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Real-world clinical outcomes among patients untreated with complement inhibitors (CIs) in paroxysmal nocturnal hemoglobinuria (PNH) – A retrospective claims database analysis in the United States

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KEY FINDINGS & CONCLUSIONS

- In this real-world study, one-fifth of untreated patients with PNH required blood transfusions and among them, one-third were blood transfusion dependent
- Considering the high cost of inpatient admission in the US (approximately $11,000),[11] PNH-related inpatient admissions in the untreated patients (15%) further highlight the significant unmet medical need
- In addition, one-fifth of the untreated patients with PNH experienced thrombosis
- Although reason why patients were untreated was unknown, these findings suggest unmet clinical needs in this population that could potentially benefit from treatment with complement inhibitors

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BACKGROUND

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and life-threatening blood disorder characterized by complement-mediated hemolytic anemia[1]
- Before complement inhibitors, patients with PNH had short life expectancy despite best supportive care such as blood transfusions and anticoagulation therapy.[2] The introduction of complement inhibitors transformed PNH treatment by improving survival to that of the general population[3]
- Current treatments for patients with PNH include the C5 inhibitors, eculizumab and ravulizumab,[4,5] which inhibit formation of the complement-initiated membrane attack complex and consequently prevent intravascular hemolysis
- Other treatment such as iptacopan, an oral complement factor B inhibitor, crovalimab, a novel anti-C5 recycling antibody, danicopan, an add on therapy for C5 inhibitors, and pegcetacoplan, a C3 inhibitor, have also received US Food and Drug Administration (FDA) approval for the treatment of PNH[6,7]
- PNH can present with a variety of disease manifestations from fully compensated asymptomatic hemolysis to hemolytic anemia, hemoglobinuria, and somatic symptoms such as fatigue and shortness of breath[8]
  - Left untreated, PNH can cause thrombosis, renal insufficiency, or bone marrow failure[9]
  - Without treatment, these complications can significantly impact the quality of life and potentially shorten the lifespan of patients with PNH

OBJECTIVE

- To assess real-world clinical outcomes among patients untreated with complement inhibitors (eculizumab, ravulizumab, or pegcetacoplan) for PNH in the US

*At the time the study was conducted, data availability did not include crovalimab, iptacopan and danicopan

METHODS

Data Source

- Health plan claims from the IQVIA PharMetrics® Plus database (01/01/2011 to 09/30/2022) was used
- IQVIA PharMetrics® Plus is a health plan claims database comprised of fully adjudicated medical and pharmacy claims for more than 215 million unique enrollees since 2006. Data contributors to the database are largely commercial health plans. It is representative of the commercially insured US national population for patients under 65 years of age. It contains a longitudinal view of inpatient [IP] and outpatient [OP] services, prescription and office/outpatient administered drugs, costs, and detailed enrollment information
- Data are de-identified and compliant with the Health Insurance Portability and Accountability Act (HIPAA)

Study Design / Sample Selection

- This was a retrospective cohort study
- Adult (aged ≥18 years) patients with ≥2 PNH diagnosis (ICD-10-CM diagnosis code: D59.5) without claims for complement inhibitors at any time were classified as untreated patients with PNH
  - **Index date** was defined as the date of the first PNH diagnosis observed in claims
- Patients were required to have continuous health plan enrollment ≥6 months prior to and ≥3 months after the index date
  - **Baseline period** was defined as the 6 months prior to the index date
- Patients were excluded if they met one of the following criteria: (1) another condition treated with C5 inhibitors (neuromyelitis optica spectrum disorder, generalized myasthenia gravis, and/or atypical hemolytic uremic syndrome), (2) codes indicating participation in a clinical trial, or (3) haematopoietic stem cell transplantation (HSCT; the only potentially curative therapy for PNH)
- **Follow-up period** was from the index date until the end of continuous health plan enrollment or end of data availability, whichever occurred first

Outcomes and Statistical Analysis

- Real-world clinical outcomes were evaluated during the follow-up period
  - Blood transfusion was defined as a day with procedure(s) for blood transfusion in medical claims in any settings (IP, emergency department [ED], or OP)[10]
    - Blood transfusion dependence was defined as ≥2 consecutive 8-week periods with ≥1 blood transfusion during each, and no interim 56-day period without a transfusion
  - PNH-related IP admission was defined as an IP admission with a diagnosis of PNH
  - PNH-related thrombosis was defined as ≥1 medical claims in any settings (IP, ED, OP) with a diagnosis for one of the following conditions: venous thrombosis (including portal vein thrombosis [Bud Chiari]), pulmonary embolism, pulmonary hypertension, arterial thrombosis, or cerebral venous sinus thrombosis, along with a diagnosis of PNH
- All analyses were descriptive; no statistical comparisons were conducted

RESULTS

Patient Characteristics

- A total of 665 untreated patients with PNH, without observed treatment with complement inhibitors, were included in the study
- Mean (SD) age at index date was 48.4 (14.8) years and 57.7% were female (**Table 1**)
- Mean (SD) [median] follow-up period was 27.3 (20.9) [21.0] months, and 88.0% had at least 6 months of follow-up post index

Table 1. Characteristics of Patients with PNH Untreated with Complement Inhibitors

	N = 665
Age at index, years	
Mean ± SD [Median]	48.4 ± 14.8 [50]
≥ 65 years, N (%)	73 (11.0%)
Female, N (%)	384 (57.7%)
Calendar year of the index, N (%)	
2015-2016	174 (26.2%)
2017-2018	189 (28.4%)
2019-2020	188 (28.3%)
2021-2022	114 (17.1%)
U.S Census region at index, N (%)	
Northeast	142 (21.4%)
South	269 (40.5%)
Midwest	143 (21.5%)
West	102 (15.3%)
Commercial health plan type at index, N (%)	
Consumer directed health care	8 (1.2%)
Health Maintenance Organization	87 (13.1%)
Indemnity/traditional	4 (0.6%)
Point of service	38 (5.7%)
Preferred provider organization	527 (79.2%)
Baseline clinical characteristics, N (%)	
Aplastic anemia	146 (22.0%)
Anemia (other than aplastic anemia)	280 (42.1%)
Blood Transfusion	89 (13.4%)
Chronic kidney disease	47 (7.1%)
Myelodysplastic syndrome	25 (3.8%)
Thrombosis	115 (17.3%)

Abbreviations: PNH: paroxysmal nocturnal hemoglobinuria, SD: standard deviation.

Blood Transfusion and Blood Transfusion Dependence

- A little more than one-fifth of patients (N = 151 [22.7%]) had ≥1 day with blood transfusion post index (**Figure 1**)
  - Among these patients, the annual incidence rate of blood transfusion was 4.3 days per patient per year
  - Among those with at least 6 months of follow-up (N = 138 [91.4%]), one-third (N = 49 [35.5%]) were blood transfusion dependent (**Figure 1**)

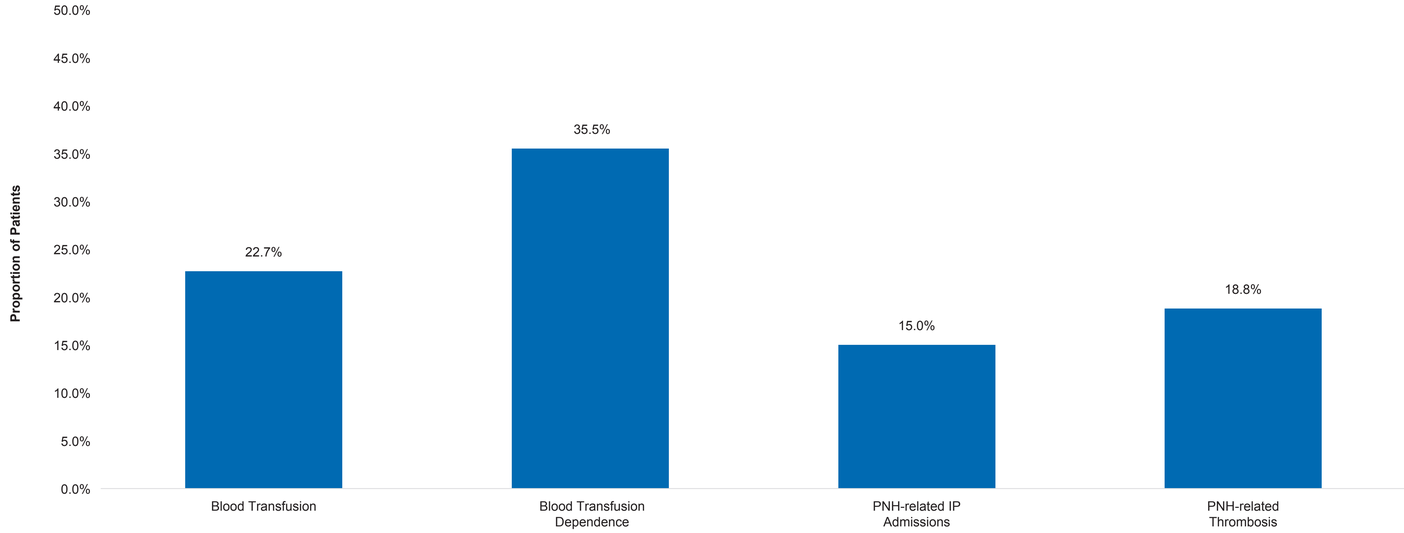
PNH-related IP Admissions

- A total of 100 (15.0%) patients had ≥1 PNH-related IP admissions post index (**Figure 1**)
  - Among these patients, the annual incidence rate was 54 PNH-related IP admissions per 100 patients per year

PNH-related Thrombosis

- Almost one-fifth of the patients (125 [18.8%]) experienced ≥1 PNH-related thrombosis event post index (**Figure 1**)
  - Among these patients, the annual incidence rate was 1.6 PNH-related thrombosis events per patient per year

Figure 1. Blood Transfusion, Blood Transfusion Dependence, PNH-related IP Admissions, and PNH-related Thrombosis among Patients with PNH Untreated with Complement Inhibitors



Limitations

- Health plan claims only include diagnosis and procedure codes that are recorded for reimbursement purposes and are subject to coding errors or data omissions
- Laboratory data, number of units of blood used for transfusion, and reasons for diagnosis and procedure codes are not available
- Given the low market uptake of pegcetacoplan, limited information exists in the data, which may have resulted in the inclusion of some patients treated with this complement inhibitor
- A conservative approach was used to define blood transfusion dependence, so the results may differ if a more relaxed definition is applied
- Some patients may have been newly diagnosed with PNH earlier than observed in claims due to ICD-10-CM diagnosis codes availability starting in October 2015
- The study sample was restricted to commercially insured patients and thus findings may not be generalizable to the entire US population

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