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Treatment of eculizumab refractory paroxysmal nocturnal hemoglobinuria: A systematic review about current treatment options and future direction

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Abstract

Objectives: C5 inhibitors such as eculizumab and ravulizumab are the first-line treatment in the management of paroxysmal nocturnal hemoglobinuria (PNH). However, some patients develop novel symptoms as part of their treatment with eculizumab, and the disease is termed as eculizumab refractory PNH. The aim of this study was to conduct a systematic review on the available treatment modalities for the management of eculizumab refractory PNH.

Methods: Two authors independently searched two databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A total of 70 studies were obtained: 4 out 70 studies were found to meet the inclusion criteria.

Results: Four studies were found to meet the inclusion criteria of our study. Two studies were published in 2021 and two studies were published in 2020. All four studies were multicenter clinical trials. Two studies were phase III clinical trials, one study was a phase II clinical trial, and one study was a phase I clinical trial. Two studies were about pegcetacoplan, one was about danicopan, and one was about iptacopan.

Conclusion: Based upon the findings of our systematic review, we recommend an individualized treatment plan based on the mechanism of eculizumab refractoriness and the mechanism of PNH breakthrough. This recommendation is subject to the available resources and clinical expertise available at different hospitals. More studies using study designs such as randomized controlled trials comparing multiple drugs should be performed to accurately assess the different medications and aid in designing guidelines of the management of eculizumab refractory PNH.

Level of evidence: Level I

Keywords

Paroxysmal nocturnal hemoglobinuria, eculizumab, refractory, review

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Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, debilitating condition of the hemopoietic stem cells which occurs due to mutation of the phosphatidylinositol glycan class A gene, located on the X-chromosomes. This mutation leads to a deficiency of glycosyl phosphatidylinositol (GPI)-anchored proteins on the affected stem cells, which then subsequently leads to deficiency of the (GPI)-anchored complement regulatory proteins CD55 and CD59. This further leads to intravascular hemolysis that is the primary clinical manifestation of the disease.[1–3]

The morbidity and mortality depend upon the severity of hemolysis, bone marrow failure, and thrombophilia. Death can occur from complications such as thrombosis or bleeding.[4] Hematopoietic stem cell transplantation is the definitive treatment option for PNH, but is associated with high transplant-related morbidity and mortality.[5]

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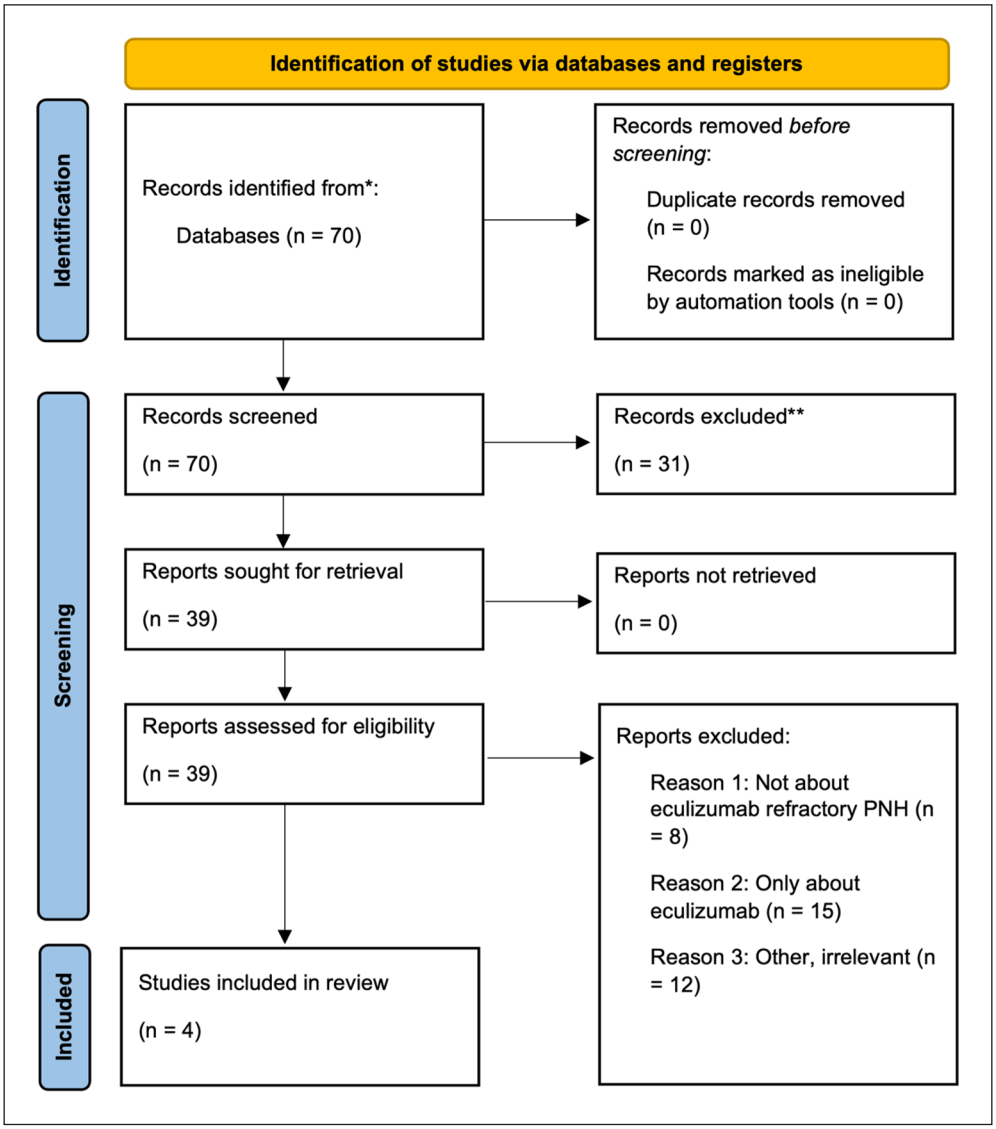

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

Eculizumab, an anti-complement monoclonal antibody was approved by the FDA in 2007 for the treatment of PNH and has been the backbone for its treatment for many years.[6] Treatment with eculizumab markedly reduces the need for blood transfusion and improves quality of life.

However, some patients develop novel symptoms as part of their treatment with eculizumab, and the disease is termed as eculizumab refractory PNH. These symptoms are primarily caused by two mechanisms: residual terminal complement activity that results in intravascular hemolysis and iatrogenic C3-mediated extravascular hemolysis by hepatosplenic phagocytes. Thus, patients treated with C5 inhibitors can have persistent residual anemia and can still be transfusion dependent.[7] Until recently, limited treatment options were available for eculizumab refractory PNH. The aim of this study was to conduct a systematic review on the available literature on the treatment modalities available for the management of eculizumab refractory PNH.

Materials and methods

Literature search

A systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines on 19 April 2022 (Figure 1 and Supplemental Figure 2).[8] Two databases (PubMed and Scopus) were searched for relevant articles. The search strategy utilized keywords with appropriate BOOLEAN operators such as PubMed search and Scopus search.

PubMed search. Eculizumab paroxysmal nocturnal hemoglobinuria. Filters: Clinical Study, Clinical Trial, Controlled Clinical Trial, Observational Study, Randomized Controlled Trial, Humans, English

Scopus search. TITLE-ABS-KEY (eculizumab AND paroxysmal AND refractory)

Table 1. Summary of the included studies.

Study	De Castro et al.	Hillmen et al.	Kulasekararaj, Risitano et al.	Risitano et al.
Study design	Non-randomized, open label trial	Open-label controlled trial	Open label trial	Non-Randomized, Open-label, Single-arm, Proof-of-concept trial
Single center/multicenter	Multicenter	Multicenter	Multicenter	Multicenter
Phase of the clinical trial	Phase I B	Phase III	Phase II	Phase II
Completed/ongoing	Completed	Completed	Ongoing	Completed
Year of publication	2020	2021	2021	2021
Number of participants at the beginning of the study	9	80	12	10
Number of participants at the end of the study	6	77	11	10
Number of participants treated with the alternate drug	9	39	12	10
Percentage of females (%)	88.9	61.25	81.8	30
Mean/median* age and range	>18 years, N/A	>18 years of age, N/A	48 (18–65)	43.5 (18–80)
Drug used	Pegcetacoplan	Pegcetacoplan	Danicopan	Iptacopan
Follow-up interval	3 years	48 weeks	24 weeks	48 weeks
Reference	11	12	7	13

*Central tendency as mentioned by the authors, N/A: not available.

Duplicate articles and articles meeting the exclusion criteria were excluded. Two authors independently performed a review of the abstracts and two other authors performed a full-text review of the articles.

Inclusion criteria

1. Original articles published between 2007 and 2022 and written in the English language.
2. Studies investigating treatment options in eculizumab refractory PNH and ongoing trials.

Exclusion criteria

1. Studies investigating treatment options in eculizumab naïve PNH or eculizumab responsive PNH
2. Case reports
3. Studies published prior to 2007
4. Review articles and meta-analyses
5. Book chapters
6. Conference abstracts
7. Expert opinions
8. Cadaveric or animal studies
9. Articles not written in English

We obtained 40 articles on PubMed and 30 articles on Scopus. The systematic search resulted in four studies which were then identified and analyzed (Table 1). The authors discussed the articles in question among themselves and they came to a mutual consensus.

Data extraction

Four authors reviewed and extracted data from studies that satisfied the inclusion criteria. The following variables were extracted from each study: study design, year of publication, number of participants in the beginning and end of the study, drug involved, gender distribution, follow-up time, change in lactate dehydrogenase (LDH) levels, breakthrough hemolysis (BTH) rate, Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) score,[9] transfusion avoidance rate, stabilized hemoglobin rate, bilirubin levels, total reticulocyte counts, and adverse events. Some of these variables are summarized in Table 1.

Results

Risk of bias assessment

Bias assessment was performed using the Methodological Index for Non-Randomized Studies (MINORS) criteria for non-randomized studies.[10] One study was found to have low risk of bias, two studies had an intermediate risk of bias, and one study was suspected to have a high risk of bias. These study biases are summarized in Table 2.

Study characteristics

Four studies were found to meet the inclusion criteria of our study. Two studies were published in 2021 and two studies were published in 2020. All four studies were multicenter clinical trials. One study was a phase III clinical trial, two

Table 2. Bias assessment.

Study bias	De Castro et al.	Hillmen et al.	Kulasekararaj, Risitano et al.	Risitano et al.
A clearly stated aim	Yes	Yes	Yes	Yes
Inclusion of consecutive patients	Yes	Yes	No	Yes
Prospective collection of data	Yes	Yes	No	Yes
Endpoints appropriate to the aim of the study	Yes	Yes	Yes	Yes
Unbiased assessment of the study endpoint	Yes	No	No	No
Follow-up period appropriate to the aim of the study	Yes	Yes	Yes	Yes
Prospective calculation of the study size	No	Yes	Yes	No
Sequence generation (in case of randomized studies)	N/A	N/A	N/A	N/A
Selection bias (in case of non-randomized studies)	Yes	N/A	Yes	No
Bias due to unequal number of participants in different groups	No	No	No	N/A
Loss to follow up more than 5%	Yes	No	Yes	No
Selective reporting	No	No	No	No
Bias due to change in research protocol over the course of the study	No	No	Yes	No
Adequate statistical analysis	No	Yes	Yes	Yes
Other biases	Yes	Yes	Yes	Yes
Level of bias	Intermediate	Low	High	Intermediate
Reference	11	12	7	13

N/A: not applicable.

studies were a phase II clinical trials, and one study was a phase I clinical trial. Two studies were about pegcetacoplan, one was about danicopan, and one was about iptacopan. Summarized below is a synopsis of each drug.

Pegcetacoplan

Pegcetacoplan (APL-2) is a pegylated complement C3 inhibitor administered through subcutaneous injections twice weekly or every 3 days. Pegcetacoplan binds to C3 preventing its activation and binds to C3b inhibiting the activity of convertases involving a C3b subunit, which include C3 and C5 convertase. C3 convertase plays a role in the alternate pathway while C5 convertase plays a role in both the alternate and classical pathways. Two studies presented data on pegcetacoplan.[11,12]

Hillmen et al. (NCT03500549) presented the data on pegcetacoplan from a 48-week trial period and assessed the safety and efficacy of pegcetacoplan in adults with PNH and hemoglobin levels lower than 10.5 g/dl despite eculizumab therapy. The primary endpoint in this study was the mean change in hemoglobin level from baseline to week 16 and clinical hematologic outcomes. The key secondary endpoints included change in LDH levels, FACIT-F score, transfusion avoidance rate, and change in absolute reticulocyte count.

De Castro et al. aimed to assess the safety, efficacy, and pharmacokinetics of pegcetacoplan in subjects with PNH who remained anemic despite treatment with eculizumab. The primary endpoints of this study included the incidence and severity of treatment-emergent adverse events and pegcetacoplan pharmacokinetic (PK) parameters. Exploratory pharmacodynamic (PD) endpoints included hemoglobin levels, LDH levels, total bilirubin levels, reticulocyte count, serum C3 levels, and an assessment of the hemolytic activity of the classical and alternative pathways. The number of packed RBC transfusions administered during the study was also recorded.

In the study by Hillmen et al., pegcetacoplan was found to be superior to eculizumab due to the change in hemoglobin levels from baseline to week 16 with an adjusted difference of 3.84 g/dl ($p < 0.001$). BTH rate was 10%. Key hematological values were normalized in a greater percentage of patients in the pegcetacoplan group than in the eculizumab, hemoglobin level (34% versus 0%), reticulocyte count (78% versus 3%), LDH level (71% versus 15%), and total bilirubin level (63% versus 8%). In the pegcetacoplan and eculizumab group the most common adverse events recorded were injection-site reaction (37%), diarrhea (22%), headache (7%), and fatigue (5%) (Table 3).

In the study by De Castro et al. increased hemoglobin levels, decreased bilirubin levels, and decreased reticulocyte count were found in the pegcetacoplan group. Reduced C3 fragment deposition and an increase in the proportion of PNH type II and III erythrocytes were observed. Serum C3 levels were increased in all subjects and they were 1.8 times higher than at baseline at week 4 and 2.7 times higher than at baseline after completing 2 years of treatment through repeated pegcetacoplan dosing, demonstrating a robust C3 inhibition. These findings suggested that pegcetacoplan may have protective effects on type II (partial CD59 deficiency) and type III (complete CD59 deficiency) erythrocytes from complement-mediated attacks and extravascular hemolysis. The most common side effect noted in this study was injection rate reactions (66.7%).

Both studies indicated that pegcetacoplan provided hemolysis control and in improving hemoglobin and clinical hematological outcomes. Eculizumab discontinuation was also possible in subjects in both studies after evaluation of pegcetacoplan effects. However, an increased FACIT-F score was noted in both studies.

Danicopan + eculizumab

Danicopan is an oral proximal complement inhibitor of alternative pathway factor D (FD), designed to control both intravascular hemolysis and extravascular hemolysis. Danicopan targets the rate-limiting step of the complement cascade amplification loop by inhibiting the activity of FD serine protease. This results in the prevention of C3 convertase formation, which in turn drastically reduces the production of C3 cleavage products (also referred to as C3 fragments) and the subsequent formation of downstream membrane attack complex (MAC). One study (NCT03472885)[7] presented data on danicopan from the 24-week primary treatment period assessing the safety and effectiveness of danicopan in addition to eculizumab. The primary endpoint was defined as a change in hemoglobin levels at baseline versus week 24. Secondary endpoints included change in LDH levels, transfusion reduction rate, and transfusion avoidance rate.

Addition of danicopan to eculizumab resulted in an increase of mean hemoglobin of 2.4 g/dL (p-value = 0.0001) at week 24. The transfusion rate was reduced from 50 units to 2 units. The mean FACIT-F score increased by 11 points (p-value = 0.0191). The most common adverse events included cough (25%), headache (25%), and URTI or flu-like illnesses (25%) (Table 3). The main limitations of this study include its small sample size, short follow-up period, and changes in the dosing regimen over the trial period with different patients adhering to different dosing regimens.

Iptacopan + eculizumab

Iptacopan (LNP023) is an orally available, highly selective reversible inhibitor of complement factor B (FB). FB, present in the blood as an inactive form, is a serine protease that triggers the alternative pathway of the complement cascade. This activation occurs when FD cleaves and activates FB. One study (NCT0349839)[13] presented the data on iptacopan from a 48-week trial period and assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics in patients who have active hemolysis despite taking a C5 inhibitor therapy (eculizumab). The primary endpoint of this study was to observe the effect of iptacopan on chronic residual hemolysis in patients taking eculizumab measured as a change in LDH levels from baseline to week 13. A significant reduction of LDH from baseline versus at week 13 was noted (Mean 539 IU/L (SD = 263) at baseline versus 235 IU/L (SD = 44), change from baseline −309.2 IU/L (SD = 265.5], 90% CI −473.77 to −144.68, p-value = 0.0081). A marked improvement in hemoglobin concentrations was also noted (Mean 97.7 g/L (SD = 10.5) versus 129.5 g/L (SD = 18.3) change from baseline 31.9 g/L (SD = 14.5), 90% CI 23.42 to 40.28, p-value < 0.0001). All other biomarkers (secondary outcomes of the study) of hemolysis such as transfusion avoidance, hemoglobin concentration, reticulocyte count, bilirubin concentration, haptoglobin, and free hemoglobin concentration also showed improvement. Three serious adverse events were observed, two of which were in the same patient but none of the serious adverse events were related to iptacopan. The most common symptoms included rhinitis and rhinorrhea (20%) and URTI and flu-like illnesses (30%). All reported adverse events resolved without sequelae (Table 3). The main limitations of this study include the small sample size, short follow-up time, and lack of data on iptacopan as a monotherapy for treatment of eculizumab refractory PNH.

Discussion

Improved knowledge about PNH has resulted in the ability to understand pharmacodynamics and pharmacokinetics of certain other pharmacological treatments. Although we aimed to include all the studies within the last 15 years, all four studies were published between 2020 and 2021, suggesting that these drugs are relatively novel and their use in eculizumab refractory PNH has not been studied extensively. These studies suggest that these novel drugs result in an improved hemolysis control and reduced number of side effects compared to eculizumab. From our review, we found that improved hemolysis rates were detected in all three of the alternative drugs. DeCastro et al. noted an increase in proportion of type II and type III erythrocytes which suggests an increased protection from complement activated hemolysis in patients treated with pegcetacoplan.[11] Danicopan and iptacopan also had an advantage due to their oral administration which patients may find convenient.

Two drugs, danicopan and iptacopan, were used in combination with eculizumab and limited data is available for their use as first-line therapy or monotherapy.[7,13] Although not tested as a monotherapy, iptacopan maintained its effect as a monotherapy even after discontinuation of anti-C5 therapy. For this reason, a phase III randomized clinical trial has been initiated to determine the superiority of iptacopan as a monotherapy compared to other anti-C5 treatments (NCT04558918).[13] Another trial has also commenced to evaluate iptacopan as a monotherapy in patients with PNH who are not responsive to C5 inhibitor therapy (NCT04558918). With respect to danicopan, a long-term extension study has been initiated to evaluate the long-term effects of danicopan as an add-on therapy to C5 inhibitors (NCT05389449). Another ongoing randomized controlled phase 3 ALPHA trial (NCT04469465) is also currently evaluating the addition of danicopan in patients receiving a C5 inhibitor and experiencing clinically evident extravascular hemolysis. A second-generation oral FD inhibitor

Table 3. Adverse events noted in the studies.

Adverse events (%)	De Castro et al.	Hillmen et al.	Kulasekararaj, Risitano et al.	Risitano et al.
Fatigue		>7	16.6	
Upper Respiratory Tract Infection flu-like illness		5	25	30
Rhinitis/rhinorrhea				40
Cough			25	
Breathlessness		2		
Pulmonary edema			8.3	10
Oropharyngeal pain				
Fever	16.7	5		20
Chest pain				10
Headache		7	25	20
Dizziness		2		
Abdominal pain		12		10
Diarrhea		22		
Constipation				
Nausea/vomiting		5	16.6	
Lower gastrointestinal hemorrhage	16.7			
Increased transaminases	16.7		8.3	
Pancreatitis	16.7			
Portal vein thrombosis	16.7			
Urinary tract infection	16.7			10
Musculoskeletal pain		14	16.6	20
Injection-site reaction	66.7	>12		10
Thromboembolism in patients with a history of thromboembolism	16.7			
Other infections		12	8.3	
Sepsis	16.7			
Anemia	16.7	10	8.3	
Serious adverse events		17		10
Other		>7		100
Reference	11	12	7	13

(ALXN2050) is also being investigated as a monotherapy in the management of eculizumab refractory PNH (NCT04170023).

One concern for drugs such as pegcetacoplan that cause broad complement inhibition is a risk of infection due to encapsulated bacteria.[12] Pegcetacoplan involves the technique of pegylation which uses high molecular weight polyethylene glycols and is useful in increasing the half-life of a drug, reducing renal clearance, and decreasing the immunogenicity of therapeutic proteins. However, pegylated drugs may elicit adaptive changes in cells and tissues. The safety profile of pegylated drugs may be in question; however, current studies show that pegylated drugs currently approved for human use are safe and well tolerated.[11] A new trial has been initiated to assess the real-world effectiveness of pegcetacoplan in patients with PNH (NCT05776472) and another trial has commenced to evaluate its effectiveness in pediatric patients with PNH (NCT04901936).

No clear guidelines exist for the management of eculizumab refractory PNH, as until recently, eculizumab and ravulizumab remained to be the only approved drugs by the FDA and the European Medicines Agency for treatment of PNH.[11,14] In 2021, pegcetacoplan became the third drug to be approved for the management of PNH.[15] Other drug therapies such as pozelimab + cemdisiran (NCT05744921) and crovalimab + eculizumab (NCT04432584) are being trialed for the management of PNH. Novel drugs such as BCX9930 (NCT05116774) are also being investigated for the management of eculizumab refractory PNH. Novel medications which target alternative factors of the complement pathway need to be investigated to minimize the risks associated with complement pathway inhibition and decrease BTH rate and transfusion dependence.

There are a number of limitations to this systematic review. We searched only two databases and included articles written only in English. We did not discuss studies that involve increasing the dose or frequency of dosing intervals of eculizumab. Three studies presented a sample size which was less than 15 patients, resulting in a low power of the studies. The studies reviewed also do not take into account

the interactions these drugs have on other possible medications the patients may be on.

Conclusion

In conclusion, based on the findings of our systematic review, we recommend an individualized treatment plan based on the mechanism of eculizumab refractoriness and the mechanism of PNH breakthrough. However, our findings are limited due to fact that a limited number of studies are published on this topic. More studies using study designs such as randomized controlled trials comparing multiple drugs should be performed to accurately assess the different medications and aid in designing guidelines to guide the management of eculizumab refractory PNH.

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Author contributions

SS drafted the study. SS, FHK, FK, and RK performed the systematic review and drafted the manuscript. DS and SUDS suggested the topic, supervised the study, and reviewed the manuscript. All authors read and approved the final manuscript.

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Supplemental material

Supplemental material for this article is available online.

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