A Matching-Adjusted Indirect Comparison of the Efficacy of Pegcetacoplan using PRINCE Trial Data vs Ravulizumab and Eculizumab in Complement Inhibitor-Naïve Patients with Paroxysmal Nocturnal Hemoglobinuria

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OBJECTIVE

Assess the comparative effectiveness of pegcetacoplan (PEG) vs ravulizumab (RAV) and eculizumab (ECU) for complement inhibitor-naïve patients with PNH, using matching-adjusted indirect comparison (MAIC) methodology to conduct cross-trial comparisons.

CONCLUSIONS

- Using data from respective clinical trials, this unanchored MAIC study provides evidence of the relative efficacy of PEG vs RAV and ECU in complement inhibitor-naïve patients with PNH
- Compared with C5 inhibitors, PEG treatment showed meaningful and significant improvements across many secondary outcomes investigated in this analysis in treatment-naïve patients

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CONTEXT

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, life-threatening disease characterized by chronic complement-mediated hemolysis and thrombosis[1,2]
- Pegcetacoplan (PEG) is the first approved C3 inhibitor for US adults with PNH[3] and EU adults with PNH who remain anemic despite stable C5 inhibitor treatment (i.e., eculizumab [ECU] or ravulizumab [RAV]) for ≥3 months[4]
- In the phase 3 randomized, open-label PRINCE trial[5] (NCT04085601), PEG demonstrated superior efficacy vs. control treatment (excluding complement inhibitors) in treatment-naïve patients with PNH
- To date, no head-to-head clinical trials have compared the efficacy of PEG with the C5 complement inhibitors in treatment-naïve patients with PNH

METHODS

- This study used individual patient data from PRINCE[5] (PEG) and aggregated published results of RAV and ECU from the ALXN1210-PNH-301 (301, NCT02946463) study[6]
- Propensity score weighting was developed using logistic regression analyses to adjust for cross-study differences and balance demographic and clinical characteristics between the PEG arm (PRINCE) and the RAV and ECU arms (301)
- Baseline characteristics were weighted on the following: Asian race, age at first infusion, female sex, and baseline EORTC QLQ-C30 general health status score. Baseline variables chosen to weight the PEG arms were based on literature, clinician input, and effective sample size considerations
- Secondary outcomes were compared at 26 weeks between PEG vs RAV and PEG vs ECU using unanchored MAIC methods, and included: transfused packed red blood cell (PRBC) units, time to first LDH normalization (<1x ULN [246 U/L] without transfusions during the randomized controlled period), breakthrough hemolysis, major adverse vascular events (MAVEs), mean change in hemoglobin level, and change in FACIT-Fatigue and EORTC QLQ-C30 (general health status, physical functioning and fatigues symptom) scores
- Weighted Wald tests and 95% CIs were computed for comparison of categorical and continuous outcomes; a p-value <0.05 was considered significant

RESULTS

Baseline Population & Characteristics, After Weighting[a]

	PRINCE		301	
	PEG (weighted vs RAV)	PEG (weighted vs ECU)	RAV	ECU
Analysis sample, n	34[b]	34[b]	125	121
Effective sample size, n	24	22	--	--
Sex, %				
Female	48.0	43.0	48.0	43.0
Age in years at first study drug infusion, mean ± SD	44.8 ± 13.4	46.2 ± 13.6	44.8 ± 15.2	46.2 ± 16.2
Race, %				
Asian	57.6	47.1	57.6	47.1
White	0.0	0.0	34.4	42.1
Black or African American	7.6	10.7	1.6	3.1
American Indian or Alaska Native	30.4	36.7	0.8	0.8
Other[c]	4.4	5.4	3.2	3.3
Not reported/unknown	0.0	0.0	2.4	3.3
Weight, kg, mean ± SD	66.8 ± 14.3	66.9 ± 14.5	68.2 ± 15.6	69.2 ± 14.9
Height, cm, mean ± SD	165.0 ± 6.8	165.5 ± 6.6	166.3 ± 9.0	166.2 ±10.7
No PRBC unit transfusions within 1 year before study entry, %	13.8	12.1	18.4	17.4
LDH, U/L, mean ± SD[d]	2,220.3 ± 883.7	2,291.0 ± 967.4	1,633.5 ± 778.8	1,578.3 ± 727.1
Hemoglobin, g/dL, mean ± SD	9.7[e] ± 1.4	9.6[e] ± 1.4	9.4 ± NR	9.6 ± NR
EORTC QLQ-C30 score, mean ± SD				
General health status	56.1 ± 18.0	57.5 ± 18.2	56.1 ± 20.3	57.5 ± 20.3
Physical functioning	80.0 ± 14.7	80.6 ± 15.0	76.6 ± 17.1	76.4 ± 17.6
Fatigue symptoms	42.1 ± 20.6	42.4 ± 21.7	39.3 ± 22.7	37.3 ± 23.4

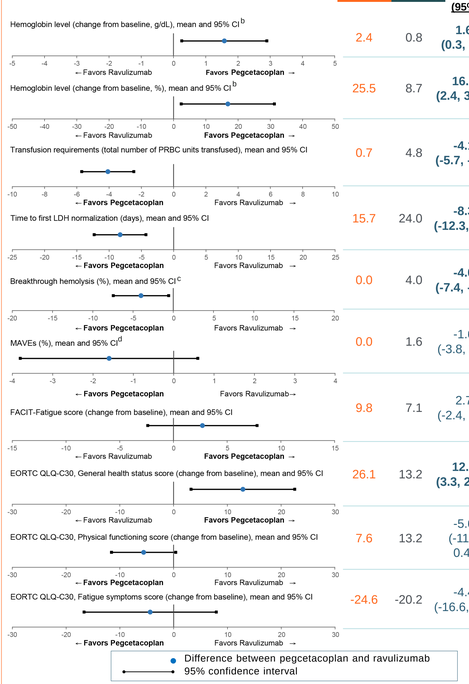
[a] The following baseline characteristics were weighted on: Asian race, age at first infusion, female sex, and baseline EORTC general health status score; [b] One patient was excluded from the PEG arm for no record of meningococcal vaccination, resulting in n=34; [c] Includes those who identified as being multiple races in the 301 study; [d] Normal range:120 to 246 U/L; [e] Normal range for PRINCE: male, 13.6–18 g/dL; female, 12–16 g/dL

After separately weighting PEG to the RAV and ECU arms to adjust for differences in baseline characteristics:

- Patient characteristics, such as mean age, sex ratio, and mean hemoglobin, were well balanced
- The differences in American Indian or Alaska Native race (p=0.0026 vs RAV, p<0.001 vs ECU) and LDH (p<0.001 vs both RAV and ECU) remained significant (adjustment would result in significant reduction in the effective sample size)

Unanchored MAIC Comparisons of Endpoints Between PEG and RAV Arms, After Matching[a]

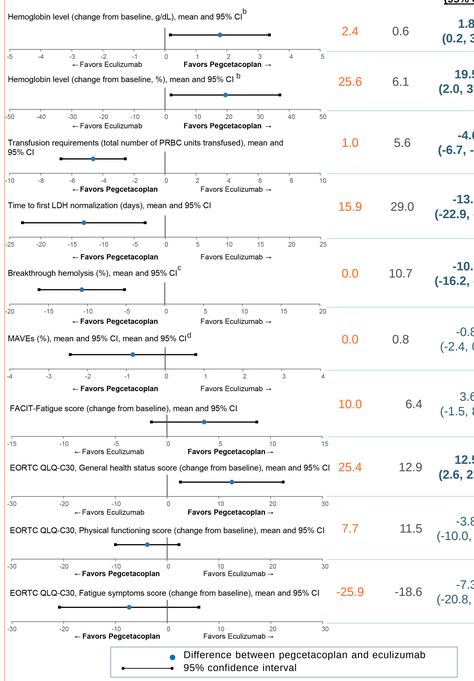
	PEG (N=24)	RAV (N=125)	MAIC Results: Difference (95% CI)	MAIC Results: p-value
Hemoglobin level (change from baseline, g/dL), mean and 95% CI[b]	2.4	0.8	1.6 (0.3, 2.9)	0.0193*
Hemoglobin level (change from baseline, %), mean and 95% CI[b]	25.5	8.7	16.8 (2.4, 31.3)	0.0223*
Transfusion requirements (total number of PRBC units transfused), mean and 95% CI	0.7	4.8	-4.1 (-5.7, -2.5)	<0.0001*
Time to first LDH normalization (days), mean and 95% CI	15.7	24.0	-8.3 (-12.3,-4.3)	<0.0001*
Breakthrough hemolysis (%), mean and 95% CI[c]	0.0	4.0	-4.0 (-7.4, -0.6)	0.0225*
MAVEs (%), mean and 95% CI[d]	0.0	1.6	-1.6 (-3.8, 0.6)	0.1540
FACIT-Fatigue score (change from baseline), mean and 95% CI	9.8	7.1	2.7 (-2.4, 7.8)	0.2973
EORTC QLQ-C30, General health status score (change from baseline), mean and 95% CI	26.1	13.2	12.9 (3.3, 22.6)	0.0087*
EORTC QLQ-C30, Physical functioning score (change from baseline), mean and 95% CI	7.6	13.2	-5.6 (-11.5, 0.4)	0.0682
EORTC QLQ-C30, Fatigue symptoms score (change from baseline), mean and 95% CI	-24.6	-20.2	-4.4 (-16.6, 7.9)	0.4870



[a] The following baseline characteristics were weighted on: Asian race, age at 1st infusion, female sex, and baseline EORTC general health status score
[b] Change in hemoglobin in the 301 study was estimated from values for percent hemoglobin stabilization and mean hemoglobin levels reported in Lee et al., 2019 and Schrezenmeier et al., 2021[7]
[c] Breakthrough hemolysis was defined as ≥1 new or worsening sign or symptom of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia [hemoglobin <10 g/dL], Major adverse vascular events [MAVEs], including thrombosis, dysphagia, or erectile dysfunction) in the presence of LDH ≥2x ULN after prior reduction of LDH to <1.5x ULN on treatment
[d] MAVEs were defined as thrombophlebitis/deep vein thrombosis; pulmonary embolus; myocardial infarction; transient ischemic attack; unstable angina; renal vein thrombosis; acute peripheral vascular occlusion; mesenteric/visceral vein thrombosis or infarction; mesenteric/visceral arterial thrombosis or infarction; hepatic/portal vein thrombosis (Budd-Chiari syndrome); cerebral arterial occlusion/cerebrovascular accident; cerebral venous occlusion; renal arterial thrombosis; gangrene (non-traumatic; nondiabetic); amputation (non-traumatic; nondiabetic);and dermal thrombosis

Unanchored MAIC Comparisons of Endpoints Between PEG and ECU Arms, After Matching[a]

	PEG (N=22)	ECU (N=121)	MAIC Results: Difference (95% CI)	MAIC Results: p-value
Hemoglobin level (change from baseline, g/dL), mean and 95% CI[b]	2.4	0.6	1.8 (0.2, 3.4)	0.0289*
Hemoglobin level (change from baseline, %), mean and 95% CI[b]	25.6	6.1	19.5 (2.0, 37.0)	0.0291*
Transfusion requirements (total number of PRBC units transfused), mean and 95% CI	1.0	5.6	-4.6 (-6.7, -2.6)	<0.0001*
Time to first LDH normalization (days), mean and 95% CI	15.9	29.0	-13.1 (-22.9, -3.2)	0.0095*
Breakthrough hemolysis (%), mean and 95% CI[c]	0.0	10.7	-10.7 (-16.2, -5.2)	0.0001*
MAVEs (%), mean and 95% CI, mean and 95% CI[d]	0.0	0.8	-0.8 (-2.4, 0.8)	0.3153
FACIT-Fatigue score (change from baseline), mean and 95% CI	10.0	6.4	3.6 (-1.5, 8.7)	0.1667
EORTC QLQ-C30, General health status score (change from baseline), mean and 95% CI	25.4	12.9	12.5 (2.6, 22.4)	0.0133*
EORTC QLQ-C30, Physical functioning score (change from baseline), mean and 95% CI	7.7	11.5	-3.8 (-10.0, 2.3)	0.2218
EORTC QLQ-C30, Fatigue symptoms score (change from baseline), mean and 95% CI	-25.9	-18.6	-7.3 (-20.8, 6.1)	0.2860



[a] The following baseline characteristics were weighted on: Asian race, age at 1st infusion, female sex, and baseline EORTC general health status score
[b] Change in hemoglobin in the 301 study was estimated from values for percent hemoglobin stabilization and mean hemoglobin levels reported in Lee et al., 2019 and Schrezenmeier et al., 2021[7]
[c] Breakthrough hemolysis was defined as ≥1 new or worsening sign or symptom of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia [hemoglobin <10 g/dL], Major adverse vascular events [MAVEs], including thrombosis, dysphagia, or erectile dysfunction) in the presence of LDH ≥2x ULN after prior reduction of LDH to <1.5x ULN on treatment
[d] MAVEs were defined as thrombophlebitis/deep vein thrombosis; pulmonary embolus; myocardial infarction; transient ischemic attack; unstable angina; renal vein thrombosis; acute peripheral vascular occlusion; mesenteric/visceral vein thrombosis or infarction; mesenteric/visceral arterial thrombosis or infarction; hepatic/portal vein thrombosis (Budd-Chiari syndrome); cerebral arterial occlusion/cerebrovascular accident; cerebral venous occlusion; renal arterial thrombosis; gangrene (non-traumatic; nondiabetic); amputation (non-traumatic; nondiabetic);and dermal thrombosis

Abbreviations: CFB, change from baseline; ECU, eculizumab; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; LDH, lactate dehydrogenase; MAIC, matching-adjusted indirect comparison; MAVE(s), major adverse vascular event(s); NR, not reported; PEG, pegcetacoplan; PNH, paroxysmal nocturnal hemoglobinuria; PRBC, packed red blood cells; RAV, ravulizumab; U, unit