Quality of Life and Symptom Burden of Paroxysmal Nocturnal Hemoglobinuria Among Patients Receiving C5 Inhibitors in the United States and Europe

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Matos JE,[1] Mnif T,[2] Costantino H,[1] Lehrhaupt K,[1] Le Calve P,[2] Sarda SP,[3] Baver SB,[3] Fishman J,[3] Hakimi Z,[4] Nazir J,[4] Persson E,[4] Desgraz R,[5] Lui B,[6] Panse J[7]

[1]Cerner Enviza (Previously Kantar Health), Malvern, PA, USA; [2]Cerner Enviza (Previously Kantar Health), Paris, France; [3]Apellis Pharmaceuticals, Inc., Waltham, MA, USA; [4]Swedish Orphan Biovitrum AB, Stockholm, Sweden; [5]Apellis Pharmaceuticals, Inc., Basel, MA, Switzerland; [6]Apellis Pharmaceuticals, Inc., Zurich, MA, Switzerland; [7]University Hospital RWTH Aachen, Aachen, Germany

Introduction

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, and potentially life-threatening hematologic disease characterized by chronic complement-mediated hemolysis.
- Complement-mediated hemolysis occurs due to the absence of the complement inhibitory proteins CD55 and CD59 on the surface of erythrocytes, which is a direct result of a somatic mutation in the *PIG-A* gene that codes for an enzyme involved in the biosynthesis of the glycosylphosphatidylinositol cell membrane anchor required by these proteins.[1]
- Treatment with the C5 inhibitor eculizumab (Ecu) has resulted in a reduction in intravascular hemolysis (IVH) and improvements in morbidity and mortality.[2,3]
- Despite improvement in morbidities, a significant proportion of patients continue experiencing hemolysis and suboptimal quality of life (QoL), with some patients still requiring transfusions due to ongoing IVH and extravascular hemolysis.[4]

Objective

- The study aimed at investigating the symptom burden of PNH in patients currently treated with C5 inhibitors, globally.

Methods

Study Design and Data Source

- This was a cross-sectional, web-based, self-report survey of patients (age 18 or older) with PNH conducted in the United States (US), United Kingdom (UK), France, and Germany.
- Inclusion criteria were a self-reported PNH diagnosis, aged ≥ 18 years, current treatment with Ecu in the US, Germany, France, and the UK or ravulizumab (Ravu) in the US and Germany only, and agreement to informed consent and adverse event reporting. Only patients who provided informed consent and met the inclusion criteria were allowed to complete the survey.
- Patients were recruited in each country using Patient Advocacy Groups (PAGs). In each country, members of the PAGs (US – Aplastic Anemia & MDS International Foundation [AAMDS]; UK – PNH UK; France – HPN France; Germany – Stiftung lichterzellen) received an email invitation to participate in the survey. The email invitation contained advertising text highlighting the details about the study objectives, methodology, and sponsor's name, as well as a link to access the study questionnaire.
- Participants received a small honorarium for their time and participation; incomplete surveys were not included in the analysis.
- Kantar Health was responsible for patient recruitment, survey administration, data collection, analysis, and reporting.
- Data were collected from July to September 2020 in the US and from February to April 2021 in Europe.

Data Collected

- Participants were asked to confirm the date of their diagnosis, name (and dose) of treatment, frequency and duration of treatment, hemoglobin level, frequency of monitoring hemoglobin level, transfusion history, thrombotic event history, and symptom history.
- Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement Scale (Likert scale: 0-4, the higher score shows not at all fatigued; total score range: 0-52).

Statistical Analysis

- Descriptive statistics were used throughout the analyses.
- Means, standard deviations (SDs), medians, and ranges were presented for continuous measures. Counts and percentages were presented for categorical measures.

Results

- Patient characteristics are shown in **Table 1**. A total of 71 adult patients with a self-reported PNH diagnosis were enrolled in EU (France, n=20; UK, n=20; Germany, n=31) and 122 in the US.
- Patients in the EU were diagnosed at a younger age than patients in the US (median; EU: 27.0, US: 34.5).
- Current medications included Ecu (EU: 69%, US: 29%) or Ravu (EU: 31%, US: 71%). Current Ecu users reported dosages of 600 mg (EU: 4.1%, US: 2.9%), 900 mg (EU: 61.2%, US: 57.1%), 1200 mg (EU: 22.4%, US: 31.4%), or specified 1500 mg for "other" (EU: 6.1%, US: 2.9%). Most patients were on treatment for ≥ 3 months (EU: 98.6%, US: 96.7%).
- The most recent hemoglobin level was reported lower than 12g/dL (mean ± SD; EU: 10.19 ± 1.9, US: 10.17 ± 2.04) for the majority of patients (EU: 85.7%, US: 84.2%), indicating that most remained anemic.
- Among patients who ever received a red blood cell transfusion and were on treatment for ≥ 1 year, 35.0% of patients in EU and 35.2% in the US received at least one transfusion in the previous year, and 18% (EU) and 22% (US) received at least four.

Table 1. Patient Characteristics

Patient and Health Characteristics	Total (n=193)	Europe (n=71)	US (n=122)
Gender*, n (%)			
Male	56 (29.0%)	24 (33.8%)	32 (26.2%)
Female	136 (70.5%)	47 (66.2%)	89 (73.0%)
Age, median (range) years	44.00 (18.00–88.00)	42.00 (19.00–74.00)	46.00 (18.00–88.00)
Age at Diagnosis, median (range) years	31.00 (9.00–70.00)	27.00 (11.00–62.00)	34.50 (9.00–70.00)
Number of Years with PNH, median range	8.00 (0.00–52.00)	13.00 (1.00–39.00)	7.00 (0.00–52.00)
Current Medication, n (%)			
Ravulizumab	109 (56.5%)	22 (31.0%)	87 (71.3%)
Eculizumab	84 (43.5%)	49 (69.0%)	35 (28.7%)
Ravulizumab Dose, n (%)			
Valid n	(n=109)	(n=22)	(n=87)
2400 mg	5 (4.6%)	1 (4.5%)	4 (4.6%)
2700 mg	1 (0.9%)	1 (4.5%)	0 (0.0%)
3000 mg	13 (11.9%)	4 (18.2%)	9 (10.3%)
3300 mg	34 (31.2%)	10 (45.5%)	24 (27.6%)
3600 mg	17 (15.6%)	2 (9.1%)	15 (17.2%)
Other (specify mg)	2 (1.8%)	1 (4.5%)	1 (1.1%)
I don't know	37 (33.9%)	3 (13.6%)	34 (39.1%)
Date of Treatment Initiation, n (%)			
Less than 1 month ago	–	0 (0.0%)	1 (0.8%)
1 to 2 months ago	4 (2.1%)	1 (1.4%)	3 (2.5%)
3 to 11 months ago	36 (18.7%)	7 (9.9%)	29 (23.8%)
1 to less than 2 years ago	80 (41.5%)	20 (28.2%)	60 (49.2%)
2 to less than 3 years ago	13 (6.7%)	8 (11.3%)	5 (4.1%)
3 or more years ago	59 (30.6%)	35 (49.3%)	24 (19.7%)
Comorbidities, n (%)			
Aplastic Anemia or Severe Aplastic Anemia	67 (34.7%)	26 (36.6%)	41 (33.6%)
Myelodysplastic Syndrome	6 (3.1%)	1 (1.4%)	5 (4.1%)
Another bone marrow disorder	6 (3.1%)	4 (5.6%)	2 (1.6%)
None of the above	112 (58.0%)	39 (54.9%)	73 (59.8%)
Unknown / not sure	5 (2.6%)	1 (1.4%)	4 (3.3%)
Most Recent Hemoglobin Level Category, n (%) Excludes patients who did not know their most recent hemoglobin level			
Valid n	(n=177)	(n=63)	(n=114)
Hb < 10.5 g/dL	103 (58.2%)	36 (57.1%)	67 (58.8%)
10.5 ≤ Hb ≤ 12 g/dL	47 (26.5%)	18 (28.6%)	29 (25.4%)
Hb > 12 g/dL	27 (15.3%)	9 (14.3%)	18 (15.8%)
Number of Transfusions in Past 12 Months, n (%) Among patients who ever received a red blood cell transfusion and were on treatment for ≥1 year			
Valid n	(n=94)	(n=40)	(n=54)
0 transfusions	54 (57.4%)	26 (65.0%)	28 (51.9%)
≥ 1 transfusion	33 (35.1%)	14 (35.0%)	19 (35.2%)
I don't know	7 (7.4%)	0 (0.0%)	7 (13.0%)

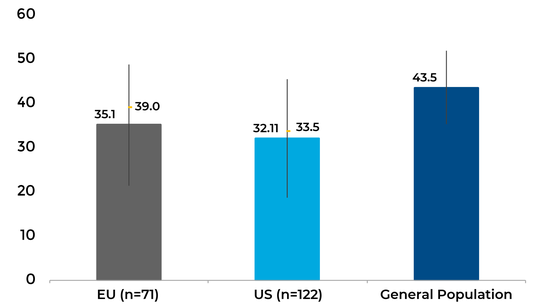
Note: *One (1) respondent answered, "I prefer not to answer."

- Patient-reported current symptoms and those experienced at diagnosis are presented in **Table 2**.
- Some symptoms seem to persist for most patients, where the proportion of patients reporting (e.g., difficulty focusing on tasks or sleeping difficulties) is similar at diagnosis and currently, or worse currently.
- Fatigue was the most commonly reported symptom (EU: 63.4%, US: 78.7%).
- Breakthrough hemolysis was experienced by US (40%) and EU (39%) patients.
- Patients treated with C5 inhibitors experienced, on average, higher rates of fatigue than those previously reported in the general population in Germany (**Figure 1**).[5] FACIT scores (EU: 35.0 ± 13.7, US: 32.1 ± 13.4) were lower than in the general population (43.5 ± 8.3).

Table 2. Reported Current and At-Diagnosis Symptoms

Symptoms, n (%)	Total (n=193)		Europe (n=71)		US (n=122)	
	Current	At-Diagnosis	Current	At-Diagnosis	Current	At-Diagnosis
Dark Urine (hemoglobinuria)	44 (22.8%)	130 (67.4%)	14 (19.7%)	49 (69.0%)	30 (24.6%)	81 (66.4%)
Abdominal Pain	47 (24.4%)	103 (53.4%)	14 (19.7%)	34 (47.9%)	33 (27.0%)	69 (56.6%)
Jaundice	45 (23.3%)	89 (46.1%)	19 (26.8%)	34 (47.9%)	26 (21.3%)	55 (45.1%)
Shortness of Breath	90 (46.6%)	124 (64.2%)	33 (46.5%)	42 (59.2%)	57 (46.7%)	82 (67.2%)
Chest Pain	29 (15.0%)	52 (26.9%)	8 (11.3%)	15 (21.1%)	21 (17.2%)	37 (30.3%)
Headaches	61 (31.6%)	82 (42.5%)	18 (25.4%)	26 (36.6%)	43 (35.2%)	56 (45.9%)
Difficulty with Swallowing	40 (20.7%)	57 (29.5%)	14 (19.7%)	11 (15.5%)	26 (21.3%)	46 (37.7%)
Fatigue	141 (73.1%)	156 (80.8%)	45 (63.4%)	52 (73.2%)	96 (78.7%)	104 (85.2%)
Difficulty Focusing on Tasks	86 (44.6%)	96 (49.7%)	28 (39.4%)	27 (38.0%)	58 (47.5%)	69 (56.6%)
Back Pain	67 (34.7%)	75 (38.9%)	21 (29.6%)	20 (28.2%)	46 (37.7%)	55 (45.1%)
Confusion (cognitive problems)	53 (27.5%)	56 (29.0%)	29 (40.8%)	20 (28.2%)	24 (19.7%)	36 (29.5%)
Sexual Difficulties	25 (12.9%)	27 (13.9%)	10 (14.1%)	9 (12.7%)	15 (12.3%)	18 (14.8%)
Sleeping Difficulties	79 (40.9%)	78 (40.4%)	24 (33.8%)	20 (28.2%)	55 (45.1%)	58 (47.5%)
Leg Pain	49 (25.4%)	48 (24.9%)	13 (18.3%)	8 (11.3%)	36 (29.5%)	40 (32.8%)
Breakthrough Hemolysis	62 (32.1%)	–	15 (21.1%)	–	47 (38.5%)	–
None of the Above	22 (11.4%)	0 (0.0%)	9 (12.7%)	0 (0.0%)	13 (10.7%)	0 (0.0%)

Figure 1. FACIT-Fatigue Total Score* for Patients with PNH Treated with C5 Inhibitors, and the General Population (as reported in the literature; assessed in the German population)[5]



Note: FACIT, Functional Assessment of Chronic Illness Therapy; *a higher FACIT score represents better quality of life.
The number on the left of the bar line is the mean; the number on the right of the bar line is the median.

Limitations

- All data is collected entirely through self-reporting.
  - Data cannot be independently verified through other data sources.
  - There might be recall errors that could potentially introduce measurement errors, more so in the case of measures having longer recall periods, such as 3 or 6 months.
- Due to the low prevalence of the disease, a convenience sampling method was used to recruit patients. All patients were recruited via a Patient Advocacy Group, and therefore patients who are not members of the association would not have been contacted. Some biases may be inherent to this particular population, and results might therefore not be generalizable to the whole PNH population.
- Respondents were asked about the number of transfusions, or the number of thrombotic events experienced in the past 12 months, independently of when they had initiated the treatment. For those questions, patients on treatment for less than one year were excluded from the analysis in order to have a more conservative approach at the cost of reducing sample size.

Conclusions

- Despite C5 treatment, PNH patients experience a substantial burden of illness.
- There is a persistent sizeable humanistic and clinical burden of PNH.
- A high proportion of patients remains anemic; symptoms such as fatigue, shortness of breath, or difficulty focusing, among others, persist even after months on treatment with eculizumab or ravulizumab.
- Overall, these results highlight a huge unmet need that PNH patients have for better treatments.

Disclosures

- This study was sponsored by Apellis Pharmaceuticals, Inc., and Swedish Orphan Biovitrum AB.
- JE Matos was an employee of Cerner Enviza at the time of study and received funding from Apellis Pharmaceuticals, Inc., and Swedish Orphan Biovitrum AB to conduct this study.
- T Mnif, H Costantino, K Lehrhaupt, and P Le Calve are employees of Cerner Enviza and received funding from Apellis Pharmaceuticals, Inc., and Swedish Orphan Biovitrum AB to conduct this study.
- SP Sarda, SB Baver, J Fishman, R Desgraz, and B Lui are employees of Apellis Pharmaceuticals, Inc.
- Z Hakimi, J Nazir, and E Persson are employees of Swedish Orphan Biovitrum AB.
- J Panse is an employee of University Hospital RWTH Aachen.

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Email: Halley.Costantino@cernerenviza.com