	28.0 (13.3)	35.1 (18.2)
Median	25.6	34.4
Range	2.4–54.0	6.6–88.0
Baseline free hemoglobin (mg/dl), median (range)	40.5 (7.5–764.0)	46.2 (11.2–502.0)
Baseline LDH (U/l), mean (standard deviation)	2,200 (1,034)	2,258 (1,027)
FACIT-F score,[b] mean (standard deviation)	36.7 (10.5)	34.3 (12.0)
Platelet count ($\times 10^9$/l), mean (standard deviation)	188.8 (83.3)	166.0 (94.2)
Hemoglobin (g/dl), mean (standard deviation)	10.0 (1.2)	9.7 (1.2)

[a]Other thrombosis included one event each of ischemic stroke, suspected pulmonary embolus during pregnancy, thrombus (not otherwise specified), thrombus artery carotis interna left, thrombus right arm after feeding infusion, pulmonary embolus, and transient ischemic attack.
[b]The FACIT-Fatigue tool was administered prior to transfusion.
Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; PRBCs, packed red blood cells; TRIUMPH, A Hemoglobin Stabilization in Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab and Paroxysmal Nocturnal Hemoglobinuria Patients.

Secondary efficacy analyses included transfusion avoidance, LDH AUC from baseline to week 26 and change in FACIT-F scale (version 4) score from baseline to week 26. Those patients who withdrew prematurely from the study during the treatment phase were considered as requiring transfusion. The analysis was carried out using the two-sided Fisher's exact test. The AUC of LDH from baseline through visit 18 was calculated for each patient. For patients with missing LDH values, the last-observation-carried-forward method was used to impute missing values. The AUC was analyzed using the Wilcoxon rank-sum test. The scoring guideline for the FACIT-F scale was used to

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Table 2. Analysis of primary efficacy endpoints

	Eculizumab, *n* (%)	Placebo, *n* (%)	*p*-value
Overall (*n*)			
Hemoglobin stabilization			<.0001
Yes	21/43 (48.8)	0/44 (0.0)	
No	22/43 (51.2)	44/44 (100)	
Median units PRBCs transfused	0.0	10.0	<.0001
4–14 units (*n*)			
Hemoglobin stabilization			<.0001
Yes	12/15 (80.0)	0/15 (0.0)	
No	3/15 (20.0)	15/15 (100)	
Median units PRBCs transfused	0.0	6.0	<.0001
15–25 units			
Hemoglobin stabilization			.0191
Yes	5/17 (29.4)	0/18 (0.0)	
No	12/17 (70.6)	18/18 (100)	
Median units PRBCs transfused	2.0	10.0	.0007
>25 units			
Hemoglobin stabilization			.0902
Yes	4/11 (36.4)	0/11 (0.0)	
No	7/11 (63.6)	11/11 (100)	
Median units PRBCs transfused	3.0	18.0	.0003

Abbreviation: PRBCs, packed red blood cells.

calculate the fatigue score. The main hypothesis of interest was that eculizumab would provide a statistically significant higher patients' total FACIT-F scale score than placebo. The change in the total FACIT-F score from baseline was analyzed using a mixed-effects model with baseline as covariate, treatment and time as fixed effects, and patient as a random effect.

Results

In the TRIUMPH study, 114 patients were screened, 108 entered the observation phase, and 88 protocol-eligible patients were randomized. One patient was removed from the analysis because of being randomized in error; therefore, 87 patients entered the treatment phase. Of the patients treated, 85 completed all visits. Two patients randomized to eculizumab discontinued treatment prematurely, one because of pregnancy and one because of not wanting to travel; 10 patients in the placebo group discontinued study drug prematurely because of a lack of efficacy but completed all study visits for follow-up.

The analysis population (intent-to-treat [ITT]) included all 87 randomized and treated patients. Demographics and baseline characteristics of the ITT population are shown in Table 1. There were no statistically significant differences between treatment groups in the pretreatment characteristics of patients.

Results of the primary efficacy analysis after 26 weeks on study are summarized in Table 2. Significantly more patients in the eculizumab treatment group showed hemoglobin stabilization than in the placebo treatment group (48.8% versus 0.0%; $p < .0001$), and patients in the eculizumab treatment group required significantly fewer packed RBC transfusions than patients in the placebo group (median, 0.0 units versus 10.0 units; $p < .0001$). For each of the three treatment strata, eculizumab treatment significantly decreased RBC transfusion requirements, and for the first two strata, eculizumab treatment significantly increased the percentage of patients with hemoglobin stabilization.

Results of secondary efficacy analyses for the overall study populations are shown in Table 3. Outcomes were statistically significantly better in the eculizumab treatment group than in the placebo group for each of these secondary endpoints. The favorable result for eculizumab with regard to efficacy was apparent across all randomization strata.

The study was not able to evaluate for efficacy of eculizumab with regard to prevention of thrombosis because most of the patients were receiving concomitant antithrombotic agents during the study and there was only one throm-

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Table 3. Efficacy analysis at completion of 26 weeks on study

Endpoint	Eculizumab (n = 43)	Placebo (n = 44)	p-value
Hemoglobin stabilization			
Yes	21/43 (48.8)	0/44 (0.0)	<.0001
No	22/43 (51.2)	44/44 (100)	
Units of PRBCs transfused			<.0001
Mean (standard error)	3.0 (0.67)	11.0 (0.83)	
Median	0.0	10.0	
Range	0.0–16.0	2.0–21.0	
Avoidance of transfusion			<.0001
Yes	22/43 (52.1%)	0/44 (0.0%)	
No	21/43 (48.8%)	44/44 (100%)	
LDH AUC (baseline to 26 weeks), U/l × day			<.0001
Mean (standard error)	81,140	459,116	
Median	58,587	441,880	
Range	32,417–792,005	234,604–711,934	
Change in FACIT-F score from baseline to week 26			<.0001
n	41	39	
Mean (standard error)	6.4 (1.2)	−4.0 (1.7)	
Median	4.0	−2.0	
Range	−5.0–28.0	−38.0–17.0	

Abbreviations: AUC, area under the curve; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; LDH, lactate dehydrogenase; PRBCs, packed red blood cells.

botic event (hepatic vein thrombosis in a patient in the placebo treatment group) during the study.

Overall, 96 of the 97 enrolled patients completed the open-label supportive study (one patient died following a thrombotic event). A reduction in intravascular hemolysis as measured by serum LDH levels was sustained for the entire treatment period and resulted in a reduced need for RBC transfusions.

Patients were tested for human antihuman antibodies (HAHAs) after eculizumab treatment, and two patients were found to have IgG titers of 1:20 and one patient had IgM titers of 1:20 and 1:100. No patient developed a rebound in hemolysis with these antibodies. Also, because of concern of rebound hemolysis after discontinuing eculizumab, it was planned to follow patients after discontinuation of eculizumab, but few patients in the controlled study discontinued eculizumab prematurely and most patients continued into extension studies of eculizumab after completing study treatment.

Safety

Safety data were available from a total of 236 eculizumab-treated PNH patients including 43 patients from the

Table 4. Adverse reactions occurring in ≥5% of patients in the TRIUMPH study

Reaction	Eculizumab (n = 43), n (%)	Placebo (n = 44), n (%)
Headache	19 (44)	12 (27)
Nasopharyngitis	10 (23)	8 (18)
Back pain	8 (19)	4 (9)
Nausea	7 (16)	5 (11)
Fatigue	5 (12)	1 (2)
Cough	5 (12)	4 (9)
Herpes simplex infections	3 (7)	0
Sinusitis	3 (7)	0
Respiratory tract infection	3 (7)	1 (2)
Constipation	3 (7)	2 (5)
Myalgia	3 (7)	1 (2)
Pain in extremity	3 (7)	1 (2)
Influenza-like illness	2 (5)	1 (2)

Abbreviation: TRIUMPH, A Hemoglobin Stabilization in Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab and Paroxysmal Nocturnal Hemoglobinuria Patients.

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TRIUMPH study and 193 patients from uncontrolled PNH clinical studies. In the controlled study, two patients in the eculizumab group discontinued prematurely, one because of an adverse event (pregnancy, which went on to delivery of a normal infant) and one because of patient choice. The most frequent adverse events occurring during this study are summarized in Table 4. Adverse events that were notably more common in eculizumab-treated patients than in placebo-treated patients were headache, back pain, fatigue, and respiratory tract infection. Viral infection, urinary tract infection, and PNH were more frequent in the placebo group. No patients died.

Among the 193 PNH patients who received eculizumab in uncontrolled studies, serious adverse events occurring in two or more patients were viral infection (2.6%), headache (2.1%), anemia (1.6%), pyrexia (1.6%), and hemolysis (1.0%). Across all PNH studies overall, infections did not seem to be more frequent in patients who received eculizumab than in those who received placebo. The incidence of herpes simplex infection appeared to be greater in PNH patients treated with eculizumab (8 of 140; 5.7%), versus none in the pivotal trial placebo control.

Because eculizumab inhibits complement activation, it may impair neutrophil and monocyte function and impair the ability of the patient to clear infections with encapsulated organisms. There were three cases of *Neisseria* meningitis in patients receiving eculizumab, including a 22-year-old unvaccinated woman with idiopathic membranous glomerulonephritis who had received eculizumab for about 7 months, a 54-year-old vaccinated female PNH patient who had been on eculizumab for approximately 14 months, and a 24-year-old male vaccinated PNH patient who had received eculizumab for approximately 12 months. No patient died, but the unvaccinated patient had a complicated course with amputation of parts of some digits because of gangrene, pulmonary embolus, and pneumonia. As a result of this experience, all study patients were required to be vaccinated against *Neisseria meningitides* at least 2 weeks prior to starting study treatment.

A total of four eculizumab-treated PNH patients died. These include a 31-year-old man with PNH and hemosiderosis who suffered a pulmonary embolus and a hemorrhagic cerebral infarction 31 days after the last eculizumab dose; a female patient with cholecystitis who became septic and died from a cerebrovascular accident about 2 months after her last eculizumab dose; a man with MDS who developed cellulitis, sepsis, and acute renal failure after a fish hook infection and died from worsening of his MDS; and a woman who died of metastatic adenocarcinoma after 13 months on eculizumab.

Discussion

Eculizumab appears to be generally safe and effective for the treatment of PNH patients with transfusion-dependent hemolysis. The efficacy of eculizumab was demonstrated by the stabilization of hemoglobin and a lower number of packed RBC transfusions in these patients. Eculizumab also improves clinically measured hemolysis parameters such as LDH. The small number of patients, the low thrombotic event rate, and the high rate of concomitant antithrombotic agent use in the controlled clinical study preclude meaningful assessment of the effect of eculizumab on thrombosis in PNH patients. Measurement of QoL as assessed by the FACIT-F scale showed improvement in the eculizumab treatment group; however, the tool was administered to patients prior to transfusion without post-transfusion tool administration, so it is not possible to determine whether any difference between groups in the FACIT-F score is a result of the eculizumab or the anemia correction. Also, the FACIT-F scale has not been validated in PNH patients.

As part of the approval of eculizumab, the sponsor agreed to a number of postmarketing commitments. The sponsor will evaluate the long-term safety of eculizumab by analyzing outcomes in the PNH registry program for a period ≥5 years. The sponsor will also evaluate serious infections necessitating or prolonging hospitalization or resulting in death. The rate of malignancy, including the nature of the malignancy and the survival status of PNH patients who develop a malignancy, will be determined. For women who become pregnant, the sponsor will evaluate the clinical course and any congenital abnormalities among offspring. A randomized clinical trial to assess the effects of anticoagulant withdrawal among patients with PNH will also be initiated. The sponsor will also evaluate HAHA formation.

Patients with PNH who are treated with eculizumab are at a higher risk for infections with *Neisseria meningitides* [13]. An early alert program and a registry program have been instituted to minimize the risk for infections. Patients who are to be treated with eculizumab must be vaccinated with *Neisseria meningitides* vaccine at least 2 weeks prior to treatment with eculizumab.

Pregnant women with PNH and their fetuses have high rates of morbidity and mortality during pregnancy and the postpartum period. There are no adequate and well-controlled studies of eculizumab in pregnant women. It is likely that eculizumab will cross the placenta and appear in breast milk.

Eculizumab has not been studied in patients ≤18 years old. Experience with eculizumab in the geriatric population is limited; in PNH studies, only 15 patients aged ≥65 years

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were treated with eculizumab. Although there were no apparent age-related differences observed in these studies, the number of patients aged ≥65 is not sufficient to determine whether they respond differently from younger patients.

Acknowledgments

The views expressed are the result of independent work and do not necessarily represent the views and findings of the U.S. Food and Drug Administration.

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