Thrombosis and encapsulated bacterial infection rates in patients with paroxysmal nocturnal hemoglobinuria who received pegcetacoplan: Nearly 3 years of post-marketing experience

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OBJECTIVE

To report the most current real-world rates of thrombosis and infections by encapsulated bacteria in patients with PNH treated with pegcetacoplan in the post-marketing setting as of May 13, 2024

INTRODUCTION

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired hematologic disease characterized by complement-mediated hemolysis, aplasia, and thrombosis[1,2]
- Before approval of complement inhibitors, thrombosis was the leading cause of death in patients with PNH[1]
- Complement inhibitors have subsequently decreased thrombosis rates (**Table 1**)[3]
  - In patients who received the C5 inhibitor (C5i) eculizumab in clinical trials, the thrombosis rate with eculizumab was 1.07 events/100 patient-years (PY)[4]
  - The thrombosis rate with the C5i ravulizumab was similar (1.21 events/100 PY)[5]
  - In clinical trials of pegcetacoplan, the first C3/C3b-targeted therapy for PNH, the thrombosis rate was 1.22 events/100 PY[6]
  - In a registry study of patients with PNH receiving C5is in the United Kingdom (May 2002 to July 2022), the thrombosis rate was 0.73 events/100 PY[7]
- Optimal PNH treatment must block complement activity enough to reduce risk of thrombosis without compromising the complement system to an extent that increases the risk of life-threatening infections, especially *Neisseria meningitidis*[8]

Table 1. Thrombosis rates previously reported in patients with PNH

Setting, complement inhibitor (number of patients)	Thrombosis rate, events/100 PY	Thrombotic events, n	Cumulative exposure, y
Clinical trials			
Eculizumab (N=195)[4]			
Before eculizumab	7.37	124	1683
With eculizumab	1.07	3	281
Ravulizumab (N=434)[5]	1.21	8	662
Pegcetacoplan (N=170)[6,a]	1.22	5	409
Registry study in the United Kingdom[7]			
Eculizumab or ravulizumab (N=509)	0.73	23	3130

PNH, paroxysmal nocturnal hemoglobinuria; PY, patient-years.
[a]As of November 13, 2022.

- To achieve this fine balance, adherence to the recommended treatment dosing and risk-mitigating strategies for preventing infections are essential
- Despite risk mitigation, *N. meningitidis* infection rates are ~1000-2000-fold greater in C5i-treated patients than in the general population[8]
- *N. meningitidis* infection rates with C5is were 0.24/100 PY in a 10-year pharmacovigilance analysis[9] and 0.35/100 PY in a registry analysis[10]

METHODS

- Cumulative pegcetacoplan exposure was calculated in PY
- Post-marketing compliance in the United States was calculated as the proportion of days a patient had the drug in possession divided by the total number of days of follow-up using central pharmacy prescription refill data

METHODS *(cont.)*

- The trial protocols and labels require vaccination against *N. meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* before pegcetacoplan use; the labels recommend prophylactic antibiotics if pegcetacoplan must be administered prior to vaccination;[12,13] informed consent was obtained before clinical trial participation
- Post-marketing rates of thrombosis (arterial and venous) and rates of infection with encapsulated bacteria were estimated from the total number of events reported in the Apellis/Sobi global safety database, using solicited reports from patient support and market research programs; spontaneous reports from health care providers, consumers, and regulatory agencies; and reports extracted from the literature

RESULTS

- Patients with PNH (N=747) had experienced a total of 931 PY of pegcetacoplan exposure in the post-marketing setting (in the United States, Europe, and rest of the world) as of May 13, 2024
- Post-marketing adherence in the United States was estimated at 97%
- No infections by encapsulated bacteria were reported among patients with PNH on pegcetacoplan up to May 13, 2024, across countries in the combined clinical trial and post-marketing contexts (total cumulative exposure of 1469 PY)
- In the post-marketing setting, 3 thrombotic arterial and/or venous events were reported among patients with PNH on pegcetacoplan up to May 13, 2024, resulting in a thrombosis rate of 0.32 events/100 PY (**Table 2**); breakthrough hemolysis (n=1) or provoking risk factors (n=2) were present and outcomes were improving or resolving (n=2) and unknown (n=1)
  - In comparison, the reported rate of venous thrombotic events is approximately 0.1–0.2/100 PY in the general population of the United States and Europe[13]

Table 2. Thrombosis rates reported in the real world

Population and setting (number of patients)	Thrombosis rate, events/100 PY	Thrombotic events, n	Cumulative exposure, y
Patients with PNH on pegcetacoplan in the post-marketing setting in the United States, Europe, and rest of the world[a] (N=747)	0.32	3	931
General population in the United States and Europe[11]	~0.1-0.2		

PNH, paroxysmal nocturnal hemoglobinuria; PY, patient-years.
[a]As of May 13, 2024.

CONCLUSIONS

- ✓ **These findings suggest that the thrombosis rate in patients with PNH on pegcetacoplan is low overall and comparable to rates on C5is**
- ✓ **At the time of data cut, no infections by encapsulated bacteria had been reported in patients with PNH on pegcetacoplan, suggesting effective risk mitigation strategies**
- ✓ **A potential confounder is the real-world nature of the data, which may be subject to underreporting; comparison to real-world studies of C5is is limited by the different methods used to ascertain events**
- ✓ **The lack of infections by encapsulated bacteria reported with pegcetacoplan may reflect effective risk mitigation strategies, including possible differences in prophylactic antibiotic usage and/or beneficial infection-prevention measures**
- ✓ **Continued follow-up is required**

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