

Real-World Data Confirms Proximal Complement Inhibition in PNH

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, life-threatening blood disorder characterized by complement-mediated hemolysis.¹ While distal complement inhibition has been a standard of care, real-world data presented at EHA 2026 provides further validation for proximal complement inhibition, offering clinicians additional insights into its practical application and patient outcomes.

KEY TAKEAWAYS

- **The Pivot:** Real-world data reinforces the established efficacy and safety profile of proximal complement inhibitors in PNH management.
- **The Data:** Patients initiating proximal complement inhibition demonstrated sustained control of intravascular hemolysis and reduced transfusion dependence.
- **The Action:** Clinicians should consider proximal complement inhibitors as a viable and effective treatment option for PNH, aligning with established clinical trial outcomes.

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired hematologic disorder characterized by chronic, uncontrolled complement activation leading to intravascular hemolysis, thrombosis, and bone marrow failure.¹ The disease results from a somatic mutation in the PIGA gene in hematopoietic stem cells, leading to a deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins, including CD55 and CD59, on the surface of blood cells.¹ CD55 and CD59 are crucial regulators of the complement cascade, and their absence renders PNH erythrocytes highly susceptible to complement-mediated destruction.² The estimated prevalence of PNH is approximately 1 to 1.5 cases per million individuals, with a median age of diagnosis in the third or fourth decade of life, though it can affect individuals of any age. The clinical manifestations are diverse, ranging from mild anemia to life-threatening complications such as thrombotic events and kidney disease, significantly impacting patient quality of life and survival if left untreated. Historically, management of PNH focused on supportive care, including blood transfusions and anticoagulation. The advent of complement inhibitors, specifically C5 inhibitors, revolutionized PNH treatment by directly targeting the terminal complement pathway, thereby reducing hemolysis and improving patient outcomes.³ However, a subset of patients may experience persistent extravascular hemolysis or suboptimal response to C5 inhibition. This can be due to genetic polymorphisms affecting C5 binding or the continued activity of upstream complement components. Proximal complement inhibition, targeting earlier components of the complement cascade, represents an alternative strategy to achieve more comprehensive complement blockade.⁴ These inhibitors typically target components such as C3 or Factor B, preventing the formation of both C3 and C5 convertases, thus inhibiting both intravascular and extravascular

hemolysis. The real-world data presented at EHA 2026 aimed to evaluate the effectiveness and safety of these agents in a broader clinical setting, beyond controlled trial environments.⁵

Real-World Insights into Proximal Complement Inhibition

The real-world study encompassed a retrospective analysis of PNH patients initiating treatment with a proximal complement inhibitor across multiple European and North American centers.⁵ The cohort included patients with active PNH, defined by evidence of hemolysis (e.g., elevated lactate dehydrogenase (LDH) levels) and transfusion dependence, or those with an inadequate response to prior C5 inhibitor therapy.⁵ Data collected included patient demographics, disease characteristics, prior treatments, and outcomes such as LDH levels, hemoglobin levels, transfusion requirements, and adverse events. The primary endpoints were the proportion of patients achieving LDH normalization (defined as 6 The study design allowed for the inclusion of a heterogeneous patient population, reflecting the variability encountered in routine clinical practice, which enhances the generalizability of the findings.

The study enrolled 287 adult patients with PNH, with a median follow-up duration of 18 months (range, 6-36 months).⁶ Of these, 62% had previously received a C5 inhibitor, while 38% were treatment-naïve.⁶ The baseline characteristics of the patient population included a median age of 45 years, with 55% being female. The median LDH level at baseline was 3.5 times the upper limit of normal, and 70% of patients were transfusion-dependent, requiring at least one red blood cell transfusion in the 6 months prior to study entry. At 6 months post-initiation of proximal complement inhibition, 78% (95% CI, 73-82%) of patients achieved LDH normalization.⁷ This proportion increased to 85% (95% CI, 80-89%) by 12 months.⁷ Among patients who were transfusion-dependent at baseline, 65% (95% CI, 59-71%) achieved transfusion independence by 6 months, and 72% (95% CI, 66-77%) by 12 months.⁸ The mean hemoglobin level increased from 8.2 g/dL (SD, 1.1) at baseline to 11.5 g/dL (SD, 0.9) at 12 months (P 0.001).⁸

The safety profile was consistent with that observed in pivotal clinical trials.⁹ The most common adverse events were headache (22%), nasopharyngitis (18%), and diarrhea (15%).⁹ Serious infections occurred in 4% of patients, with no cases of meningococcal infection reported in vaccinated individuals.⁹ One patient experienced a thrombotic event, which was considered unrelated to the study drug.¹⁰ Discontinuation due to adverse events occurred in 7% of patients.¹⁰ The overall safety profile supports the favorable risk-benefit assessment of proximal complement inhibitors in the PNH population.

This real-world evidence corroborates the efficacy and safety data from controlled clinical trials of proximal complement inhibitors in PNH.¹¹ The high rates of LDH normalization and transfusion independence observed in a diverse patient population, including those refractory to C5 inhibition, underscore the clinical utility of this therapeutic approach.¹¹ Limitations of the study include its retrospective nature and the potential for selection bias inherent in real-world data collection.¹² The absence of a direct comparator arm also limits definitive conclusions regarding superiority over other treatment modalities.¹² Furthermore, the reliance on medical record data may introduce variability in data completeness and accuracy. The relatively short follow-up duration for some patients also restricts the assessment of long-term outcomes and safety. Future prospective studies and head-to-head comparisons would provide further clarity on the optimal sequencing and choice of complement inhibitors in PNH management.¹³

CLINICAL IMPLICATIONS

The consistent real-world performance of proximal complement inhibitors in PNH, mirroring the robust outcomes seen in controlled trials, provides welcome reassurance for clinicians. The high rates of LDH normalization and transfusion independence, even in patients previously failing C5 inhibition, suggest that these agents are not merely an alternative but a genuinely effective option for a broader spectrum of PNH patients. This data should encourage earlier consideration of proximal complement blockade, particularly in those with persistent hemolysis or significant transfusion burden despite standard C5 inhibitor therapy. It also reinforces the importance of comprehensive complement inhibition to address the multifaceted pathology of PNH.

For the pharmaceutical industry, this real-world validation strengthens the market position of proximal complement inhibitors, such as pegcetacoplan, against established C5 inhibitors like eculizumab and ravulizumab. The ability to demonstrate sustained clinical benefit in a heterogeneous patient population, including those with suboptimal C5 inhibitor response, provides a clear differentiator. This evidence supports broader adoption and potentially influences formulary decisions, emphasizing the value proposition of more complete complement pathway blockade. The continued investment in understanding the nuances of complement inhibition across different patient profiles will be critical for future drug development and market penetration.

From a patient perspective, these findings translate into tangible improvements in quality of life. Reduced transfusion dependence means fewer hospital visits, less fatigue, and greater autonomy. The consistent safety profile, with manageable adverse events, further bolsters confidence in these therapies. While the cost of these highly specialized treatments remains a significant consideration, the demonstrated clinical benefits in preventing life-threatening complications and improving daily functioning underscore their value. Patients and their physicians now have stronger evidence to support treatment choices that can profoundly impact their long-term health and well-being.

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