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A Systematic Literature Review of Clinical Response Among Patients with Paroxysmal Nocturnal Hemoglobinuria in Clinical Trials and Real-World Settings

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Introduction

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired hematopoietic stem cell disorder characterized by abnormal hemolysis, resulting in low hemoglobin (Hb), high lactate dehydrogenase (LDH), and symptoms including fatigue, dyspnea, pain, and hemoglobinuria.[1-5]
- Various measures of clinical response are used to assess treatment outcomes for patients, including laboratory values and transfusion dependence.

Aim

- The aim of this study was to systematically collect and summarize published literature reporting on measures of clinical response in PNH used in clinical trials and real-world settings.

Methods

- Data were collected through systematic searches of MEDLINE, Embase, and Cochrane libraries via Ovid (on January 25, 2022) with unrestricted publication dates, supplemented by manual searches of abstracts and posters from leading hematology and health economics and outcomes research (HEOR) conferences within the previous 2 years (2020-2021). Search strings were designed to identify studies of patients with PNH reporting relevant clinical, economic, or humanistic outcomes. Studies were included in this qualitative synthesis if they reported outcomes (e.g., Hb level, LDH level, reticulocyte count, transfusion frequency or number) in English for patients with PNH who received any or no treatment intervention in a clinical trial or observational study.
- Studies were selected for inclusion following the Centre for Review and Dissemination guidelines for conducting reviews in health care,[6] and reasons for exclusion were recorded per PRISMA guidelines.[7]
  - Studies were screened for relevance at 2 levels (title/abstract and full-text) by 2 researchers independently, with any disagreements (<2%) adjudicated by an independent third reviewer.
  - Study and patient characteristics and key outcomes were extracted for included studies by 2 researchers independently.
- This systematic literature review (SLR) is registered with PROSPERO (CRD42022314640).

Limitations

- Only studies that were published in English were included in the search. Publication bias and the quality of the included studies may impact the generalizability of our study findings.
- The screening decisions and data extraction efforts are subject to human error, though they were conducted in parallel.
- No statistical testing was conducted, and ranges are reported in lieu of formal aggregation of metrics.

Results

- Among 1,607 unique publications, 123 clinical trials and observational studies with sample sizes of ≥25 patients reported outcomes of interest (**Figure 1**).
  - Of these, 105 reported clinical response outcomes of interest (29 clinical trials and 76 observational studies) and were included in this qualitative synthesis.
  - Among the 76 observational studies that reported clinical outcomes of interest, study geographies included the US (6), other North America (2), Europe (19), Asia (23), South America (5), multinational (16), and not reported (5).
- Methods of measuring clinical response varied.
  - Twelve (41.4%) clinical trials and 23 (30.3%) observational studies reported mean or median Hb levels.
  - Eleven (37.9%) clinical trials and 15 (19.7%) observational studies reported mean or median LDH levels.
  - Four (13.8%) clinical trials and 6 (7.9%) observational studies reported mean or median reticulocyte counts.
  - Seventeen (58.6%) clinical trials and 14 (18.4%) observational studies reported the proportion of patients requiring ≥1 transfusion at baseline, while 4 (13.8%) clinical trials and 8 (10.5%) observational studies reported the proportion of patients requiring ≥1 transfusion at study completion.

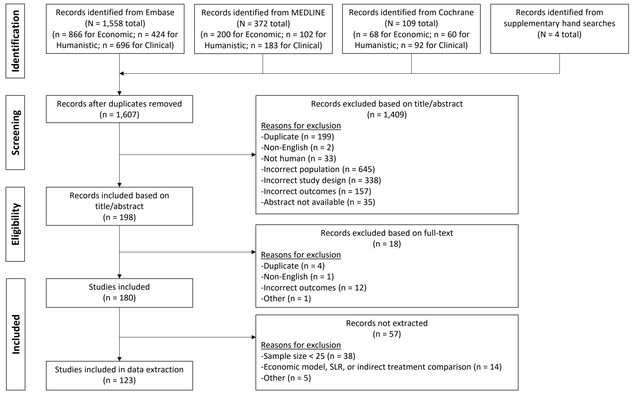


Figure 1. *PRISMA Diagram*

Reticulocyte Counts

- Mean and median reticulocyte counts in observational studies were generally lower than those in clinical trials at baseline and during follow-up.
- Reticulocyte counts during study follow-up were only reported in 10 studies, limiting interpretability.

Hemoglobin Levels

- Mean and median Hb levels were broadly consistent across clinical trials and observational studies.
- During study follow-up, mean Hb levels ranged from 7.6 – 12.8 g/dL and 6.8 – 11.9 g/dL for patients in clinical trials and observational studies, respectively.
- Mean change from baseline in Hb levels ranged from -0.9 to 3.4 g/dL and -1.5 to 2.1 g/dL for patients in clinical trials and observational studies, respectively.
- Reported Hb levels remained low from baseline through follow-up timepoints across studies. At study completion, mean and median Hb levels were <12.3 g/dL in all studies reporting values (n = 35), except for 1 clinical trial (**Figure 2**).

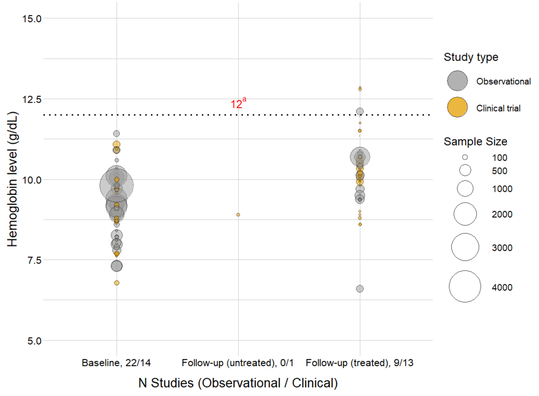


Figure 2. *Hemoglobin Levels of Patients with PNH, by Study Type and Sample Size*
[a] The dashed line indicates the Hb threshold level for a complete response per Risitano et al.[8]

Transfusions

- Mean annual transfused units at baseline ranged from 8.5 – 22.4 for patients in clinical trials and from 5.6 – 26 for patients in observational studies, lowering to 0.7 – 16.6 and 2 – 8, respectively, at the end of study follow-up.
- The proportions of patients in treated study populations who needed ≥1 transfusion and those who were transfusion-independent ranged from 15 – 85% and 0 – 96%, respectively, in clinical trials.
- In observational studies, the proportions of patients in treated study populations who needed ≥1 transfusion, who were transfusion-dependent, and who were transfusion-independent ranged from 0 – 100%, 54%, and 0 – 94%, respectively.
- The proportions of patients with unknown treatment status who needed ≥1 transfusion and who were transfusion-dependent ranged from 32 – 77% and 55 – 62%, respectively.
- The proportion of patients needing ≥1 transfusion appeared broadly lower during the follow-up periods than at baseline; however, only one study reported that no patients required transfusions at study completion. Residual transfusion requirements remain for treated patients with PNH (**Figure 4**).

Lactate Dehydrogenase Levels

- LDH levels and ratios (expressed relative to the upper limit of normal [ULN]) were generally higher in observational studies than in clinical trials at baseline, though LDH levels during follow-up varied.
- LDH levels for patients in observational studies were generally lower during follow-up than at baseline.
- During study follow-up, mean LDH levels ranged from 189 – 2419 U/L and 246.29 – 1555.45 U/L for patients in clinical trials and observational studies, respectively.
- Reported LDH levels appeared to decrease at study follow-up relative to baseline, though LDH levels remained >1.5 x ULN following treatment in several studies (**Figure 3**).

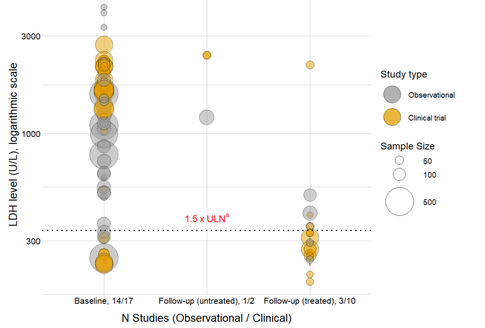


Figure 3. *Lactate Dehydrogenase Levels of Patients with PNH, by Study Type and Sample Size*
[a] The dashed line indicates 1.5 x ULN, with 225 U/L defined as the high end of the normal range for LDH per the Cleveland Clinic.[9]

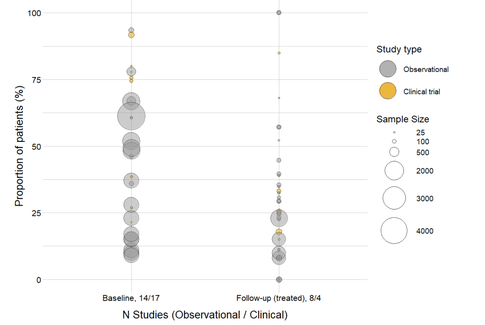


Figure 4. *Patients with PNH Requiring ≥1 Transfusion, by Study Type and Sample Size*

Conclusions

- The SAAWP of the EBMT recently proposed clinical response classification for PNH based on hemoglobin level, lactate dehydrogenase level, absolute reticulocyte count, and transfusion requirements.[8]
- This systematic literature review has identified considerable gaps and inconsistencies in the reporting of these outcomes. Relatively few studies reported each outcome, while very few reported all four outcomes.
  - The substantial variability observed in reported values for each outcome may be driven by differences in study design and patient characteristics across clinical trials and observational studies.
- Available data show that hemoglobin levels often remain below normal and that lactate dehydrogenase levels can remain >1.5 x ULN despite treatment across both clinical trial and real-world study publications.

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Disclosures

Anem Waheed received consulting fees from Novartis. Samantha Kaufhold and Dave Nellesen are employed by Analysis Group, Inc., which received funding from Novartis to conduct this study. Anumaxine Lincy Geevarghese and Glorian Yen are employed by Novartis.

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