Efficacy of Clinical Interventions in Paroxysmal Nocturnal Hemoglobinuria Patients Previously Treated with C5 inhibitors: A Systematic Literature Review

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KEY FINDINGS & CONCLUSIONS

- This SLR identified three treatments studied in the C5i-experienced PNH population with anemia: pegcetacoplan (infusion), and oral therapies: iptacopan (monotherapy) and danicopan (add-on to C5i [infusion]).
- Data for these treatments came from two phase 3, and two phase 2 trials published during the search timeframe, with variations in design, endpoints, and timepoints assessed.
- Each of the treatments achieved the prespecified endpoints in their respective trials but were not studied head-to-head.
- An update of the SLR and an indirect treatment comparison is warranted to assess their relative efficacy.

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INTRODUCTION

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disorder characterized by complement-mediated hemolytic anemia (low hemoglobin [Hb]), peripheral blood cytopenias, and thrombosis.[1] Intravascular hemolysis (IVH) is predominant in treatment-naive PNH patients.[1]
- First treatments approved for PNH were intravenous infusion complement 5 inhibitors (C5i) such as eculizumab,[2] and later ravulizumab,[3] which can control IVH. However, extravascular hemolysis may emerge in up to 25-50% of patients.[4]
- More recently approved treatments include subcutaneous infusion complement 3 inhibitor (C3i; pegcetacoplan),[5] oral Factor D inhibitor (danicopan) as an add-on to C5i,[6] and the first oral Factor B inhibitor monotherapy drug iptacopan.[7]

AIM

- This systematic literature review (SLR) aimed to identify evidence on the clinical efficacy of iptacopan and treatment comparators in adult PNH patients.

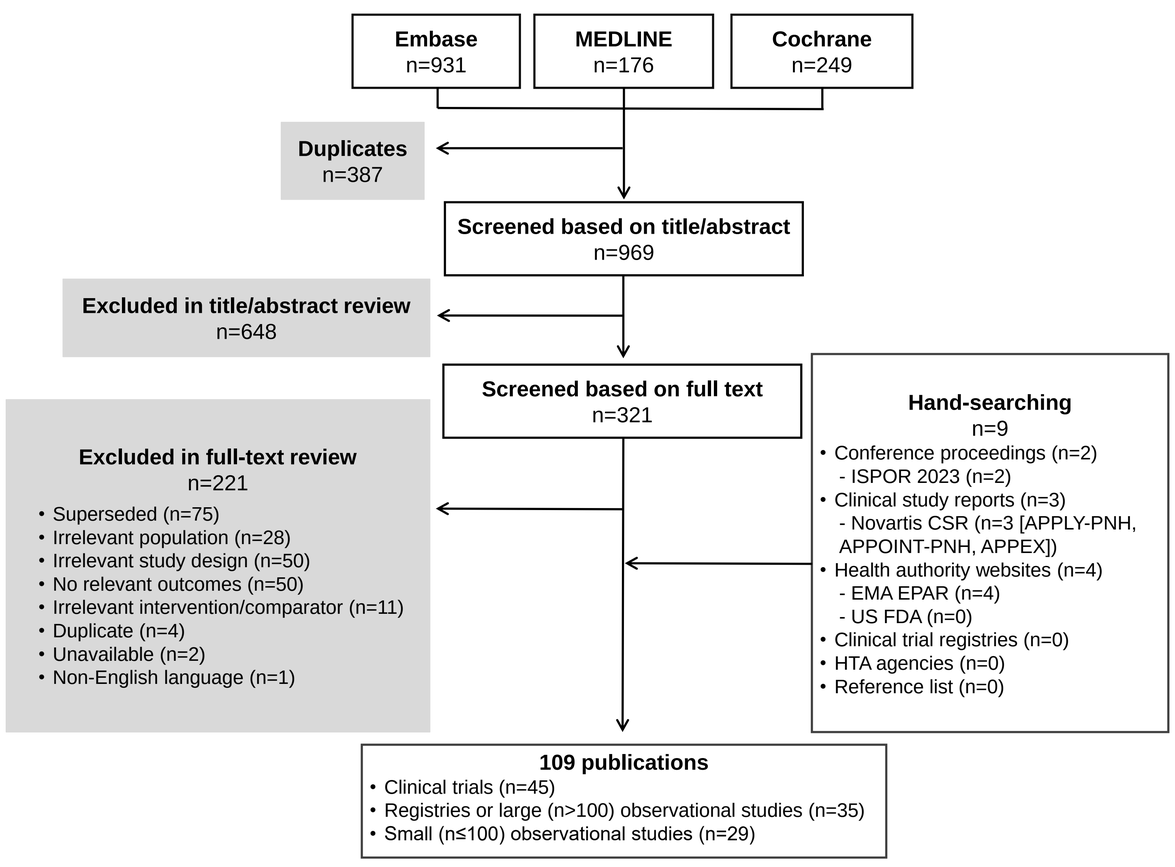
METHODS

- The SLR was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions v6.3.
- Study eligibility was assessed according to the following PICOS: population (adults with PNH: naive to C5i, and C5i-experienced with anemia), intervention (iptacopan), comparators (approved or upcoming treatments), efficacy outcomes (including Hb outcomes, and transfusion avoidance), and study design (clinical trials and observational studies).
- Searches were conducted on biomedical literature databases (Embase®, MEDLINE®, CENTRAL, and Cochrane Database of Systematic Reviews) until April 19th, 2023.
- Other sources were also searched for relevant literature, including conference proceedings (2020 – 2023), health technology assessment body websites, clinical trial registries,[8,9] regulatory websites, bibliographic reference lists, and clinical study reports (CSR).
- Here we present outcomes from the clinical trials identified in this SLR that focus on hematologic response (e.g. Hb outcomes, transfusion avoidance) in C5i-experienced patients with anemia.

RESULTS

- A total of 109 publications were included in the SLR, with 45 of these reporting on 16 clinical trials (**Figure 1**).
- Four of the clinical trials included C5i-experienced patients with anemia, as follows: two phase 3 trials - PEGASUS[10] (pegcetacoplan vs. eculizumab), and APPLY-PNH[11] (iptacopan vs. C5i: either eculizumab or ravulizumab), and two phase 2 single-arm trials - iptacopan + eculizumab,[12] and danicopan + eculizumab.[13]

Figure 1. PRISMA flow diagram (searches conducted until 19th April 2023)



PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Study characteristics

- PEGASUS and APPLY-PNH were phase 3 randomized, active-comparator controlled, open-label trials conducted in patients who were anemic despite C5i-treatment (**Table 1**).[11,12]
  - Mean baseline Hb was comparable across the treatment arms in the studies (8.68 – 8.93 g/dL).
  - Mean baseline FACIT-Fatigue score in each study was lower than the general population indicating presence of fatigue.
  - Mean baseline lactate dehydrogenase (LDH) reflected controlled IVH for most of the patients.
- The baseline characteristics in the phase 2 trials had higher variations (e.g., mean Hb, LDH, etc.) (**Table 1**).

Table 1. Baseline characteristics of clinical trials in C5i-experienced patients with anemia

Trial	Intervention	N	Female, n (%)	Age, years Mean (SD) or (range)	No transfusions (last 1 year), n (%)	Hb, g/dL Mean (SD)	LDH, U/L Mean (SD)	FACIT-Fatigue Mean (SD)
Phase 3 trials								
PEGASUS* Hillmen 2021[10], RCT, open label	PEG	41	27 (66)	50.2 (19-81)	10 (24)	8.69 (1.1)	257.5 (97.6)	32.2 (11.4)
	ECU	39	22 (56)	47.3 (23-78)	10 (26)	8.68 (0.9)	308.6 (284.8)	31.6 (12.5)
APPLY-PNH CSR[11], RCT, open label	IPTA	62	43 (69.4)	51.7 (16.9)	25 (40.3)	8.93 (0.7)	269.1 (70.1)	34.7 (9.8)
	C5i (ECU or RAVU)	35	24 (68.6)	49.8 (16.7)	13 (37.1)	8.85 (0.9)	272.7 (84.8)	30.8 (11. 5)
Phase 2 trials								
Risitano 2021[12], Single-arm	IPTA + ECU	10	3 (30)	44.4 (15.6)	0 (0)	9.76 (10.5)	539.0 (263.0)	-
Kulasekararaj 2021[13], Single-arm	DANI + ECU	12	10 (83.3)	48.0† (19-72)	-	7.94 (1.4)‡	244.5 (744.0)‡	34.0 (14.1)‡

*4-week run-in period when PEG and ECU were both administered, followed by a 16-week randomized controlled period of monotherapy of each drug, baseline refers to the start of run-in period. †Median reported, ‡n=11. C5i: C5 inhibitors; CSR: clinical study report; DANI: danicopan; ECU: eculizumab; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue (13-item, score 0 – 52, higher score, less fatigue); Hb: hemoglobin; IPTA: iptacopan; LDH: lactate dehydrogenase; PEG: pegcetacoplan; PNH: paroxysmal nocturnal hemoglobinuria; RAVU: ravulizumab; RCT: randomized controlled trial; SD: standard deviation

Efficacy outcomes

Change in hemoglobin

- In PEGASUS,[10] the primary endpoint was mean change from baseline (CFB) to week 20 (week 16 + the 4-week run-in period) in Hb, in the absence of transfusions: pegcetacoplan: 2.37 g/dL, and eculizumab: -1.47 g/dL resulting in a mean treatment difference of 3.84 g/dL (95% confidence interval [CI]: 2.3 – 5.3; p<0.001) (**Figure 2**).
- In APPLY-PNH,[11] the primary objective was the proportion of patients achieving hematological response in the absence of transfusions at week 24, defined with two endpoints: 1) increase in Hb levels ≥2 g/dL from baseline, and 2) achieving ≥12 g/dL Hb. Mean CFB to week 24 in Hb was one of the secondary endpoints.
  - Iptacopan was superior to C5i with treatment difference for patients achieving a hematological response: 1) 80.2% (95% CI: 71.2 – 87.6; p<0.0001) and 2) 67.0% (95% CI: 56.4 – 76.9; p<0.0001).
  - Iptacopan was superior to C5i with an adjusted mean treatment difference of 3.7 g/dL (95% CI: 3.2 – 4.1; p<0.0001) for CFB in Hb; iptacopan: 3.6 g/dL and C5i: -0.06 g/dL (**Figure 3**).

Figure 2. Mean CFB in Hb in PEGASUS[10]

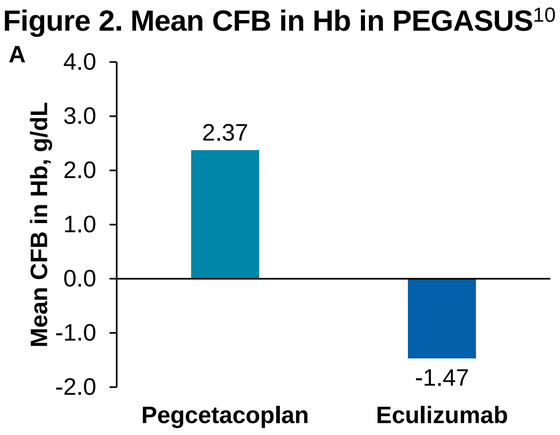
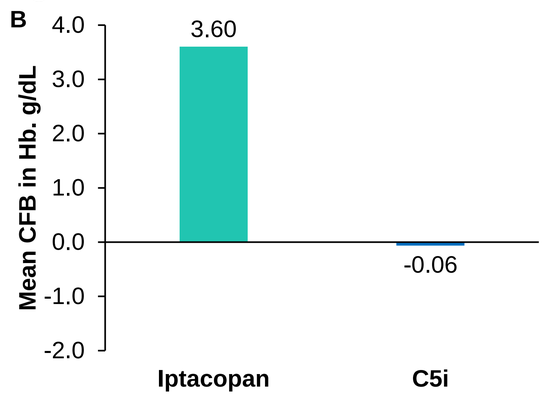


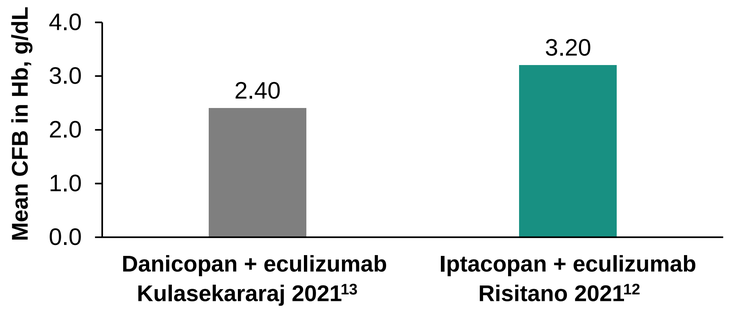
Figure 3. Mean CFB in Hb in APPLY-PNH[11]



CFB: change from baseline; Hb, hemoglobin

- In the phase 2 trials (**Figure 4**):
  - Iptacopan + eculizumab: mean Hb at week 13 was 12.95 g/dL, with a significant mean CFB (p<0.0001). After discontinuing eculizumab treatment, the treatment effect was maintained with iptacopan monotherapy.[12]
  - Danicopan + eculizumab: mean Hb at week 24 was 10.3 g/dL, with a significant mean CFB (p=0.0001).[13]

Figure 4. Mean CFB in Hb in Phase 2 trials



CFB: change from baseline; Hb, hemoglobin

Transfusion avoidance (assessed as secondary endpoint in all trials)

- In PEGASUS, pegcetacoplan was superior to eculizumab in percentage of patients avoiding transfusions (85% vs 15%, p<0.001; treatment difference of 63% [95% CI: 48 – 77]).[10]
- In APPLY-PNH, iptacopan (95%) was superior to C5i (26%) with a treatment difference in marginal proportions of patients avoiding transfusions of 68.9% (95% CI: 51.4 – 83.9; p<0.0001).[11]
- In the each of the phase 2 trials, most patients avoided transfusions (iptacopan + eculizumab [100%];[12] danicopan + eculizumab [91%]).[13]

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