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Indirect Treatment Comparison of Iptacopan versus Eculizumab and Ravulizumab for Patients with Paroxysmal Nocturnal Hemoglobinuria Naive to C5 Inhibitors

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KEY FINDINGS & CONCLUSIONS

- The results of this ITC suggest that iptacopan is more effective than eculizumab and ravulizumab, respectively, in reducing LDH levels and transfusion rate in C5i-naive PNH patients.
- Conclusions from this study should be interpreted in the context of this being an ITC.

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INTRODUCTION

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare blood condition characterized by hemolysis, anemia and thrombosis.[1]
- The first approved drugs for PNH were complement 5 inhibitor (C5i) infusions; eculizumab,[2] and later ravulizumab.[3]
- Iptacopan is the first-in-class, oral monotherapy, factor B inhibitor recently approved for adults with PNH who have hemolytic anemia[4,5] which was not compared in a head-to-head (H2H) trial vs the above drugs in patients who were not previously treated with C5i (named hereafter C5i-naive).
- In the absence of H2H trials, indirect treatment comparisons (ITC) are commonly performed to compare efficacy of two treatments in the context of Health Technology Assessment.[6-8]

AIM

- To conduct an ITC of iptacopan vs eculizumab and ravulizumab for the treatment of patients with PNH who were C5i-naive.

METHODS

- A systematic literature review identified Study 301 (NCT02946463; ravulizumab vs eculizumab),[9] a phase 3 trial, as the most relevant comparator trial for the single-arm phase 3 trial of iptacopan APPOINT-PNH (NCT04820530),[10] in the target population.
- ITC feasibility assessment (trial design, inclusion/exclusion criteria, and endpoints) concluded that unanchored matching-adjusted indirect comparison (MAIC) was most suitable, using individual patient data (IPD) from APPOINT-PNH[10] for iptacopan (N=40) and published aggregated data from Study 301[9] for eculizumab (N=121) and ravulizumab (N=125).
- Outcomes assessed were lactate dehydrogenase (LDH; mean % change from baseline [CFB]) and transfusion rate per patient-month and reported as difference between iptacopan vs eculizumab and iptacopan vs ravulizumab.

Statistical Analysis MAIC

- Due to high overlap in the eligibility criteria of the trials, no patient in APPOINT-PNH was excluded for this analysis.
- Patients from APPOINT-PNH were re-weighted via entropy balancing[7] to match patient characteristics in Study 301; adjusting for age, gender, % transfusion-free 12 months prior, LDH at baseline and history of major adverse vascular events (MAVE) after consulting with clinicians and health economics experts.
- The percent change from baseline LDH was derived by fitting a mixed model for repeated measures to the reweighted IPD from APPOINT-PNH. The treatment effect between iptacopan vs eculizumab and iptacopan vs ravulizumab was then derived as the difference between the adjusted mean CFB for iptacopan and the published mean CFB for eculizumab and ravulizumab.
- Transfusion rate per patient-month was reported by adjusting for differences in assessment windows between trials and were modelled using a log-Poisson distribution. This approach makes the assumption of a constant rate of transfusion events throughout the follow-up period.

RESULTS

- After matching and adjusting, baseline characteristics were similar across trials, with an effective sample size of 31 for APPOINT-PNH (**Table 1**).

Table 1. Baseline characteristics in APPOINT-PNH and Study 301

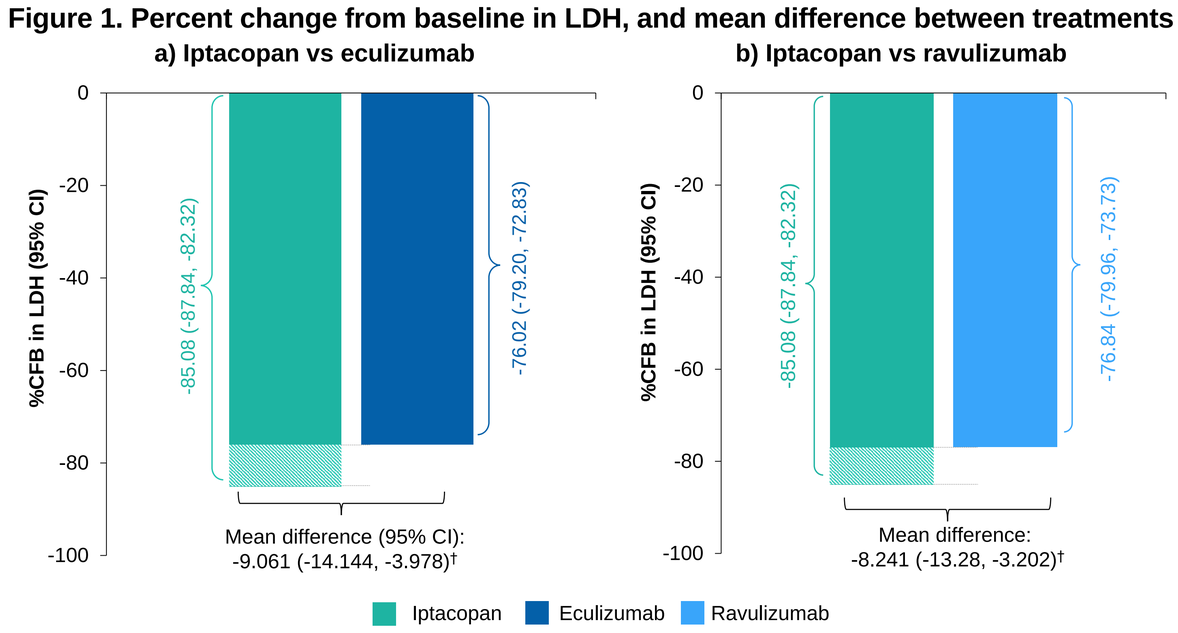
Baseline characteristics	Study 301, N=246 Eculizumab, N=121 Ravulizumab, N=125	Before matching and adjusting APPOINT-PNH Iptacopan, N=40	 SMDs*	After matching and adjusting APPOINT-PNH Iptacopan, ESS=31	 SMDs*
Age, mean (SD)	45.5 (15.7)	42.1 (15.9)	0.216	45.5 (15.7)	0.000
Gender, male, n (%)	134 (54.5)	23 (57.5)	0.061	54.5	0.001
Transfusion free 12 months prior, n (%)	44 (17.9)	12 (30.0)	0.342	17.8	0.000
LDH, U/L, mean (SD)	1606.4 (752.7)	1698.8 (683.3)	0.129	1606.4 (684.7)	0.000
History of MAVE, n (%)	42 (17.1)	5 (12.5)	0.129	17.1	0.001

*SMD ≤ 0.1 indicates small difference. ESS: effective sample size; LDH: lactate dehydrogenase; MAVE: major adverse vascular events; SD: standard deviation; SMD: standardized mean difference

Change from baseline in LDH

- The mean % CFB in LDH (reduction in LDH) was higher for iptacopan (-85.08%) compared to eculizumab (-76.02%) and ravulizumab (-76.84%) (**Figure 1**).
- The mean difference in % CFB in LDH was significantly in favor of iptacopan compared to eculizumab and ravulizumab.
  - Iptacopan vs. eculizumab: -9.061%, p=0.0005
  - Iptacopan vs. ravulizumab: -8.241%, p=0.0013

Figure 1. Percent change from baseline in LDH, and mean difference between treatments



CFB: change from baseline; CI: confidence interval; LDH: lactate dehydrogenase. †P < 0.05

Transfusion rate

- The transfusion rate per patient-month was lower for iptacopan (0.00037) compared to eculizumab (0.050) and ravulizumab (0.045) (**Table 2**).
- The rate ratio of iptacopan vs. eculizumab, and vs. ravulizumab, respectively, <1 suggests a significantly lower need for transfusions for patients treated with iptacopan (**Table 2**).

Table 2. Transfusion rate per patient-month and rate ratio

Transfusion rate	Eculizumab	Ravulizumab	Iptacopan
Transfusion rate per patient-month (95% CI)	0.050 (0.041, 0.060)	0.045 (0.033, 0.060)	0.00037 (0.00025, 0.00053)
Rate ratio (95% CI)†; p-value			
Iptacopan vs eculizumab	-	-	0.0065 (0.0042, 0.0101) p=0.0004
Iptacopan vs ravulizumab	-	-	0.0082 (0.0052, 0.0131) p=0.0008

†Rate ratio <1 implies a lower rate of transfusion for iptacopan. Results are statistically significant when the CI does not contain the null value (1.00). CI: confidence interval.

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