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ORIGINAL ARTICLE

# Pegcetacoplan in paroxysmal nocturnal hemoglobinuria: A systematic review on efficacy and safety

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## Abstract

**Introduction:** Pegcetacoplan, a pegylated penta-decapeptide, targets complement C3 to control both intravascular and extravascular hemolysis. This systematic review aims to study the efficacy and safety of pegcetacoplan in paroxysmal nocturnal hemoglobinuria (PNH).

**Methods:** We performed a comprehensive and systematic literature search for all studies on PubMed, Google Scholar, Cochrane Library, and clinicaltrials.gov. The studies were searched using keywords "paroxysmal nocturnal hemoglobinuria" or "PNH," "Pegcetacoplan" or "Empaveli." The primary outcomes included change in hemoglobin level, transfusion independence, absolute reticulocyte count, and lactate dehydrogenase (LDH) level after pegcetacoplan therapy. The safety outcomes included the proportion of deaths and adverse effects.

**Results:** We included a total of three studies. The total number of patients with PNH was112. 59.83% were female. In the PADDOCK study and study by Hillmen et al., the average increase in hemoglobin was 3.68 g/L and 2.37 g/L, respectively. In the study by de Castro et al., the hemoglobin level increased from below the lower limit of normal and stayed in the normal range (11.1–15.9 g/L). Absolute reticulocyte count and LDH levels decreased in all patients receiving pegcetacoplan. In the study by de Castro et al., LDH level remained stable, and within <1.5× upper limit of normal, whereas in the study by Hillman, the mean change of LDH from baseline was −15 ± 43 U/L. Two of six, seven of 23, and seven of 41 patients reported adverse events in the study by de Castro et al., PADDOCK, and Hillmen et al., respectively.

**Conclusion:** Pegcetacoplan effectively improves hemoglobin level and transfusion requirements in patients with PNH, including those unresponsive to eculizumab.

KEYWORDS
efficacy, eculizumab, paroxysmal nocturnal hemoglobinuria, pegcetacoplan, safety

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**Essentials**

- Eculizumab has been used in a treatment for paroxysmal nocturnal hemoglobinuria.
- This systematic review aims to study efficacy and safety of Pegcetacoplan for PNH.
- Pegcetacoplan improves Hemoglobin level and transfusion requirements.
- Further evidence is required to determine benefit of adjunctive complement inhibition.

## 1 | INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematopoietic stem cell disorder characterized by an increased risk of thrombosis, bone marrow failure, fatigue, and complement-mediated red blood cell lysis.[1] The prevalence of PNH is 12–13 per 1,000,000.[2] Dark discoloration of the urine is the classic sign of PNH because of hemoglobin and hemosiderin in urine from the breakdown of red blood cells.[3] The color is most pronounced in morning as the urine is more concentrated. Patients with PNH mainly experience the symptoms of anemia, such as tiredness, shortness of breath, and palpitations.[4] Some patients present with chest or abdominal pain, difficulty swallowing, and erectile dysfunction in men.

The expansion of abnormal hematopoietic clones that lack cell-surface complement inhibitory proteins attached to the membrane through glycosyl-phosphatidylinositol (GPI) anchors results in PNH.[5–8] CD55 and CD59, two of the missing GPI-linked proteins, are key regulators of the complement pathway, and these proteins protect host cells from complement-mediated destruction of red blood cells.[9–11] This lack of CD55 in PNH erythrocytes leads to reduction in C3-convertase enzyme dissociation resulting in an increase in the production of C3 fragments and subsequent opsonization.[10] This complement dysregulation leads to chronic hemolysis and thrombosis in PNH.

Hemoglobinuria is due to intravascular hemolysis of CD59-deficient erythrocytes. The C5 inhibitors reduce terminal complement-mediated hemolysis and platelet and white cell activation, thus reducing the risk of thrombosis, the main life-threatening complication of PNH.[12,13] C5 inhibition reduces anemia and transfusion needs and prevents complications of PNH, including kidney failure and pulmonary hypertension.[12,14] Eculizumab prevents C5-dependent intravascular hemolysis mediated by the membrane attack complex (C5-C9). The red blood cells that evade complement-mediated destruction because of eculizumab could be opsonized with C3b fragments and still succumb to extravascular hemolysis in the liver and spleen.[15] Extravascular hemolysis is seen in most patients with PNH treated with C5 inhibitors, thus leading to reduced erythrocyte half-life (10–13 days).[15,16] The hematological response of eculizumab is often inconsistent, with only one-third of PNH patients obtaining normal hemoglobin levels. Although eculizumab improves intravascular hemolysis, transfusion dependency, and thrombosis risk, some patients remain anemic and transfusion dependent.[15,17,18] It is likely due to the extravascular hemolysis, which remained unchecked.

New terminal complement inhibitors that target C5, and proximal complement inhibitors that interfere with C3 or further upstream, have been categorized according to the target of the complement system on which they work (factors B and D).[19] Pegcetacoplan, a pegylated Penta decapeptide, targets complement C3, which allows targeting both intravascular and extravascular hemolysis.[20] This study aims to study the efficacy and safety of pegcetacoplan in PNH.

## 2 | METHODS

### 2.1 | Study selection

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and protocol for reviews detailed in the Cochrane Handbook for Systematic Reviews of Interventions were followed to prepare and report this systematic review.[21, 22] We performed a comprehensive and systematic literature search in the PubMed, Google Scholar, Cochrane Library, and clinicaltrials.gov database for all studies and review articles on the use of pegcetacoplan in patients with PNH (CRD42021262830). Keywords "paroxysmal nocturnal hemoglobinuria" or "PNH" and "Pegcetacoplan" or "Empaveli," were used to screen for the manuscripts published before June 2021 (Supplementary file S1). The keywords were connected with the Boolean operators "OR", "AND" to identify the relevant articles. We searched reference lists of all screened manuscripts to identify any relevant studies missed in the initial search. The details of the search strategy are shown in Figure 1.

Two reviewers independently screened the retrieved studies that met the predefined selection criteria. Discussions with another author solved any discrepancies regarding inclusion of the studies. Finally, three studies met the inclusion criteria and were included in our analysis.

### 2.2 | Inclusion and exclusion criteria

We included the studies on patients with PNH who were treated with pegcetacoplan. Only papers published in English were included. Case reports and studies with <2 patients were excluded.

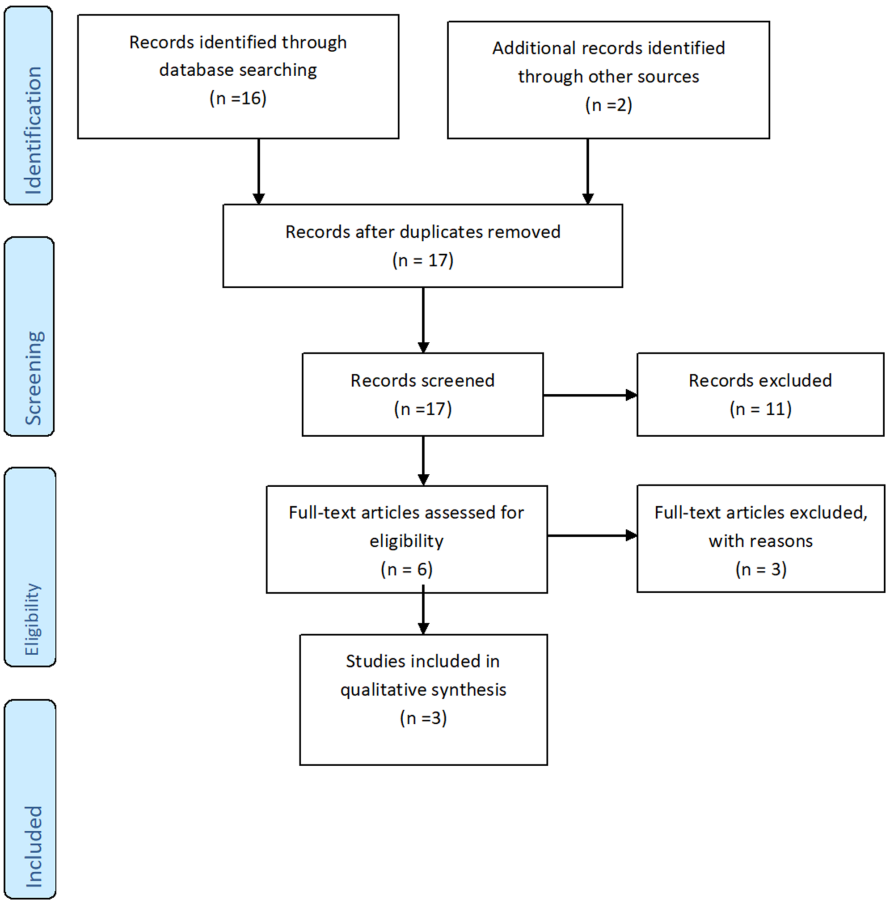


**FIGURE 1** PRISMA guidelines for article identification and selection.

## 2.3 | Main variables

We assessed three primary efficacy outcomes: change in hemoglobin level, transfusion requirements, absolute reticulocyte count, and lactate dehydrogenase (LDH) level after pegcetacoplan therapy. Safety outcomes included the proportion of deaths and adverse effects.

## 2.4 | Data extraction

We extracted the following information from the studies: the first author's name, year of publication, duration of treatment, sample size, mean age, mean disease duration, and efficacious endpoints after pegcetacoplan therapy, and adverse effects in Microsoft Excel 2016. Two authors independently extracted the data, and discussion solved any discrepancies.

## 2.5 | Quality assessment

We assessed the following items: (1) clarity of the study objectives; (2) whether the study period (start date and end date) was clearly stated; (3) whether the description of the patient selection criteria was clear; (4) whether the study was conducted in a multicenter; (5) pegcetacoplan treatment method and dose; (6) whether the baseline equivalence groups were clearly considered; (7) the definition of the primary outcome prior to the study; (8) whether the follow-up period was long enough; (9) whether a clear hazard ratio (HR) with 95% confidence intervals (95% CI) was stated or not; (10) if the limitation of the study was mentioned or not; quality assessment was not used as an exclusion criterion (Table 1). Individual questions of the study were answered in "yes" or "no" with 1 point for "yes" and no points for "no." The total score was added for the individual study as denoted in the respective columns.

## 2.6 | Data synthesis

The narrative summary contained all recognized studies and summary tables for features. Descriptive statistics were used to summarize the data. For continuous variables, we utilized means, and for dichotomous variables, we used frequencies and percentages.

# 3 | RESULTS

## 3.1 | Study characteristics

Our initial search identified 18 studies; 10 were excluded after screening their titles and abstracts. After reviewing the full texts of the remaining six studies, three with a total of 112 patients were included in this systematic review (Figure 1). The most common

**TABLE 1** Quality assessment of the included studies

| Criteria | Studies | | |
|---|---|---|---|
| | Hillmen | De Castro | PADDOCK NCT02588833 |
| Clarification of the study objectives | Yes | Yes | Yes |
| Whether the study period (start date and end date) was stated clearly or not | Yes | | Yes |
| Whether the description of the patient selection criteria was clear or not | Yes | Yes | Yes |
| Pegcetacoplan treatment method and dose was clear or not | Yes | Yes | Yes |
| Study was multicenteric or not | Yes | Yes | Yes |
| Whether the baseline equivalence groups were clearly considered or not | Yes | No | No |
| The definition of the primary outcome was mentioned or not (change in hemoglobin level, proportion of patients who did not require transfusion, change in absolute reticulocyte count, LDH from baseline) before the study | Yes | Yes | Yes |
| If the follow-up period was long enough (at least 2 months) | Yes | Yes | Yes |
| Whether a clear hazard ratio with 95% confidence intervals was stated or not | No | No | No |
| The limitations of each study were considered | No | No | No |
| Overall score | 8 | 6 | 7 |

*Note*: Average score = 7.

Abbreviation: LDH, lactate dehydrogenase.

reasons for excluding the searched articles were review articles, patients not diagnosed as PNH, articles not in English, case reports or studies with <2 patients, and insufficient data. The details of the search strategy are shown in Figure 1. The main characteristics of the patients included are summarized in Table 2.

## 3.2 | Quality assessment results

With the use of quality assessment tool, individual questions of the study were answered in "yes" or "no" with 1 point for "yes" and no points for "no." The total score was added for the individual study as denoted in the respective columns. The quality of the three included studies was fair with an average quality score of 7 and a median score of 7 out of a total score of 10.

## 3.3 | Literature identification

The study by Hillmen et al. was a multinational phase 3 open-label, controlled trial conducted across 44 centers.[23] The remaining two studies were interventional, open-label, phase Ib and nonrandomized.[24,25] The study by de Castro et al. was conducted in the United States, whereas the PADDOCK study was conducted in five different countries, including the United States.[24,25] The study duration, sample size, efficacy measures, adverse reactions, and dose of pegcetacoplan are presented in the Table 3.

## 3.4 | Patient characteristics

A total of 112 patients >18 years with PNH were included from these three studies; 45 (40%) were males. In the study by de Castro et al. and Hillmen et al., the patients had already received eculizumab therapy, whereas in the PADDOCK, patients had not received eculizumab treatment.[23–25] In the study by Hillmen, patient's hemoglobin level was <10.5 g/dl, and in the study by de Castro et al., hemoglobin level was <10 g/dl before enrollment in the study. Therefore, these two studies focused on the patient population who remained anemic despite eculizumab therapy, and patient's hemoglobin level was not in the inclusion criteria.[23,24]

## 3.5 | Measures of efficacy

### 3.5.1 | Change in hemoglobin level from baseline

Increase in hemoglobin level was seen in all three studies. In the study by Hillmen et al. and the PADDOCK study, the average increase in hemoglobin was 2.37 g/L and 3.68 g/L, respectively. In the study by

**TABLE 2** Characteristics of the included study

| Author and year of study | Study duration | Stage of trial | Sample size | Study design | Country of study | Mean age | Efficacy measures | Adverse reactions | Pegcetacoplan dose |
|---|---|---|---|---|---|---|---|---|---|
| Hillmen et al, 2020 | 4 weeks run-in 16 weeks RCT 32 weeks Open label Pegcetacoplan | Phase III | 80 | Open label-controlled trial | 44 centers | 50.2 (19–81) | Change in hemoglobin level, proportion of patient who did not require transfusion, change in absolute reticulocyte count, LDH from baseline, FACIT-F score | Injection site reactions (37%), diarrhea (22%), breakthrough hemolysis (10%), headache (7%), and fatigue (5%) | Pegcetacoplan 1080 mg subcutaneously twice weekly |
| de Castro et al, 2021 | Not clearly mentioned, but the pharmacokinetic properties and side effects were studied at each 28 days interval of ascending doses administered | Phase I-b | 9 | Interventional, open label, prospective, | USA | 46.6 years for cohort 4 (35–57) | Change in hemoglobin level, reticulocyte count, LDH, serum C3 level and total bilirubin from baseline, FACIT-F score | Injection site reactions | Multiple ascending doses were used (25 mg and 50 mg single dose then 5 mg/d and 30 mg/d then 180 mg/d followed by 270 mg/d up to 440 mg/d each for 28 days) |
| PADDOCK NCT02588833 | Cohort 1: 28 days Cohort 2: 444 days (total: 24 months from screening of cohort 1 to completion of cohort 2) | Phase I-b | 23 | Interventional, open label, pilot study with multiple ascending dose | 5 (Hong Kong, Malaysia, New Zealand, Thailand, USA) | >18 years (not clearly mentioned) | Mean change in LDH level, haptoglobin, hemoglobin level, absolute reticulocyte count and total bilirubin from baseline, need for red blood cells transfusion | Upper respiratory tract infection (25%), injection site erythema (20%), hypokalemia (20%), neutropenia (15%), QT prolongation (15%), epistaxis (15%) and many more with less frequency | Subcutaneous 180 mg/d in cohort 1 and 270 mg/d in cohort 2 |

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; LDH, lactate dehydrogenase; RCT, randomized controlled trial.

**TABLE 3** Efficacy measures of included studies

| Author | Efficacy outcomes | Description |
|---|---|---|
| Hillman et al, 2020 | Change in hemoglobin level from baseline | Adjusted mean change from baseline = 2.37 g/dl<br>Mean difference with respect to eculizumab = 3.84 g/dl (95% CI, 2.33–5.34; $p < 0.001$) |
| | Patients who did not require transfusion | 35 patients (85%), ($p < 0.001$) |
| | Change in absolute reticulocyte count | (adjusted mean [± SE] changes, $-136 \pm 7 \times 10^9$ per liter) |
| | Change in LDH level from baseline | Adjusted mean change from baseline = −15 ± 43 U per liter |
| | FACIT-F scores | Increased by 9.2 points |
| de Castro et al., 2021 | Change in hemoglobin level | At baseline, all the subjects hemoglobin were below the lower limit of normal (LLN) ranging (7–10.5) but after treatment the hemoglobin level increased and stayed in the reference range (11.1–15.9) from day 29 onwards |
| | Transfusion requirement | At baseline, all the 6 patients received transfusion in the prior 12-month period but after treatment, transfusion avoidance was achieved in all 4 patients who completed the study but was required in remaining 2 who could not complete the study |
| | Reticulocyte count | At baseline, reticulocyte count was above the upper limit of normal (i.e., $>123 \times 10^9$/L) in all patients but after treatment, reductions were observed and the value at the end was <1.5× upper limit of normal |
| | Total bilirubin | At baseline, in all patients, total bilirubin was above the upper limit of normal (i.e., >1.2 mg/dl) but after the treatment, bilirubin level was found to be within reference range (0.2–1.2 mg/dl) in all patients. |
| | LDH level | At baseline, 5 subjects had LDH < 1.5× upper limit of normal (reference range 119–226 U/L). During treatment, LDH remained stable and at the end of treatment 3 of 4 patients who completed the study had LDH < 1.5× upper limit of normal |
| | Serum C3 levels | An increase in serum C3 level was observed in all patients from baseline |
| | FACIT-F scores | >3 points increase in the FACIT-F total score from baseline was observed in 3 of 4 patients who completed the study |
| PADDOCK NCT02588833 | Mean percentage change from baseline in LDH at day 365 | Average decrease in LDH from baseline was −84.8% with standard deviation (SD) of 14.04%<br>Actual change was −2105.2 U/L with SD of 1078.79 U/L |
| | Mean Percentage change from baseline in haptoglobin at day 365 | Mean increase in haptoglobin level was 166.176% with SD of 311.365<br>Actual increase was 0.066 g/L with SD of 0.1245 g/L |
| | Mean percentage change from baseline in hemoglobin at day 365 | Mean increase in hemoglobin level was 49.86% with SD of 43.254%.<br>Actual increase was 3.68 g/L with SD of 2.69 g/L |
| | Mean change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score at day 365 | Mean increase in FACIT-F score was 7.1 with SD of 11.09 |
| | Mean percentage change from baseline in absolute reticulocyte count at day 365 | Mean decrease in absolute reticulocyte count was −47.5% with SD of 26.86%<br>Actual decrease in absolute reticulocyte count was $-105.9 \times 10^9$ cells/L with SD of 70.28 cells/L |
| | Mean percentage change from baseline in total bilirubin at day 365 | Mean decrease in total bilirubin was −60.9% with SD of 19%<br>Actual decrease in total bilirubin was −29.9 µmol/L with SD of 24.34 µmol/L |
| | Number of subjects receiving red blood cell transfusions | 1 out of 3 subjects in cohort 1 and 7 out of 20 subjects in cohort 2 received transfusions |

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; SE, standard error.

de Castro et al., the hemoglobin level increased from below the lower limit of normal and stayed within the normal range (11.1–15.9 g/L).[23–25]

### 3.5.2 | Transfusion requirement

In the study by de Castro et al., all the patients required transfusion at baseline, but transfusion independence was achieved in all four patients who completed the study. In the study by Hillmen and PADDOCK, transfusion independence was achieved in 35 (85%) patients and 65% of patients, respectively.[23–25]

### 3.5.3 | Change in absolute reticulocyte count

Absolute reticulocyte count decreased in all patients receiving pegcetacoplan. In the study by de Castro et al., the absolute reticulocyte count level was more than the upper limit of normal, but absolute reticulocyte count remained within <1.5× upper limit of normal in all the patients after treatment. In the study by Hillmen and PADDOCK, mean decrease in absolute reticulocyte count was $136 \pm 7 \times 10^9$ cell/L and $105.9 \times 10^9$ cells/L, respectively.[23–25]

### 3.5.4 | Change in LDH level

Mean level of LDH decreased in the patients receiving pegcetacoplan therapy.[25] In the study by de Castro et al., LDH level remained stable and within <1.5× upper limit of normal while in the study by Hillmen et al., the mean decrease of LDH from baseline was 15 ± 43 U/L.[23,24]

### 3.5.5 | Functional Assessment of Chronic Illness Therapy-Fatigue score

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score increased in all the patients receiving pegcetacoplan therapy. In the study by de Castro et al., a more than 3-point increase in the FACIT-F total score from baseline was observed in three of four patients who completed the study. In the study by Hillmen and the PADDOCK study, average increase in FACIT-F score was 9.2 and 7.1.[23–25]

### 3.5.6 | Other outcomes

Other efficacious outcomes, including increased haptoglobin level, increased serum C3 level, and change in the total bilirubin, were observed (Table 3).

## 3.6 | Adverse effects

Treatment-emergent adverse events were reported in four of six, 20 of 23, and 36 of 41 patients on pegcetacoplan in the study by de Castro et al., PADDOCK, and Hillmen, respectively.[23–25] Serious adverse events after receiving pegcetacoplan were reported in two of six, seven of 23, and seven of 41 patients in the study by de Castro et al., the PADDOCK study, and Hillmen, respectively.[23–25] The common treatment-emergent adverse events were injection site reactions, diarrhea, upper respiratory tract infections, neutropenia, hypokalemia, and breakthrough hemolysis (Table 2). Treatment-emergent adverse events resulting in death were reported in one patient in the PADDOCK study, whereas no cases were found in the remaining two studies.[25]

# 4 | DISCUSSION

Our review evaluated the efficacy of pegcetacoplan, a C3 inhibitor, in improving both intravascular hemolysis and extravascular hemolysis from PNH. As shown in the above studies, treating such patients with pegcetacoplan will control hemolysis.

We report the efficacy of pegcetacoplan in improving hemoglobin above the baseline, most likely because it prevents both intravascular hemolysis and extravascular hemolysis.[23–25] We found that 4/5th of total patients remained transfusion independent after therapy. In the study by de Castro et al., hemoglobin levels were persistently decreased with eculizumab in a few patients until pegcetacoplan was resumed.[24] Other results showed a rise in haptoglobin, and reduction in total bilirubin, indicating improvement in intravascular hemolysis. LDH level, often considered a marker of intravascular hemolysis, also decreased and mostly remained within the normal range. Increase in the serum C3 level, a surrogate marker of effective inhibition of classical complement pathway and reduced opsonization, indicates decreased extravascular hemolysis. Although absolute reticulocyte count and bilirubin levels are not very specific, normal, or improved with pegcetacoplan likely suggest reduced extravascular hemolysis. Absolute reticulocyte count and LDH levels, when checked in all three studies, showed lowered values at least 1.5 times of upper limits.[23–25] These findings show that pegcetacoplan can control both the extravascular hemolysis and intravascular hemolysis and has good efficacy as a monotherapy, including patients unresponsive to eculizumab.

In addition to the clinical and laboratory parameters, patient-reported outcomes improved with pegcetacoplan. Fatigue is the most common complaint affecting the quality of life of patients with PNH. A significant improvement in the FACIT-F score was demonstrated in all three studies.

Pegcetacoplan was generally well tolerated by the patients, and most of the treatment-emergent adverse events were mild and suspected to be unrelated to the pegcetacoplan use. The most reported adverse event was mild injection site reaction that did not lead to drug discontinuation. One concern with complement inhibitors is increased risk of infection with encapsulated bacteria. However, it was not reported in these studies with pegcetacoplan. Effective immunizations against encapsulated organisms

(Hemophilus B, *Streptococcus pneumonia*, and *Neisseria meningitides*), increased awareness and use of Penicillin V prophylaxis, and short follow-up duration could have led to a lower reported incidence of infections.

Our study has strengths and limitations. This is the first systematic review we know of that reports efficacy and safety of pegcetacoplan as a first-line treatment for PNH. The research design was consistent, and all studies were of high quality. However, the studies had a small sample size, inconsistent data distribution, and short follow-up time. Despite these limitations, we address the critical concern of patients with PNH who have limited treatment options.

## 5 | CONCLUSION

Pegcetacoplan effectively reduces transfusions, maintains improved hemoglobin levels, and improves fatigue in patients with PNH. Pegcetacoplan can be used in patients unresponsive to eculizumab with better outcomes. Further evidence is required to determine whether patients with PNH may benefit from adjunctive complement inhibition.

### AUTHOR CONTRIBUTIONS

S.S., R.C., and Z.H.M. wrote the original manuscript, reviewed, and edited the original manuscript. S.C., Y.R.A., S.P., K.G., and P.D. reviewed and edited the original manuscript.

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### RELATIONSHIP DISCLOSURE

None.

### DATA AVAILABILITY STATEMENT

All the required information is in manuscript itself.

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## SUPPORTING INFORMATION

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

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