Long-term effectiveness of eculizumab: Data from the International PNH Registry

Louis Terriou, Jong Wook Lee, Cecily Forsyth, Morag Griffin, Jeff Szer, Alexander Röth, Philippe Gustovic, Jesse Metzger, Ami S. Patel, Christopher J. Patriquin

Received: 23 January 2023 | Revised: 28 July 2023 | Accepted: 31 July 2023

DOI: 10.1111/ejh.14080

ORIGINAL ARTICLE

European Journal of Haematology

WILEY

Long-term effectiveness of eculizumab: Data from the International PNH Registry

Louis Terriou[1] | Jong Wook Lee[2] | Cecily Forsyth[3] | Morag Griffin[4] | Jeff Szer[5] | Alexander Röth[6] | Philippe Gustovic[7] | Jesse Metzger[8] | Ami S. Patel[9] | Christopher J. Patriquin[10]

[1]Université de Lille, Inserm, CHU Lille, Service de Médecine Interne et Immunologie Clinique, Centre de Référence des Maladies Autoimmunes Systémiques Rares du Nord et Nord-Ouest de France (CeRAINO), Institut de Recherche Translationnelle sur l'Inflammation (INFINITE) – U1286, Lille, France

[2]Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea

[3]Central Coast Haematology, North Gosford, New South Wales, Australia

[4]Department of Haematology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

[5]Department of Clinical Haematology, Peter MacCallum Cancer Centre and the Royal Melbourne Hospital, Melbourne, Victoria, Australia

[6]Department of Hematology and Stem Cell Transplantation, University Hospital Essen and University of Duisburg-Essen, Essen, Germany

[7]Alexion, AstraZeneca Rare Disease, Zürich, Switzerland

[8]Parexel, Newton, Massachusetts, USA

[9]Alexion, AstraZeneca Rare Disease, Boston, Massachusetts, USA

[10]Division of Hematology, University of Toronto, Toronto, Ontario, Canada

Correspondence
Christopher J. Patriquin, Toronto General Hospital, 200 Elizabeth St. Toronto, ON, Canada M5G 2C4.
Email: christopher.patriquin@uhn.ca

Funding information
Alexion, AstraZeneca Rare Disease

Abstract

Objectives: Data from the International PNH Registry (NCT01374360) were used to estimate the overall survival and first occurrence of thromboembolic events/major adverse vascular events (TEs/MAVEs) for eculizumab-treated patients with paroxysmal nocturnal hemoglobinuria (PNH) compared with a contemporaneous untreated cohort.

Methods: Patients enrolled in the Registry from March 16, 2007, to February 14, 2022, were included. Treated patients received eculizumab for >35 days; untreated patients did not receive eculizumab at any time. Univariable and multivariable analyses were performed using a Cox proportional hazards regression model comparing eculizumab treatment periods to untreated periods and were adjusted for baseline covariates (e.g., high disease activity [HDA], transfusion dependency, and eculizumab treatment status).

Results: The analysis included 4118 patients. The univariable hazard ratio (HR) (95% CI) for mortality in eculizumab-treated time versus untreated time was 0.51 (0.41–0.64; $p < 0.0001$). Significant baseline covariates included age, sex, history of bone marrow failure, ≥4 erythrocyte transfusions within 12 months before baseline, and an estimated glomerular filtration rate ≤ 60 mL/min/1.73 m^2 (all $p < 0.0001$). In the adjusted analysis, patients with baseline HDA had the greatest reduction in mortality risk (HR [95% CI], 0.51 [0.36–0.72]). Treated patients had approximately 60% reduction in TE/MAVE risk during treated versus untreated time (HR [95% CI]: TE: 0.40 [0.26–0.62], MAVE: 0.37 [0.26–0.54]; $p < 0.0001$).

Conclusion: Using data from the largest Registry of patients with PNH, with ≥14 years of overall follow-up, we demonstrate that treatment with eculizumab conferred a 49% relative benefit in survival and an approximately 60% reduction in TE/MAVE risk.

KEYWORDS

C5 inhibitor, major adverse vascular events, PNH Registry, real-world, survival, thromboembolic events

1 | INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, chronic hematologic disease that leads to significant morbidity and premature mortality.[1–3] It is caused by clonal expansion of hematopoietic stem cells with somatic mutations in phosphatidylinositol-glycan (*PIG-A*), leading to a reduction in glycosylphosphatidylinositol (GPI)-anchored proteins that regulate complement on the surface of blood cells.[1,3] The dysregulated terminal complement activation results in intravascular hemolysis and activation of platelets and white blood cells, which contribute to increased risk of thromboembolic events (TEs), anemia, organ damage, and fatigue.[1,4]

Mortality in untreated patients with PNH is high.[5–8] A 10-year mortality rate of 24% has been reported.[7] Thrombosis is the most frequent cause of mortality in patients with untreated PNH, accounting for 40% to 67% of deaths for which the cause is known.[8–11] History of TEs or TEs during follow-up has been associated with ≥4-fold higher rate of mortality.[5,6] Additionally, age >55 years, use of transfusions, and TEs at diagnosis have been identified as independent risk factors for thrombosis in untreated patients with PNH.[7] Renal failure is an independent risk factor for mortality[5] and in a study evaluating patients with PNH from the United States and Japan, renal failure contributed to death in 8% to 18% of patients.[12] In a univariate analysis, lactate dehydrogenase (LDH) ratio ≥1.5 × upper limit of normal (ULN), abdominal pain, and dyspnea were significantly associated with an increase in mortality risk in patients with PNH.[5]

Eculizumab is a recombinant antibody specific for complement component 5 (C5).[13,14] It inhibits cleavage of C5 to C5a and C5b, which prevents formation of the terminal complement complex (C5b-9) and therefore inhibits the cell lysis and activation caused by complement.[13–15] It was approved in 2007 in the United States and EU for the treatment of patients with PNH and has become the standard of care for the treatment of PNH.[13,14] Long-term effectiveness data of eculizumab on patient survival and prevention of clinical outcomes such as TEs have been previously demonstrated in real-world settings.[6,11,16] However, these data have limitations with respect to study population size, contemporaneous data for comparator populations, and analysis of time on eculizumab.

The International PNH Registry (NCT01374360) is an ongoing, prospective, multicenter, global, observational study; patients of any age with a clinical diagnosis of PNH and/or a detectable PNH clone (defined as a population of GPI-deficient granulocytes and/or erythrocytes) of ≥0.01% are included.[4,17,18] The Registry is the largest global database of patients with PNH, recording comprehensive data on the progression of PNH and its management in the clinical setting.[4,17,18] Data from the Registry offer an opportunity to quantify the impact of eculizumab on survival as well as the occurrence of major adverse vascular events (MAVEs), including TEs, while providing a substantial sample size and contemporaneous data for comparator populations. The objectives of this analysis were to describe and compare the overall survival as well as the first incidence of TEs/MAVEs in patients with PNH while treated with eculizumab versus while untreated, adjusting for key baseline clinical risk factors.

2 | METHODS

2.1 | Patients

Details for the design and patient population included in the International PNH Registry have been previously reported.[4,17,18] The institutional review boards (or equivalent) of participating centers approved the Registry in accordance with the International Council for Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent before study entry. The Registry is sponsored by Alexion, AstraZeneca Rare Disease and is overseen by an executive committee of independent international clinical experts in PNH.

Patients enrolled in the Registry from March 16, 2007, to February 14, 2022, with complete information for birthdate, sex, enrollment date, and treatment status, were included in the analysis. Patients were excluded if they were ever treated with an anti-complement treatment other than eculizumab. The study population was characterized by eculizumab treatment status (treated vs. untreated). Patients in the treated cohort were those who received eculizumab for a treatment period of at least 35 continuous days (i.e., treatment induction). Patients in the untreated cohort did not receive eculizumab or any other anti-complement inhibitor at any time before or during Registry participation. Patients contributed untreated and/or treated person time to the analysis. Additionally, overall treatment status was assigned on the basis of whether a patient was ever versus never treated with eculizumab. Patient demographics, disease characteristics (e.g., high disease activity [HDA], transfusion dependency), and medical history (e.g., history of TE, history of bone marrow failure [BMF]) were captured at baseline. Baseline was defined as the date of PNH Registry enrollment for untreated patients and the earliest date of either eculizumab treatment initiation or PNH Registry enrollment for treated patients. HDA was defined as LDH ratio ≥1.5 × ULN and ≥1 of the following: history of MAVEs (including TEs), anemia (hemoglobin <10 g/dL), or physician-documented abdominal pain, dyspnea, dysphagia, fatigue, hemoglobinuria, or erectile dysfunction (for males only) at any time before or at baseline. Transfusion dependence was defined as ≥4 erythrocyte transfusions within 12 months before baseline.

2.2 | Survival analysis

Hazard ratios (HRs) for survival analysis of time to death were estimated using the Cox proportional hazards regression method to compare the eculizumab treatment period(s) to the untreated time period(s). In addition to the time-dependent covariate of treatment, the model incorporated the following parameters at baseline: age, sex, history of BMF (yes/no/unknown), history of TE (yes/no/unknown), transfusion dependence (yes/no/unknown), estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 (yes/no/unknown), HDA (yes/no/unknown), and interaction between treatment status and HDA. The interaction term was included as patients with HDA are observed to have clinical benefit with eculizumab.[19]

Survival time was calculated as the number of months from the PNH disease start date ($T = 0$ for all patients) to the death date. The PNH disease start date was defined as the earliest date of the first-reported PNH diagnosis, PNH symptom, or first consistent flow cytometry result (i.e., GPI-deficient granulocyte lab test). Additional details on the risk set time for survival analysis can be found in the Supplementary Methods section (Supplementary Figure 1).

2.3 | TE and MAVE analysis

HRs for the first occurrence of TEs and MAVEs were estimated using similar methods to those employed for the overall survival, but with modifications in the observed start time, time horizons, and in some covariates (i.e., overall treatment status [ever treated vs. never treated], age at baseline). Additional details on the risk set time for TE and MAVE analysis can be found in the Supplementary Methods section (Supplementary Figure 1).

2.4 | Data analyses

Kaplan Meier curves, estimated survival probabilities, number of patients at risk, and number of TEs and MAVEs are presented. Both unadjusted and adjusted HRs with 95% CIs were estimated.

3 | RESULTS

3.1 | Baseline patient demographics and disease characteristics

A total of 4118 patients were included in the analysis, of whom 1613 were treated with eculizumab and 2505 were untreated. Baseline patient data are shown in Table 1. Overall, 52.5% of patients were female, and the median (Q1, Q3) age at PNH disease onset was 38.8 (25.0, 57.3) years. Patients treated with eculizumab were younger at disease onset (median [Q1, Q3]: 35.2 [24.0, 53.1] vs. 42.1 [25.9, 59.3]) and baseline (median [Q1, Q3]: 39.2 [28.1, 56.6] vs. 45.1 [29.0, 61.7]) compared to untreated patients.

Differences were observed with respect to baseline laboratory values. Patients treated with eculizumab had higher median (Q1, Q3) percentages of GPI-deficient granulocytes than untreated patients (79.4% [54.0, 92.8] and 5.1% [0.5, 33.0], respectively). The percentage of patients with GPI-deficient granulocytes ≥50% was 78.1% in the treated group and 19.6% in the untreated group. In addition, 87.8% of treated patients and 32.4% of untreated patients had an LDH ratio ≥1.5 × ULN.

Compared to the untreated group, a larger proportion of eculizumab-treated patients had a history of MAVEs (treated, 23.9% and untreated, 10.8%) or TEs (19.8% and 7.0%) and less BMF (45.5% and 79.2%). Similar proportions of patients in each group had transfusion dependency at baseline.

TABLE 1 Baseline patient demographics and disease characteristics.

	Treated with eculizumab ($N = 1613$)	Never treated with eculizumab ($N = 2505$)
Female, *n* (%)	851 (52.8)	1311 (52.3)
Age at baseline,[a] years		
Mean (SD)	42.7 (17.8)	45.7 (19.3)
Median (Q1, Q3)	39.2 (28.1, 56.6)	45.1 (29.0, 61.7)
Age at PNH disease start,[b] years		
Mean (SD)	39.3 (18.1)	43.2 (19.6)
Median (Q1, Q3)	35.2 (24.0, 53.1)	42.1 (25.9, 59.3)
% GPI-deficient granulocytes		
Mean (SD)	70.2 (27.8)	22.1 (31.1)
Median (Q1, Q3)	79.4 (54.0, 92.8)	5.1 (0.5, 33.0)
<10%,[c] *n*/*N* (%)	49/1021 (4.8)	1051/1787 (58.8)
≥10% to 50%,[c] *n*/*N* (%)	175/1021 (17.1)	385/1787 (21.5)
≥50%,[c] *n*/*N* (%)	797/1021 (78.1)	351/1787 (19.6)
LDH ratio (×ULN)		
<1.5,[c] *n*/*N* (%)	138/1128 (12.2)	1328/1965 (67.6)
≥1.5,[c] *n*/*N* (%)	990/1128 (87.8)	637/1965 (32.4)
Hemoglobin (g/dL), *n*	1262	2240
Mean (SD)	9.5 (2.1)	10.2 (2.7)
Median (Q1, Q3)	9.4 (8.1, 10.7)	10.0 (8.3, 12.1)
eGFR, mL/min, *n*	1143	2063
Mean (SD)	96.8 (31.3)	90.5 (28.3)
Median (Q1, Q3)	100.5 (78.4, 118.6)	92.7 (71.1, 110.8)
HDA,[d] *n*/*N* (%)	912/1127 (80.9)	585/1965 (29.8)
History of BMF,[c] *n*/*N* (%)	705/1549 (45.5)	1878/2371 (79.2)
History of MAVE,[c] *n*/*N* (%)	371/1550 (23.9)	246/2275 (10.8)
History of TE,[c] *n*/*N* (%)	305/1537 (19.8)	156/2241 (7.0)
Transfusion dependency,[c,e] *n*/*N* (%)	428/1277 (33.5)	738/2411 (30.6)

Abbreviations: BMF, bone marrow failure; eGFR, estimated glomerular filtration rate; GPI, glycosylphosphatidylinositol; HDA, high disease activity; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; PNH, paroxysmal nocturnal hemoglobinuria; TE, thromboembolic event; ULN, upper limit of normal.

[a]Baseline was defined as the earlier of either date of eculizumab treatment initiation or International PNH Registry enrollment date for patients treated with eculizumab and Registry enrollment date for patients never treated with any anti-complement treatment.

[b]PNH disease start was defined as the earliest date of first reported PNH symptoms, first detected GPI-deficient granulocytes, or PNH diagnosis.

[c]*N* = number of patients with reported values for that parameter.

[d]HDA was defined as LDH ratio ≥1.5 × ULN and ≥1 of the following: history of MAVEs (including TEs), anemia (hemoglobin <10 g/dL), or physician-documented abdominal pain, dyspnea, dysphagia, fatigue, hemoglobinuria, or erectile dysfunction (for males only) at any time before or at baseline.

[e]Transfusion dependency was defined as having ≥4 erythrocyte transfusions in the 12 months before baseline.

3.2 | Survival analysis

Univariable Cox proportional HR (95% CI) for mortality in eculizumab-treated time versus eculizumab-untreated time was 0.51 (0.41–0.64), indicating a 49% improvement in survival in the treated period (Table 2; Figure 1A). Other covariates associated with survival included lower age at PNH disease start ($p < 0.0001$), female sex ($p = 0.0003$), no history of BMF at baseline ($p < 0.0001$), no transfusion dependence at baseline ($p < 0.0001$), and eGFR >60 mL/min/1.73 m^2 at baseline ($p < 0.0001$, Table 2).

In the adjusted analysis comparing survival in eculizumab-treated time versus untreated time, patients with HDA at baseline had the largest reduction in mortality risk (49%; HR [95% CI], 0.51 [0.36–0.72]; Table 3; Figure 1B). Decreased mortality risk was also observed in eculizumab-treated time versus untreated time for the 10.3% of patients who had unknown HDA status, largely owing to missing labs at baseline (50%; HR [95% CI], 0.50 [0.32–0.80]), with a slight decrease in patients without HDA (9%; HR [95% CI], 0.91 [0.55–1.51]; Figure 1C). Stratified analyses showed significant survival benefits in eculizumab-treated patients with clone size ≥50% (55%; HR [95% CI], 0.45 [0.28–0.72]), age >40 years (48%; HR [95% CI], 0.52 [0.35–0.75]), and regardless of a history of BMF (history of BMF: 42%; HR [95% CI], 0.58 [0.37–0.89]; no history of BMF: 58%; HR [95% CI], 0.42 [0.24–0.74]).

In a stratified analysis by GPI-deficient granulocytes, the univariable Cox proportional HR (95% CI) for mortality in eculizumab-treated time versus eculizumab-untreated time was 1.11 (0.45–2.70) for individuals with <10% GPI-deficient granulocytes ($p = 0.8266$), 1.14 (0.64–2.03) for individuals with 10% to <50% GPI-deficient granulocytes ($p = 0.6474$), and 0.39 (0.26–0.58) for individuals with ≥50% GPI-deficient granulocytes ($p < 0.0001$) (Supplementary Figure 2A–C). Patients with ≥50% GPI-deficient granulocytes had a 61% improvement in survival during eculizumab-treatment time versus eculizumab-untreated time.

3.3 | TEs and MAVEs

When comparing the incidence of TEs and MAVEs during treated versus untreated time periods among treated patients, the average risk of TEs or MAVEs was approximately 6-fold greater. The HR (95% CI) for TEs for untreated versus treated time for treated patients was 6.26 (3.78–10.36); for MAVEs, the HR (95% CI) was 6.69 (4.43–10.10). Among treated patients, a 60–63% reduction in TE and MAVE risk was observed during treated time compared to untreated time (TEs, adjusted HR [95% CI], 0.40 [0.26–0.62]; $p < 0.0001$; MAVEs, HR [95% CI], 0.37 [0.26–0.54]; $p < 0.0001$).

4 | DISCUSSION

This study examined the real-world, long-term survival benefit associated with eculizumab in patients with PNH enrolled in an international

TABLE 2 Univariate cox analysis of factors associated with survival.

Covariate/parameter	Covariate baseline value, *n/N* (%)[a]	Covariate reference value, *n/N* (%)[a]	Hazard ratio (95% CI)	*p* value
Treatment exposure	Eculizumab-treated time	Eculizumab-untreated time	0.51 (0.41–0.64)	<0.0001
HDA at baseline[b,c]	No 204/1595 (12.8)	Yes 152/1500 (10.1)	1.19 (0.95–1.49)	0.1260
	Unknown 106/1026 (10.3)	Yes 152/1500 (10.1)	0.95 (0.74–1.24)	0.7227
Age at PNH disease start, years			1.05 (1.05–1.06)	<0.0001
Sex	Male 263/1959 (13.4)	Female 199/2162 (9.2)	1.43 (1.18–1.73)	0.0003
History of BMF at baseline	No 105/1339 (7.8)	Yes 349/2584 (13.5)	0.55 (0.43–0.69)	<0.0001
History of TE at baseline	No 380/3320 (11.4)	Yes 57/461 (12.4)	1.03 (0.77–1.39)	0.8365
Transfusion dependence at baseline[d]	No 198/2525 (7.8)	Yes 218/1166 (18.7)	0.42 (0.34–0.52)	<0.0001
eGFR ≤60 mL/min/1.73 m^2 at baseline	No 251/2737 (9.2)	Yes 123/472 (26.1)	0.30 (0.24–0.37)	<0.0001

Abbreviations: BMF, bone marrow failure; eGFR, estimated glomerular filtration rate; HDA, high disease activity; TE, thromboembolic event.
[a]*N* = number of patients with reported values for that parameter.
[b]HDA was defined as lactate dehydrogenase ratio ≥1.5 × upper limit of normal closest to baseline and ≥1 of the following: history of major adverse vascular event, including TE; and/or anemia as defined by hemoglobin <10 g/dL; and/or history of physician-reported symptoms including abdominal pain, shortness of breath, dysphagia, fatigue, hemoglobinuria, and/or erectile dysfunction (for males only) at any time before and including baseline.
[c]Baseline was defined as the earlier of either date of eculizumab treatment initiation or International PNH Registry enrollment date for patients treated with eculizumab and Registry enrollment date for patients never treated with any anti-complement treatment.
[d]Transfusion dependency was defined as having ≥4 erythrocyte transfusions in the 12 months before baseline.

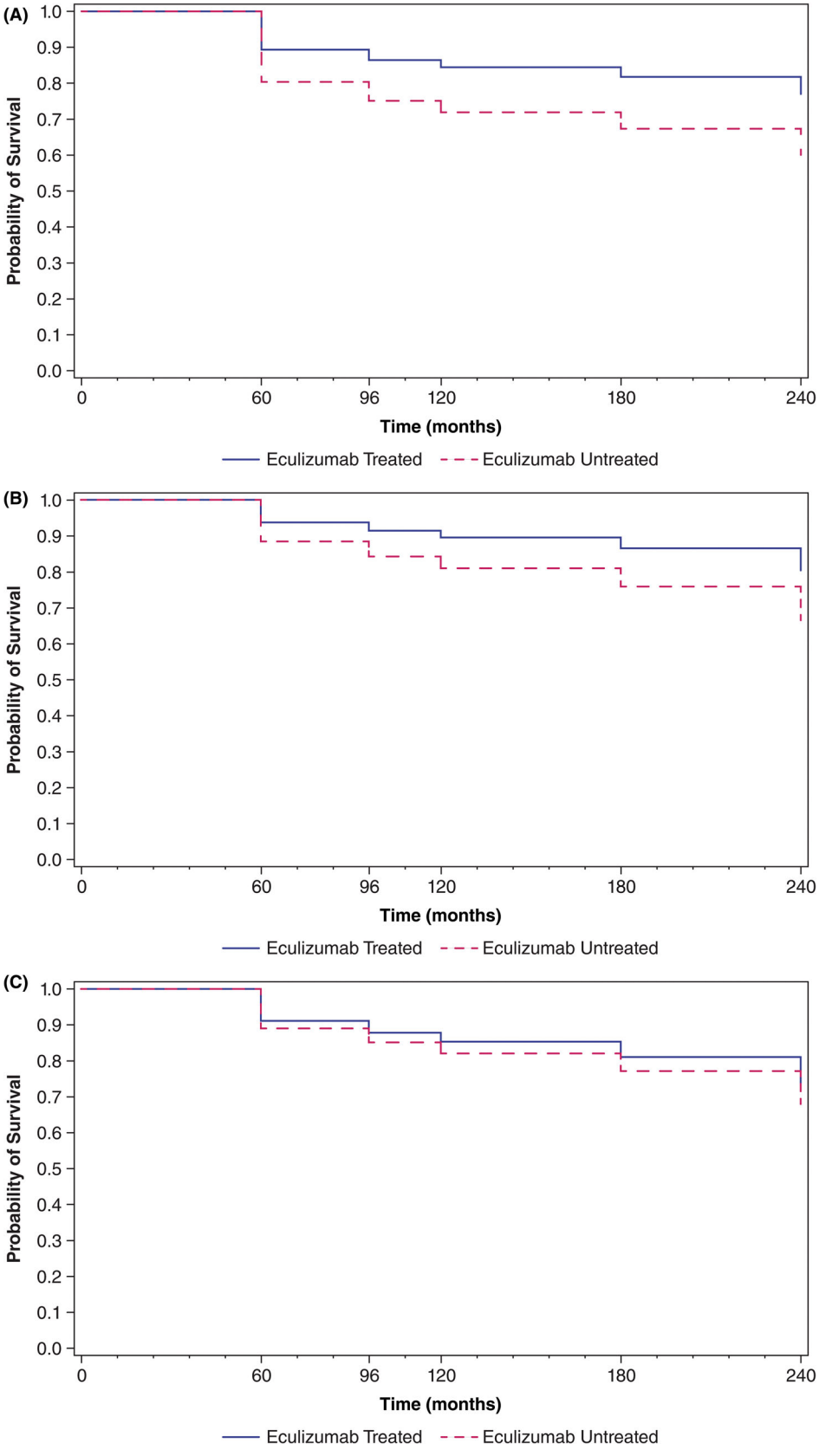

FIGURE 1 Survival time for eculizumab-treated time compared to untreated time. Survival time for eculizumab-treated time compared to untreated time overall (A) and for patients with (B) and without (C) high disease activity at baseline.

Registry containing the largest reported data set to date. In this study, a greater proportion of treated patients at baseline demonstrated features typical of hemolytic PNH such as LDH levels ≥1.5 × ULN and GPI-deficient granulocytes ≥50%. More treated patients had history of TEs/MAVEs and HDA, indicating a more severe clinical presentation. While treatment recommendations support the use of

TABLE 3 Adjusted Cox analysis of factors associated with survival.

Covariate/parameter	Covariate baseline value, *n/N* (%)[a]	Covariate reference value, *n/N* (%)[a]	Hazard ratio (95% CI)	*p* value
Treatment exposure	Eculizumab-treated time	Eculizumab-untreated time	NA	0.0001
HDA at baseline[b,c]	No 204/1595 (12.8)	Yes 152/1500 (10.1)	NA	0.3230
	Unknown 106/1026 (10.3)	Yes 152/1500 (10.1)	NA	0.3792
Treatment exposure × HDA at baseline	Eculizumab-treated time; HDA at baseline = no	Eculizumab-untreated time; HDA at baseline = yes	NA	0.0551
	Eculizumab-treated time; HDA at baseline = unknown	Eculizumab-untreated time; HDA at baseline = yes	NA	0.9718
Age at PNH disease start,[d] years			1.05 (1.04–1.05)	<0.0001
Sex	Male 263/1959 (13.4)	Female 199/2162 (9.2)	1.41 (1.16–1.72)	0.0006
History of BMF at baseline	No 105/1339 (7.8)	Yes 349/2584 (13.5)	0.76 (0.59–0.97)	0.0291
	Unknown 8/198 (4.0)	Yes 349/2584 (13.5)	0.44 (0.19–1.06)	0.0665
History of TE at baseline	No 380/3320 (11.4)	Yes 57/461 (12.4)	1.11 (0.82–1.51)	0.4993
	Unknown 25/340 (7.4)	Yes 57/461 (12.4)	1.09 (0.62–1.92)	0.7673
Transfusion dependence at baseline[e]	No 198/2525 (7.8)	Yes 218/1166 (18.7)	0.46 (0.37–0.56)	<0.0001
	Unknown 46/430 (10.7)	Yes 218/1166 (18.7)	0.65 (0.45–0.94)	0.0233
eGFR ≤60 mL/min/1.73 m^2 at baseline	No 251/2737 (9.2)	Yes 123/472 (26.1)	0.71 (0.56–0.90)	0.0056
	Unknown 88/912 (9.6)	Yes 123/472 (26.1)	0.86 (0.61–1.22)	0.3951
Eculizumab-treated time versus eculizumab-untreated time				
HDA at baseline = yes			0.51 (0.36–0.72)	
HDA at baseline = no			0.91 (0.55–1.51)	
HDA at baseline = unknown			0.50 (0.32–0.80)	

Abbreviations: BMF, bone marrow failure; eGFR, estimated glomerular filtration rate; HDA, high disease activity; MAVE, major adverse vascular event; PNH, paroxysmal nocturnal hemoglobinuria; TE, thromboembolic event.

[a]*N* = number of patients with reported values for that parameter.

[b]HDA was defined as lactate dehydrogenase ratio ≥1.5 × upper limit of normal closest to baseline and ≥1 of the following: history of MAVE, including TE; and/or anemia as defined by hemoglobin <10 g/dL; and/or history of physician-reported symptoms including abdominal pain, shortness of breath, dysphagia, fatigue, hemoglobinuria, and/or erectile dysfunction (for males only) at any time before and including baseline.

[c]Baseline was defined as the earlier of either date of eculizumab treatment initiation or International PNH Registry enrollment date for patients treated with eculizumab and Registry enrollment date for patients never treated with any anti-complement treatment.

[d]PNH disease start was defined as the earliest date of first reported PNH symptoms, first detected GPI-deficient granulocytes, or PNH diagnosis.

[e]Transfusion dependency was defined as having ≥4 erythrocyte transfusions in the 12 months before baseline.

eculizumab for patients with hemolytic PNH, eculizumab may not be readily accessible, such as in low-middle income countries.[1,20,21]

Previous studies showed survival rates of 95–100% at 5 years with eculizumab.[11,16,22] However, these previous studies had limitations with respect to the sample size, contemporaneous data for comparator populations, and duration of time on eculizumab.[6,11,16] In this study, treated and untreated time were compared and indicated that treatment with eculizumab improved patient survival. Survival benefits were most pronounced in eculizumab-treated patients with HDA compared with those without. Meaningful survival benefits associated with eculizumab treatment were observed in patients with HDA or with unknown HDA status at baseline and were maintained

through ≥14 years of real-world follow-up. Despite this, there are some limitations to this analysis. At least in countries where eculizumab is available, treated patients generally have more significant hemolytic disease than untreated patients, which leads to confounding effects when comparing the groups. Other confounding factors may include the impact and severity of BMF between groups, other causes of anemia and transfusion dependence, and not including clone size as a covariate in the data analysis owing to missing data.

Findings from the subanalysis using percentage of GPI-deficient granulocytes indicated that ≥50% GPI-deficient granulocytes was associated with a statistically significant improvement in survival within the eculizumab-treated group versus untreated group ($p < 0.0001$). However, certain limitations must be considered when interpreting the data and drawing conclusions owing to the frequency with which GPI-deficient granulocyte information is missing. An imbalance in the distribution of the percentage of GPI-deficient granulocytes by treatment status was observed across subgroups with <10% and ≥50% GPI-deficient granulocytes. Notably, a greater proportion of eculizumab-treated patients (78.1%) versus untreated patients (19.6%) had ≥50% GPI-deficient granulocytes; as such, our findings should be interpreted with caution.

TEs and MAVEs are serious, life-threatening complications in patients with PNH.[23] TEs have been reported in approximately one-third of patients not receiving eculizumab.[11,24] For treated patients, a greater reduction in TE and MAVE risk (60%–63%) was observed while being treated with eculizumab compared to untreated time. When comparing the risk of TEs or MAVEs during untreated time among ever-treated patients and never-treated patients, the average risk of TEs/MAVEs was approximately 6-fold greater. This is in line with other studies, which showed 6- to 7-fold reductions in rates of thromboses after eculizumab treatment. In a retrospective study, eculizumab treatment reduced the rate of TE to 0.8 events per 100 patient-years from 5.6 events per 100 patient-years at baseline.[11] Similarly, a pooled analysis of eculizumab trials reported rates of thromboembolism of 7.4 per 100 patient-years at baseline compared to 1.1 per 100 patient-years after treatment with eculizumab.[24]

In this study, there are other limitations to the analysis than those described above. First, adjusting for baseline HDA, history of TEs, and other covariates does not fully control for differences in disease severity among treated versus untreated patients. However, incorporation of an "ever-treated" status may in part address confounding by indication. Additionally, while this study investigated all-cause mortality, it is not possible to differentiate between PNH-related causes of death. Last, this is a noninterventional retrospective study; thus, there is potential for missing data and incomplete reporting.

In conclusion, this analysis of the International PNH Registry of more than 4000 patients found that treatment with eculizumab improved patient survival compared with the untreated cohort at a comparable time point in their disease course. The most pronounced improvement in survival was observed in individuals with HDA at baseline. Survival benefits conferred by eculizumab treatment were maintained through ≥14 years of real-world follow-up. Furthermore, for treated patients, a greater reduction in the risk of TEs and MAVEs, which are significant contributors to mortality risk, was observed while being treated compared to untreated. The findings of this analysis add to the considerable body of real-world evidence demonstrating the long-term survival benefits as well as meaningful reduction in the occurrence of TEs and MAVEs associated with eculizumab in patients with PNH and provide a substantial patient sample and contemporaneous data for comparator populations.

AUTHOR CONTRIBUTIONS

Jong Wook Lee contributed to the study conceptualization and refining of the research idea, data acquisition, data analysis and interpretation, and writing of the original draft, as well as reviewed and edited the manuscript. Morag Griffin contributed to the study conceptualization and refining of the research idea, data acquisition, data analysis and interpretation, and writing of the original draft, as well as reviewed and edited the manuscript. Jeff Szer contributed to the study conceptualization and refining of the research idea, data acquisition, data analysis and interpretation, and writing of the original draft, as well as reviewed and edited the manuscript. Alexander Röth contributed to the study conceptualization and refining of the research idea, data acquisition, data analysis and interpretation, and writing of the original draft, as well as reviewed and edited the manuscript. Philippe Gustovic contributed to the study conceptualization and refining the research idea, data analysis and interpretation, and writing of the original draft, as well as reviewed and edited the manuscript. Jesse Metzger contributed to refining the research idea, statistical analysis, data analysis and interpretation, and writing of the original draft, as well as reviewed and edited the manuscript. Ami S. Patel contributed to the study conceptualization and refining the research idea, data analysis and interpretation, and writing of the original draft, as well as reviewed and edited the manuscript. Christopher J. Patriquin contributed to the study conceptualization and refining the research idea, data analysis and interpretation, and writing of the original draft, as well as reviewed and edited the manuscript. All authors take responsibility for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors approved the final version for publication.

ACKNOWLEDGMENTS

The authors and sponsor would like to acknowledge Adrienne Aiello, Anita Hill, Åsa Lommele, Cynthia Carrillo-Infante, and Michael Yamauchi of Alexion, AstraZeneca Rare Disease for reviewing the manuscript. The authors would like to acknowledge Grace He of Parexel, who provided statistical support. Writing support was provided by Lauriaselle Afanador, PhD, and Miranda Tradewell, PhD, of The Curry Rockefeller Group, LLC (Tarrytown, NY), and was funded by Alexion, AstraZeneca Rare Disease (Boston, MA).

FUNDING INFORMATION

This study was funded by Alexion, AstraZeneca Rare Disease, Boston, MA.

CONFLICT OF INTEREST STATEMENT

Louis Terriou has served as a consultant and an advisory board member for Alexion, AstraZeneca Rare Disease. Jong Wook Lee has received grants and honoraria from and has served as an advisory board member for Alexion, AstraZeneca Rare Disease. Cecily Forsyth has served on advisory boards and received honoraria from Alexion, AstraZeneca Rare Disease and Sobi. Morag Griffin has received honoraria from Alexion, AstraZeneca Rare Disease and Sobi and has served as an advisory board member for Alexion, AstraZeneca Rare Disease; Amgen; Novartis; Biocryst; and Sobi. She has served as a consultant for Biocryst and Regeneron Pharmaceuticals. She has also received educational grant support from Apellis. Jeff Szer has served on advisory boards and speaker bureaus and has received honoraria from Alexion, AstraZeneca Rare Disease; Apellis; Novartis; Pfizer; Sanofi; and Eli Lilly. Alexander Röth has received research support from Roche and has received honoraria as well as provided consultancy to Alexion, AstraZeneca Rare Disease; Apellis Pharmaceuticals; Biocryst; Kira; Novartis; Roche; Bioverativ, a Sanofi company; and Sanofi. Philippe Gustovic is an employee of Alexion, AstraZeneca Rare Disease. Jesse Metzger is an employee of Parexel. Ami S. Patel is an employee of Alexion, AstraZeneca Rare Disease. Christopher J. Patriquin has received honoraria for participation in speaker bureaus and/or consulting for Alexion, AstraZeneca Rare Disease; Apellis; Sobi; and Biocryst and has served as a clinical site investigator for Alexion, AstraZeneca Rare Disease and Apellis.

DATA AVAILABILITY STATEMENT

Alexion, AstraZeneca Rare Disease will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods such as data de-identification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed-consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at http://alexion.com/our-research/research-and-development. Link to data-request form: https://alexion.com/contact-alexion/medical-information.

CLINICAL TRIAL REGISTRATION

clinicaltrials.gov, NCT01374360.

ORCID

Jeff Szer https://orcid.org/0000-0001-6783-2301
Christopher J. Patriquin https://orcid.org/0000-0002-2089-8650

REFERENCES

1. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124:2804-2811.
2. Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. *Nat Rev Dis Primers*. 2017;3:17028.
3. Parker C, Omine M, Richards S, et al. Interest group. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood*. 2005;106:3699-3709.
4. Schrezenmeier H, Muus P, Socie G, et al. Baseline characteristics and disease burden in patients in the international paroxysmal nocturnal hemoglobinuria registry. *Haematologica*. 2014;99:922-929.
5. Jang JH, Kim JS, Yoon SS, et al. Predictive factors of mortality in population of patients with paroxysmal nocturnal hemoglobinuria (PNH): results from a Korean PNH registry. *J Korean Med Sci*. 2016;31:214-221.
6. Loschi M, Porcher R, Barraco F, et al. Impact of eculizumab treatment on paroxysmal nocturnal hemoglobinuria: a treatment versus no-treatment study. *Am J Hematol*. 2016;91:366-370.
7. Peffault de Latour R, Mary JY, Salanoubat C, et al. Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. *Blood*. 2008;112:3099-3106.
8. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 1995;333:1253-1258.
9. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood*. 2013;121:4985-4996; quiz 5105.
10. Moyo VM, Mukhina GL, Garrett ES, Brodsky RA. Natural history of paroxysmal nocturnal haemoglobinuria using modern diagnostic assays. *Br J Haematol*. 2004;126:133-138.
11. Kelly RJ, Hill A, Arnold LM, et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. *Blood*. 2011;117:6786-6792.
12. Nishimura J, Kanakura Y, Ware R, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. *Medicine*. 2004;83:193-207.
13. Alexion Europe SAS. Soliris. Located At: Eculizumab, Paris, France. 2021.
14. Alexion Pharmaceuticals, Inc. Soliris. *eculizumab*. New Haven, CT. 2020.
15. 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.
16. Füreder W, Sperr WR, Heibl S, et al. Prognostic factors and follow-up parameters in patients with paroxysmal nocturnal hemoglobinuria (PNH): experience of the Austrian PNH network. *Ann Hematol*. 2020;99:2303-2313.
17. ClinicalTrials.gov. Paroxysmal Nocturnal Hemoglobinuria (PNH) Registry. Accessed April 8, 2022. https://clinicaltrials.gov/ct2/show/NCT01374360
18. Schrezenmeier H, Röth A, Araten DJ, et al. Baseline clinical characteristics and disease burden in patients with paroxysmal nocturnal hemoglobinuria (PNH): updated analysis from the International PNH Registry. *Ann Hematol*. 2020;99:1505-1514.
19. Hochsmann B, de Fontbrune FS, Lee JW, et al. Effect of eculizumab treatment in patients with paroxysmal nocturnal hemoglobinuria with or without high disease activity: real-world findings from the international paroxysmal nocturnal hemoglobinuria registry. *Eur J Haematol*. 2022;109:197-204.
20. Nga HS, Palma LMP, Ernandes Neto M, Modelli de Andrade LG. Eculizumab in low-middle income countries: how much does a life cost? *J Nephrol*. 2022;35:1255-1257.
21. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Hematology Am Soc Hematol Educ Program*. 2016;2016:208-216.
22. Hillmen P, Muus P, Röth A, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2013;162:62-73.
23. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA*. 2005;293:1653-1662.

24. 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.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Terriou L, Lee JW, Forsyth C, et al. Long-term effectiveness of eculizumab: Data from the International PNH Registry. *Eur J Haematol*. 2023;111(5):796-804. doi:10.1111/ejh.14080