Eculizumab Protects Against Thromboembolism and Prolongs Survival in Patients with Paroxysmal Nocturnal Hemoglobinuria: An International PNH Registry Study

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3480

BACKGROUND

- Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic and life-threatening hematopoietic stem-cell disorder characterized by uncontrolled complement-mediated hemolysis.[1]
- Complement-mediated platelet hyperactivation and chronic hemolysis can lead to thromboembolism (TE), the leading cause of mortality in PNH, which accounts for 40%–67% of PNH-related deaths with known causes.[2]
- Median survival in untreated patients ranges from 10 to 15 years.[3]
- Prior TE, infection, or age >54 years at diagnosis have been associated with poorer long-term survival.[4]
- Eculizumab, a monoclonal antibody that inhibits terminal complement activation, has been shown in clinical trials to reduce hemolysis, reduce the incidence of TE, and improve survival to a level comparable to healthy age- and sex-matched controls.[1,2,5–8]
- The International PNH Registry provides the opportunity to understand from real-world experience the impact of eculizumab on TE reduction in PNH patients.

OBJECTIVE

- Assess the risk factors for TE and mortality in PNH patients enrolled in the International PNH Registry and assess the effectiveness of eculizumab in reducing PNH-associated TE.

METHODS

- Patients are eligible for the registry if they have a detectable PNH clone, regardless of disease severity, comorbidities, or treatments (past, current, or planned).
- Endpoints for this study were thrombotic events (any type) and all-cause mortality.
- In this analysis, patients enrolled in the registry were excluded if any of the following information was unavailable:
  - Enrollment date
  - Date of birth
  - Gender
  - Use of eculizumab
  - Follow-up data
- The cumulative incidence of TE was determined using the **competing-risks** methods to take into account bone marrow transplantation (BMT) and death.
- The cumulative incidence of mortality was assessed using Kaplan-Meier methods.
- Risk factors for TE and mortality were explored using a Cox proportional hazards model with stepwise selection (with significance level set at P=0.20 because of the potentially low power of the model based on the limited number of events).
- Variables considered for selection in the model included:
  - Sex
  - Age at enrollment into registry
  - Ethnicity
  - Medical history
    - Prior TE
    - Bone marrow disorders
    - Impaired renal function
    - Impaired hepatic function
  - Clinical symptoms at enrollment
    - Abdominal pain
    - Dysphagia
    - Dyspnea
    - Easy bruising/bleeding
    - Fatigue
    - Headache
    - Hemoglobinuria
  - Clinical variables at enrollment
    - Karnofsky performance score
    - Granulocyte clone size
    - Lactate dehydrogenase (LDH) concentration
  - Red blood cell (RBC) transfusions 6 months prior to enrollment
  - Use of anticoagulants during follow-up
- The analysis model for mortality also included the following variables:
  - BMT during follow-up
  - TE during follow-up

RESULTS

Patient Characteristics

- As of June 30, 2012, a total of **1547 patients from 25 countries** on 5 continents had been enrolled.
- A total of 1047 patients were eligible for analysis:
  - 536 patients (51.2%) were treated with eculizumab during follow-up.
  - 511 patients (48.8%) were untreated.
- **Table 1** presents demographic and clinical characteristics of all eligible patients at the time of enrollment.

Table 1. Demographic and Clinical Characteristics at Enrollment

Parameter	All Eligible Patients (N=1047)
Female, n (%)	537 (51.3)
Age, mean (SD)	44.2 (17.0)
<30 years, n (%)	230 (22.0)
30–59 years, n (%)	570 (54.4)
≥60 years, n (%)	247 (23.6)
Caucasian, n (%)	868 (82.9)[a]
LDH, ×ULN, mean (SD)	2.7 (2.8)[b]
LDH, ×ULN, median	1.4[b]
LDH ≥1.5 ULN, n (%)	355 (46.7)[b]
Median granulocyte clone size, %	71.0[c]
RBC transfusions in prior 6 months, n (%)	374 (37.7)[d]
Karnofsky score, mean (SD)	85.9 (11.8)[e]
Symptoms, n (%)	
Fatigue	766 (77.5)[f]
Hemoglobinuria	601 (60.8)[g]
Dyspnea	420 (42.5)[g]
Abdominal pain	399 (38.1)[h]
Headache	362 (36.7)[h]
Easy bruising/bleeding	234 (23.8)[i]
Dysphagia	171 (17.3)[h]
Eculizumab use during follow-up, n (%)	536 (51.2)
Anticoagulant use during follow-up, n (%)	296 (28.3)

[a]n=1023; [b]n=760; [c]n=920; [d]n=991; [e]n=917; [f]n=989; [g]n=988; [h]n=986; [i]n=985.

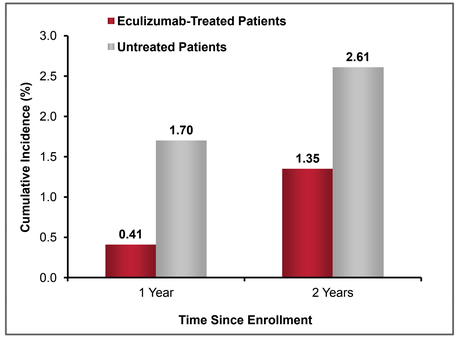
- **Outcomes** for all eligible patients are reported in **Table 2.**

Table 2. Patient Outcomes During Mean Follow-up of 23 Months

Event/Outcome	All Eligible Patients (N=1047)
Months of follow-up, mean (SD)	22.5 (18.4)
TE during follow-up, n (%)	16 (1.5)
Bone marrow transplant, n (%)	30 (2.9)
Death, n (%)	51 (4.9)
PNH	2 (3.9)
Bone marrow transplant	3 (5.9)
Bone marrow disorder (including acute myelogenous leukemia)	7 (13.7)
Cancer	5 (9.8)
Cardiovascular	11 (21.6)
Infection	13 (25.5)
Other	3 (5.9)
Unknown	7 (13.7)

- During a mean follow-up of 22.5 months, 16 patients had a TE event and 51 patients died (Table 2).
- The most frequent causes of death were cardiovascular events and infections (Table 2).
- **A comparison of cumulative incidence of TE in treated and untreated patients over time is shown in Figure 1.**

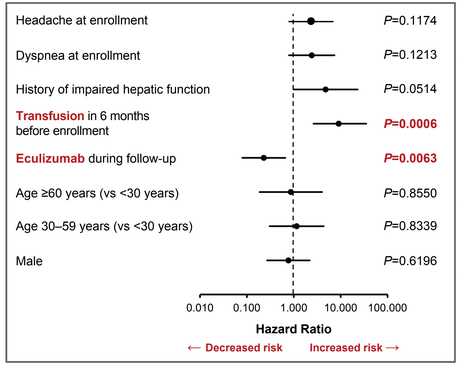
Figure 1. Cumulative Incidence of TE at 1 Year and 2 Years



- Despite the small number of TEs reported during the follow-up period, the cumulative incidence of TE was greater in the untreated patients compared with eculizumab-treated patients (Figure 1).

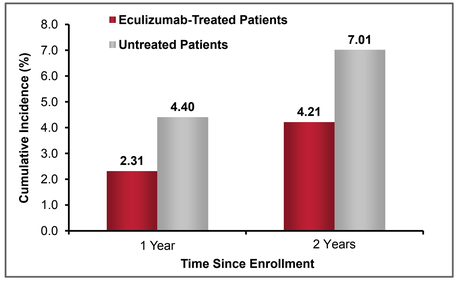
- **TE risk factors were assessed using a multivariate Cox model (Figure 2).**

Figure 2. Multivariate Analysis of Risk Factors for TE



- In the multivariate Cox model, the greatest associations with TE were RBC transfusions in the 6 months before enrollment (hazard ratio [HR]=9.61), history of impaired hepatic function (HR=4.78), and the presence of dyspnea (HR=2.42) or headache (HR=2.33) at enrollment (Figure 2).
- While controlling for these variables, eculizumab had a significant protective effect against the occurrence of TE (HR=0.23; 95% CI=0.08–0.66; P=0.0053; Figure 2).
- A comparison of cumulative incidence of mortality in treated and untreated patients over time is shown in Figure 3.

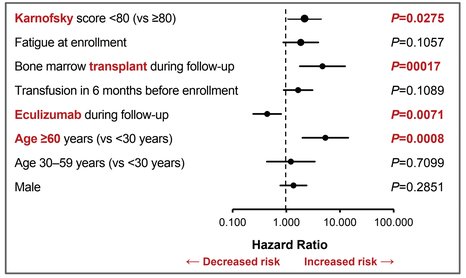
Figure 3. Cumulative Incidence of Mortality at 1 Year and 2 Years



- The cumulative incidence of mortality was consistently higher in untreated patients than in eculizumab-treated patients (Figure 3).

- **Mortality risk factors were assessed using a multivariate model (Figure 4).**

Figure 4. Multivariate Mode of Risk Factors for Mortality



- From the multivariate model of mortality, the greatest associations with increased risk of death were age ≥60 years (HR=5.33), BMT during follow-up (HR=4.71), Karnofsky score <80 (HR=2.19), fatigue at enrollment (HR=1.86), and recent RBC transfusion (HR=1.75; Figure 4).
- When these variables were controlled, eculizumab had a significant effect in preventing mortality (HR=0.41; 95% CI=0.23–0.73; Figure 4).

CONCLUSIONS

- This analysis of a large international cohort of patients with PNH treated in clinical practice showed that eculizumab is associated with reduced risk of TE and mortality.
- Recent RBC transfusion, a surrogate marker for hemolysis, was associated with increased risk of TE and mortality.
- Risk of TE was also increased in patients with hepatic dysfunction and the presence of headache and dyspnea at enrollment.
- Older age and lower Karnofsky performance score at enrollment, along with BMT during follow-up, were associated with a significantly higher risk of mortality.
- Administration of eculizumab resulted in reductions in the cumulative incidence of TE and mortality at both 1 and 2 years and had a significant protective effect against TE and premature mortality in patients with PNH.

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