Abstract: P1700

Title: INDIRECT TREATMENT COMPARISON OF IPTACOPAN VERSUS PEGCETACOPLAN FOR PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA AND PERSISTENT ANEMIA DESPITE ANTI-C5 TREATMENT

Abstract Type: Poster Presentation

Topic: Ethics and health economics

Background:

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, non-malignant disease characterized by hemolysis, thrombosis and bone marrow failure. Iptacopan is the first oral proximal complement inhibitor that targets factor B within the alternative pathway of the complement system. Pegcetacoplan is a proximal complement inhibitor that targets C3 and is administered via subcutaneous infusion. The efficacy and safety of iptacopan and pegcetacoplan in patients with PNH and persistent anemia despite anti-C5 treatment were assessed individually in the randomized Phase III APPLY-PNH (NCT04558918) and PEGASUS (NCT03500549) trials, respectively. In their respective clinical trials, both iptacopan and pegcetacoplan led to sustained improvements in hematological and clinical outcomes, including hemoglobin (Hb) levels and transfusion avoidance; however, their comparative efficacy has not yet been evaluated. When data from head-to-head trials are not available, indirect treatment comparisons are commonly performed to help assess the comparative efficacy of two treatments.

Aims:

We performed an indirect treatment comparison to assess efficacy on Hb and transfusions for iptacopan versus pegcetacoplan.

Methods:

A systematic literature review identified PEGASUS as the only relevant pegcetacoplan comparator trial for APPLY-PNH. Unanchored matching-adjusted indirect comparisons were conducted using individual patient data from APPLY-PNH for iptacopan (N=62) and published aggregate data from PEGASUS for pegcetacoplan (N=41). Endpoint definitions and the assessment period in APPLY-PNH were aligned to match PEGASUS (140 days, including 28 days run-in and the randomized controlled period of 112 days). Patients not meeting PEGASUS eligibility criteria were excluded from the APPLY-PNH dataset. The remaining patients in APPLY-PNH were weighted to match patient characteristics reported in PEGASUS. Two scenarios are presented: A) adjusting for three (baseline Hb, sex and transfusion avoidance within the 12 months prior to baseline) and B) six characteristics (baseline Hb, sex, transfusion avoidance within the 12 months prior to baseline, absolute reticulocyte count at screening, baseline lactate dehydrogenase, and age). The mean differences in change from baseline in Hb, excluding post-transfusion data and odds ratios (OR) of transfusion avoidance, were calculated.

Results:

Eight patients were removed from APPLY-PNH who would not have been eligible for PEGASUS. After matching and adjusting, baseline characteristics were similar across trials, with an effective sample size for APPLY-PNH of 16 in Scenario A and 15 in Scenario B. The mean difference in change from baseline in Hb level at Day 140 for iptacopan versus pegcetacoplan was 1.31 g/dL (95% confidence interval [CI] 0.52, 2.10) in Scenario A and 1.01 g/dL (95% CI 0.21, 1.82) in Scenario B, both in favor of iptacopan. Patients receiving iptacopan were 9.17-fold more likely (OR=9.17 [95% CI 1.59, 52.89]) to avoid transfusion between Days 29–140 than patients receiving pegcetacoplan in Scenario A and 12.71-fold more likely (OR=12.71 [95% CI 1.87, 86.22]) in Scenario B (**Table**).

Summary/Conclusion:

In the absence of a head-to-head randomized trial, this analysis matched baseline characteristics of iptacopan and pegcetacoplan trials. When comparing key outcomes across the matched populations, this analysis suggests that iptacopan is more effective than pegcetacoplan at improving Hb levels and provides higher odds of remaining transfusion free. The results should be interpreted in the context of estimates being derived from an indirect comparison.

Table. Unanchored MAIC results: comparative efficacy of iptacopan in APPLY-PNH versus pegcetacoplan in PEGASUS

		Change from baseline in Hb at Day 140 (excluding post-transfusion data)		Transfusion avoidance between Days 29–140	
Indirect treatment comparison – MAIC	Clinical trial, treatment arm (sample size)	Change from baseline (95% CI)	Mean difference (95% CI; *P* value) (*iptacopan vs pegcetacoplan*)	Proportion of patients who achieved transfusion avoidance, %	Odds ratio (95% CI; *P* value) (*iptacopan vs pegcetacoplan*)
Scenario A (matched* and adjusted for three characteristics)	PEGASUS, pegcetacoplan (N=41)	+2.37 (+1.66, +3.08)	1.31 (0.52, 2.10; *P*<0.001)†	85.4	9.17 (1.59, 52.89; *P*=0.013)†
	APPLY-PNH, iptacopan (ESS=16)	+3.68 (+3.33, +4.04)		98.2	
Scenario B (matched* and adjusted for six characteristics)	PEGASUS, pegcetacoplan (N=41)	+2.37 (+1.66, +3.08)	1.01 (0.21, 1.82; *P*=0.014)†	85.4	12.71 (1.87, 86.22; *P*=0.009)†
	APPLY-PNH, iptacopan (ESS=15)	+3.38 (+2.99, +3.77)		98.7	

*Eight patients were removed from APPLY-PNH who would not have been eligible for PEGASUS based on the following criteria: absolute reticulocyte count >1.0 × upper limit of normal at screening, platelet count of >50,000/mm^3 and body mass index <35 kg/m^2; †In favor of iptacopan versus pegcetacoplan. Estimates were considered statistically significant if the 95% CI excluded the null value (0.00 for mean differences and 1.00 for odds ratios), which corresponds to a two-tailed *P* value <0.05

CI, confidence interval; ESS, effective sample size; Hb, hemoglobin; MAIC, matching-adjusted indirect comparison

Keywords: Clinical outcome, Transfusion, Paroxysmal nocturnal hemoglobinuria (PNH), Hemoglobin