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Navigating the Paroxysmal Nocturnal Hemoglobinuria (PNH) Landscape

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Abstract: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal hematopoietic stem cell disorder in which a somatic mutation in *PIGA* leads to reduced or absent expression of glycosylphosphatidylinositol-anchored complement regulatory proteins. PNH presents with the central manifestations of complement-mediated hemolytic anemia, bone marrow failure, and thrombosis. The introduction of terminal complement inhibitors that block complement protein 5 (C5) has revolutionized the management of PNH by reducing the risk for thrombosis, extending survival to be similar to that of healthy controls, and improving quality of life. C5 inhibitors approved by the US Food and Drug Administration (FDA) include eculizumab (administered intravenously every 2 weeks), ravulizumab (administered intravenously every 8 weeks), and, most recently, crovalimab (administered subcutaneously every 4 weeks). Given the chronic nature and life-threatening complications of PNH, long-term efficacy and safety data of treatment approaches are invaluable. The most extensive experience has been gained with eculizumab, and now 6-year data with ravulizumab point to its durable control of terminal complement activity and intravascular hemolysis. Although terminal complement inhibitors effectively control intravascular hemolysis, approximately 30% of patients receiving C5 inhibitors develop clinically significant extravascular hemolysis with ongoing transfusion requirements or symptomatic anemia. Upstream complement inhibitors that inhibit components of the alternative complement system have been developed with the goal of addressing both intravascular and extravascular hemolysis. The C3 inhibitor pegcetacoplan (administered subcutaneously twice weekly) and the factor B inhibitor iptacopan (administered orally twice daily), both used as single agents, have demonstrated effective control of hemolysis with increased hemoglobin and transfusion avoidance in both C5 inhibitor–naive and C5 inhibitor–experienced patients with clinically significant extravascular hemolysis. The factor D inhibitor danicopan (administered orally 3 times a day) is used as an add-on to ravulizumab or eculizumab and offers a combination approach by targeting both terminal complement and the alternative pathway. Breakthrough hemolysis in the event of a strong complement trigger is possible on any complement inhibitor, but these breakthrough events could be more severe with alternative pathway inhibitor monotherapy. Rates of breakthrough hemolysis and whether they differ between the alternative pathway inhibitors remain to be determined in the real-world setting.

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About PNH: Brief Overview

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal hematopoietic stem cell disorder in which uncontrolled terminal complement activation leads to intravascular hemolysis. PNH presents with the cardinal manifestations of complement-mediated hemolytic anemia, bone marrow failure, and thrombosis.[1] The reported prevalence of PNH is approximately 12 per million and the incidence is approximately 1 to 10 per million person-years.[2] Actual rates may be higher, as obtaining a timely diagnosis can be challenging. The median age of onset is in the 30s, although PNH can be diagnosed in children and in older adults.[3] No clear racial, ethnic, or sex differences in incidence have been reported. As a chronic disease, PNH affects individuals throughout their lifetime, including during their reproductive years.

PNH is a clonal disorder that arises from expansion of hematopoietic stem cells harboring a somatic mutation in *PIGA*. An X-linked gene, *PIGA* encodes a protein necessary for synthesis of glycosylphosphatidylinositol (GPI), a glycolipid that covalently anchors proteins to the cell surface.[4] Because they lack GPI, PNH cells have reduced or absent expression of GPI-anchored cell surface proteins, including the complement regulatory proteins CD55 and CD59. Deficiency of CD55 and CD59 cause dysregulation of complement, leading to hemolysis and its consequences.

PIGA mutations alone are insufficient to cause PNH, as the mutation does not confer the stem cell with a survival advantage. Very small polyclonal PNH populations can be found in healthy individuals. However, a *PIGA* mutation may confer a conditional survival advantage in the event of an autoimmune attack, leading to expansion of the PNH clone.[4] PNH can arise de novo or in the setting of another defined bone marrow disorder. PNH is strongly associated with acquired aplastic anemia and can develop in patients with myelodysplastic syndrome. Rarely, expansion of a PNH clone also may occur in stem cells harboring a second genetic alteration that confers a selective growth advantage, such as *JAK2V617F* or *CALR*.

Pathophysiology

The clinical manifestations of PNH arise because of dysregulation of the complement system, a part of the innate immune system involved in defense against foreign pathogens, clearance of cellular debris, and handling of immune complexes.[5] The complement system is initiated through 3 pathways: the classical pathway, the lectin pathway, and the alternative pathway (Figure 1). Each pathway leads to the formation of the complement protein 3 (C3) convertase and converge on a common terminal pathway, which leads to the formation of the membrane attack complex (MAC), resulting in red blood cell (RBC) lysis. Normally, CD55 and CD59 on RBC surfaces act to regulate complement activation. CD55 regulates the formation and stability of C3 and C5 convertases, and CD59 regulates terminal complement by blocking the formation of the MAC and the insertion of C9 into the lipid bilayer.

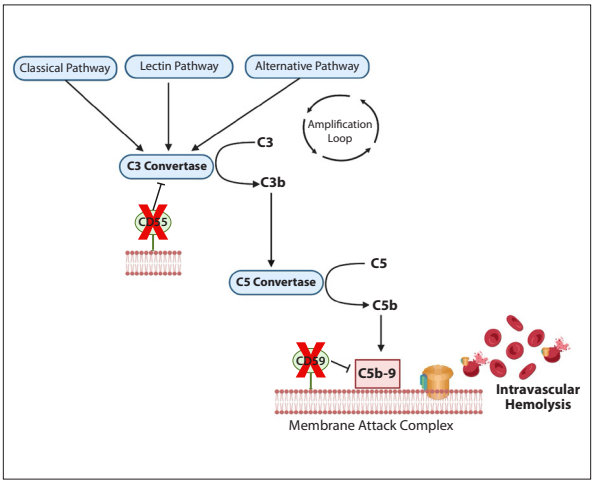

Figure 1. The complement system in PNH. Courtesy of Gloria F. Gerber, MD.
PNH, paroxysmal nocturnal hemoglobinuria.

In patients with PNH, there is constant low-level complement activity through the alternative pathway, leading to chronic intravascular hemolysis.[6] Complement-amplifying events such as infection, surgery, pregnancy, vaccination, or other inflammatory triggers can lead to complement activation through any of the proximal pathways, causing severe paroxysmal events.

Presentation and Clinical Sequelae

Intravascular hemolysis can cause a variety of clinical sequelae including anemia-associated symptoms such as fatigue and dyspnea, smooth muscle dystonia, erectile dysfunction, and esophageal spasms.[4] Abdominal pain is common in patients with PNH. Magnetic resonance imaging studies have shown impaired small bowel blood supply in patients with PNH with abdominal pain.[7] Moreover, imaging and endoscopic studies have demonstrated small bowel ischemic changes in patients with PNH.[8] Rarely, these findings are misdiagnosed as inflammatory bowel disease.

Intravascular hemolysis can lead to hemoglobinuria, the namesake manifestation of PNH, owing to the release of heme pigments into the urine. However, hemoglobinuria develops in only approximately one-third of patients with PNH.

Thrombosis is the most clinically significant manifestation of PNH, as it was the leading cause of mortality before the development of complement inhibitors and occurred in up to 40% of patients. Venous thrombosis is more common than arterial thrombosis, although either one can occur. Thrombotic events tend to occur in unusual sites such as the splanchnic veins, including hepatic vein thrombosis leading to Budd-Chiari syndrome and a risk of liver failure, and cerebral venous sinus thrombosis.

Thrombosis in patients with PNH is complement-mediated. Anticoagulation alone does not prevent recurrent thrombosis, whereas complement inhibitors abrogate the thrombotic phenotype, and thrombosis is an urgent indication to start complement inhibitor therapy in PNH. The mechanisms of hypercoagulability are complex and multifactorial. Hemolysis leads to the release of (1) free hemoglobin and nitric oxide scavenging, altering vasoconstriction and endothelial function; and (2) adenosine diphosphate leading to platelet activation. Complement may activate platelets, leading to procoagulant microparticle formation. There are also impaired fibrinolytic and antithrombotic mechanisms and inflammatory cytokine signaling through C5a, which may promote hypercoagulability in PNH. The risk of thrombosis in PNH is associated with the size of the PNH white blood cell (WBC) clone, with clones exceeding 50% conferring a higher risk of thrombosis.[3] Rarely, patients can develop an ahemolytic form of PNH with a large WBC clone and a small RBC clone, in which hemolysis is not prominent but thrombosis can be severe.[9] This suggests that hypercoagulability is not fully accounted for by hemolysis.

Data from a Korean PNH National Registry indicate that, in patients with complement inhibitor–naive PNH, increased lactate dehydrogenase (LDH) to at least 1.5 times the upper limit of normal (ULN) (P=.016), male sex (P=.045), and pain (P=.033) are independently associated with an increased risk of thromboembolism.[10]

Prior to the development of complement inhibitors, the 5-year mortality rate of PNH was approximately 30%, with thromboembolic events accounting for up to 67% of deaths.[11] Thrombosis at presentation was associated with a 40% survival rate at 4 years.[12] Today, with the use of complement protein 5 (C5) inhibitors, survival rates are similar to age-matched controls, and thrombosis no longer contributes to an increased mortality rate. However, bone marrow failure and an approximately 2% to 3% risk of transformation to myeloid malignancy do contribute to a small increase in mortality in patients with PNH.

Diagnosis and Classification

PNH is diagnosed using flow cytometry of peripheral blood to evaluate the presence and size of a PNH clone by quantifying the proportion of cells with absent GPI-anchored proteins (eg, CD59 on erythrocytes) and fluorescein-labeled proaerolysin, which is a fluorescently conjugated prototoxin that binds to GPI anchors on WBCs.[11] At least 2 different GPI markers on 2 cells lines is recommended for the diagnosis of PNH.

A PNH clone is classified into 3 groups with differing pathologic and clinical features.[13-15]

1. Approximately one-third of patients with a PNH clone have **classical PNH**, which is associated with intravascular hemolysis, a risk of thrombosis, and larger PNH WBC clones. Complement inhibition is beneficial in most patients in this subgroup.
2. A second group includes patients with **PNH in the setting of an acquired bone marrow failure syndrome (eg, aplastic anemia)**. These PNH clones tend to be smaller (<50%); however, it is important to assess for markers of hemolysis, reticulocyte count, LDH, and thrombosis in patients with bone marrow failure and a PNH clone. Complement therapy does not address the underlying bone marrow failure, and definitive therapy for bone marrow failure may be required; however, complement inhibition may play a role in patients with bone marrow failure and larger PNH clones who have evidence of hemolysis or thrombosis, and, in some cases, to prevent symptoms and thrombotic events associated with stem cell transplantation.[11] Regular monitoring is warranted to identify progression to classical PNH in patients with a history of aplastic anemia and, conversely, to identify progressive bone marrow failure in patients with classical PNH.
3. The third group includes patients with **subclinical PNH** with small PNH clones in the setting of a co-occurring bone marrow failure disorder and no clinical or laboratory evidence of intravascular hemolysis. There

is no role of complement inhibition in these patients.

Disease Burden

PNH is a chronic, resource-intensive condition that requires lifelong therapy. The advent of complement inhibition with the terminal complement inhibitors—eculizumab and later the extended half-life ravulizumab—led to substantial clinical benefits for patients with PNH.[11] By controlling intravascular hemolysis and its consequences, C5 inhibitors reduce thrombotic risk, lead to transfusion avoidance in 80% of patients, improve quality of life, and extend survival. Extravascular hemolysis is a mechanistic consequence of C5 inhibition, and up to 30% of patients develop clinically significant extravascular hemolysis with symptomatic anemia and transfusion dependence and benefit most from proximal complement inhibition. However, anemia in PNH may be owing to a variety of factors not responsive to complement inhibition, including bone marrow failure.[4]

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Complement Inhibitors: A Significant Advance in the Treatment of PNH

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The observation that the clinical manifestations of PNH are primarily owing to loss of regulation of complement at the terminal end of the complement pathway has led to the development of terminal complement inhibition as a therapeutic strategy in PNH. Targeting the terminal components of the pathway provides a second advantage of limited risk of bacterial infections, aside from *Neisseria* infections.[1] A third advantage is the reduction in hemostatic activation and a reduction in thromboembolic complications. However, breakthrough hemolysis owing to extravascular clearance of C3b-coated cells remains a concern with terminal complement inhibitors. This led to the development of proximal complement inhibitors to target extravascular hemolysis.

Today multiple complement inhibitors are available with different targets, including terminal pathway complement inhibitors that target C5, and upstream or alternative pathway inhibitors that target C3, factor B, and factor D. Agents also differ in their mode of administration and dosing frequency; an overview of current

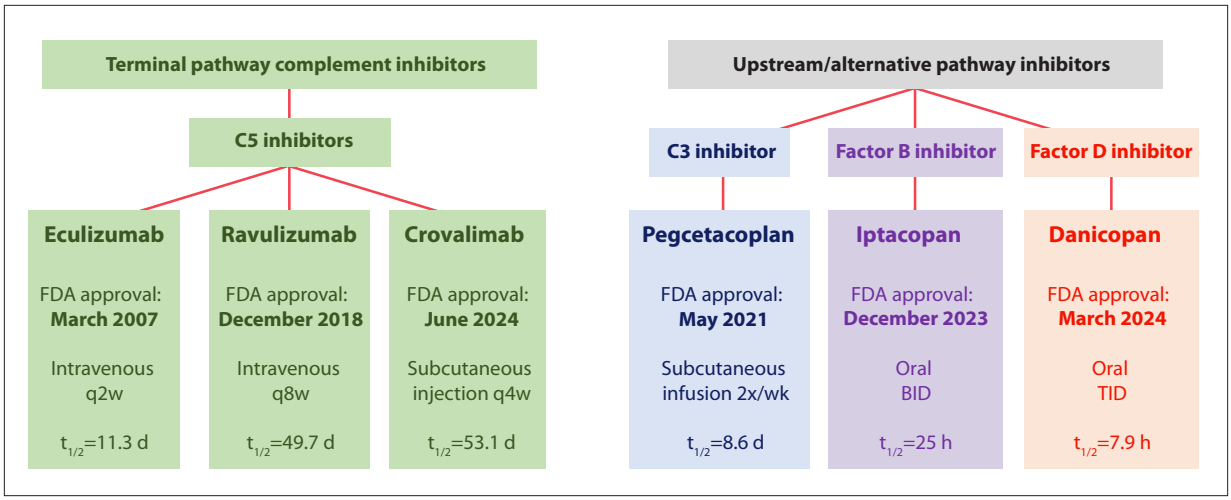

Figure 2. FDA-approved agents for the management of PNH.[2-7]
BID, twice daily; d, days; FDA, US Food and Drug Administration; h, hours; PNH, paroxysmal nocturnal hemoglobinuria; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; $t_{1/2}$, half-life; TID, 3 times daily; wk, week.

FDA-approved agents is provided in Figure 2.[2-7]

Terminal Complement Inhibitors

The first complement inhibitor to be introduced was the C5 inhibitor **eculizumab**, approved in March 2007 for the reduction of hemolysis in patients with PNH.[2] Eculizumab is dosed intravenously weekly for the first 4 weeks followed by a fifth dose 1 week later and then is dosed every 2 weeks thereafter. Since the introduction of eculizumab, 2 additional C5 inhibitors have received FDA approval. **Ravulizumab**, approved in December 2018, is also dosed intravenously but allows for less frequent dosing than eculizumab.[3] Ravulizumab is administered using weight-based dosing, with doses administered in adults every 8 weeks starting 2 weeks after a loading dose.[3] The most recent C5 inhibitor to receive FDA approval was **crovalimab**, approved in June 2024.[4] After an initial intravenous loading dose, crovalimab is administered subcutaneously as 4 weekly loading doses followed by maintenance doses every 4 weeks.[4]

Over the past 20 years, C5 inhibition has demonstrated long-term safety and efficacy, reducing or eliminating the need for RBC transfusions, reducing the risk of thrombosis by more than 90%, and yielding survival outcomes comparable to age-matched controls.[8] The demonstrated improvement in survival with terminal complement inhibition alone illustrates the critical role of terminal complement in the progression of PNH.[9]

Upstream or Alternative Pathway Inhibitors

Other agents for the management of PNH target upstream or alternative components of the complement pathway. In May 2021, the C3 inhibitor **pegcetacoplan** received FDA approval for the treatment of adults with PNH.[5] Pegcetacoplan is administered subcutaneously twice weekly, or every 3 days if LDH levels are greater than 2 × ULN. In December 2023, the factor B inhibitor **iptacopan** received FDA approval for use in adults with PNH.[6] Iptacopan is administered orally twice daily. In March 2024, the factor D inhibitor **danicopan** received FDA approval as add-on therapy to ravulizumab or eculizumab for the treatment of extravascular hemolysis in adults with PNH.[7] Danicopan is administered orally 3 times a day.

Breakthrough Hemolysis With Complement Inhibitors

Patients receiving a C5 inhibitor can develop a resurgence of the signs and symptoms of intravascular hemolysis. This breakthrough hemolysis, which is associated with increased LDH levels and a substantial reduction in hemoglobin, can result from several causes. Pharmacokinetic breakthrough hemolysis occurs because of low levels of C5 inhibitor, whereas pharmacodynamic hemolysis occurs when a significant complement-activating event occurs, such as infection or inflammation, that is strong enough to overcome the C5 blockade.[10] Pharmacodynamic breakthrough hemolysis is often self-limited, resolving after the additional complement activation diminishes. Hemolysis can also occur through a different mechanism in patients receiving a C5 inhibitor. Extravascular hemolysis occurs as a result of C3 fragments being deposited on the surface of defective RBCs, making them susceptible to destruction

by macrophages of the reticuloendothelial system.[10]

Newer proximal complement inhibitors, including the C3 inhibitor pegcetacoplan, were developed with the goal of addressing both intravascular and extravascular hemolysis. Severe episodes of breakthrough hemolysis have been reported in patients with PNH receiving pegcetacoplan, reflecting incomplete C3 inhibition. The mechanism of this type of breakthrough hemolysis with proximal complement inhibitors is not well understood.[10]

Inadequate and inconsistent control of intravascular hemolysis characterized by inadequate LDH suppression has also been reported with single-agent use of the investigational proximal complement inhibitor vemircopan, again suggesting the importance of controlling terminal complement activity in patients with PNH.[9] If patients with PNH experience anemia owing to extravascular hemolysis, dual complement inhibition may be considered, using a proximal complement inhibitor to address the symptomatic anemia and a terminal complement inhibitor to maintain control of intravascular hemolysis. The factor D inhibitor danicopan, the parent compound of vermicopan, is very effective in reducing extravascular hemolysis when added to C5 inhibition. However, danicopan is insufficient, in its current form, to work as a single agent.

Pregnancy and PNH

Pregnancy is a complement-amplifying condition that creates challenges for patients living with PNH. Historically, maternal and fetal mortality rates in the setting of PNH were high, approaching 20% and 9%, respectively.[11] Complement inhibition provides benefits for women with PNH during pregnancy, reducing rates of maternal mortality and thrombosis.[12] However, registry data report a 4% fetal death rate in pregnant patients receiving PNH therapy, owing to premature births.[12] Breakthrough hemolysis is common during pregnancy and up to 50% of patients require increased dosing. The most experience has been reported with eculizumab; levels of eculizumab that cross the placenta are not high enough to affect complement and are not detected in breast milk. Ravulizumab is also likely to be safe but there is little clinical experience. Pregnant women with PNH should receive multidisciplinary care including obstetrics and hematology.[11] Pregnant patients should be considered high risk for thrombosis and should receive prophylactic anticoagulation.

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Monotherapy With Terminal Pathway C5 Inhibitors

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The past 20 years of experience with C5 inhibitors have demonstrated the efficacy and safety of terminal complement inhibition as a treatment strategy for PNH. Clinical benefits include a reduced risk of thrombosis, a reduced or eliminated need for RBC transfusions, and survival rates comparable to age-matched controls.[1,2] The key safety issue with C5 inhibition is an increased risk for *Neisseria* infections owing to the requirement for terminal complement activation for serum bactericidal activity.[3] Because PNH is a chronic

Table 1. Pivotal Efficacy and Safety Data for C5 Inhibitors

Agent	Trial details	Key efficacy findings in experimental vs control arm	Safety findings
Eculizumab	Eculizumab vs placebo in adults with PNH (n=87)[4]	**Rate of stabilization of hemoglobin without transfusions at 26 weeks:** 49% vs 0% (*P*<.001) **Median number of packed RBCs administered by 26 weeks:** 0 vs 10 units (*P*<.001) Reduction in thromboembolic events *P*<.0001	**Serious AEs:** 9% vs 20% with placebo (including exacerbation of PNH, 2% vs 7% with placebo) **AEs more frequent with eculizumab vs placebo:** headache (44% vs 27%), back pain (19% vs 9%); number of headaches similar after first 2 weeks of therapy
Ravulizumab	**301 study:** ravulizumab vs eculizumab in complement inhibitor–naive adults with PNH (n=246)[5]	**Proportion of patients remaining transfusion-free at 26 weeks:** 73.6% vs 66.1% **LDH normalization at 26 weeks:** 53.6% vs 49.4%	Similar safety and tolerability; no meningococcal infections reported
	302 study: ravulizumab vs eculizumab in eculizumab-experienced patients (n=195)[6]	**Difference in percentage change in LDH from baseline to day 183:** 9.21% (*P*=.058 for superiority)	**Most frequent AE:** headache (26.8% vs 17.3%); no meningococcal infections
Crovalimab	**COMMODORE 1:** crovalimab vs eculizumab in C5 inhibitor–experienced patients (n=89)[7]	**Exploratory efficacy analysis:** sustained terminal complement inhibition, maintained disease control	AE rates 77% vs 67%; no meningococcal infections; transient immune complex reactions in 16% of crovalimab-treated patients
	COMMODORE 2: crovalimab vs eculizumab in C5 inhibitor–naive patients (n=204)[8]	**Proportion of patients with hemolysis control (LDH ≤1.5 × ULN) at 24 weeks:** 79.3% vs 79.0% **Transfusion avoidance:** 65.7% vs 68.1%	Similar safety outcomes; no meningococcal infections

AE, adverse event; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; ULN, upper limit of normal.

condition that can cause life-threatening complications, evaluating the long-term efficacy and safety data of treatment approaches is critical. The most extensive experience has been gained with eculizumab, and now 6-year data with ravulizumab point to its durable control of terminal complement activity and intravascular hemolysis.

Clinical Trials of C5 Inhibitors

An overview of the pivotal trials of C5 inhibitors in patients with PNH is shown in Table 1.[4-8]

Eculizumab was evaluated in a double-blind, randomized, 26-week phase 3 trial in which it demonstrated greater stabilization of hemoglobin levels and reduced need for RBC transfusions compared with placebo.[4] Eculizumab was also associated with reduced intravascular hemolysis compared with placebo, as assessed by an 85.8% reduction in the median area under the curve for LDH, and clinically significant improvements in quality of life. No serious treatment-related adverse events were noted. The effects of eculizumab on the risk of thrombosis appear to be rapid, as levels of D-dimers begin to decline within a week of starting eculizumab, are low by week 4, and remain low during maintenance treatment.[9]

Ravulizumab administered every 8 weeks was compared with eculizumab administered every 2 weeks in 2 phase 3 trials. The 301 study demonstrated the noninferiority of ravulizumab vs eculizumab in complement inhibitor–naive patients, whereas 302 study demonstrated its noninferiority in patients with clinically stable PNH during prior eculizumab therapy. Ravulizumab demonstrated noninferiority to eculizumab in both populations, as assessed by transfusion avoidance, LDH parameters, change in Functional Assessment of Chronic Illness

Therapy (FACIT)-Fatigue score, breakthrough hemolysis, and stabilized hemoglobin.[5,6] Moreover, breakthrough hemolysis events appear to be less common with ravulizumab, which could be owing to the elimination of pharmacokinetic breakthrough hemolysis with ravulizumab and the use of weight-based dosing.[10] Demonstrated noninferiority of ravulizumab, along with its more convenient dosing schedule, makes it a preferred option in PNH.

The third commercially available C5 inhibitor, **crovalimab**, is administered every 4 weeks and allows for subcutaneous self-administration after the initial intravenous dose. The randomized phase 3 COMMODORE 1 trial compared crovalimab with eculizumab in C5 inhibitor–experienced patients with PNH.[7] Patients receiving crovalimab had sustained inhibition of terminal complement activity and maintenance of disease control; 85% of patients preferred crovalimab over eculizumab. The randomized phase 3 COMMODORE 2 trial evaluated the noninferiority of crovalimab vs eculizumab (2:1) in patients with PNH not previously treated with a C5 inhibitor.[8] Crovalimab demonstrated noninferiority compared with eculizumab in the coprimary endpoints of hemolysis control and transfusion avoidance and in breakthrough hemolysis and hemoglobin stabilization. Safety profiles were similar between arms. However, a transient immune complex rash has been noted in some patients switching from eculizumab or ravulizumab to crovalimab.

Long-Term Safety and Efficacy of C5 Inhibitors

Long-term follow-up with eculizumab reported after 66 months showed a significant improvement in clinical outcomes, with a 3-year survival rate of 97.6%, sustained reductions in LDH, freedom from thrombotic events in 96.4% of patients, and a 90% increase in transfusion independence.[11] There was no evidence of cumulative toxicity, and adverse events decreased in frequency over time. A key safety consideration with eculizumab is the increased risk of meningococcal disease owing to *Neisseria* infections. The estimated absolute risk is approximately 0.5% per 100 patient-years; even with vaccination, the risk remains more than 1000-fold higher than that in healthy controls.[3,11]

Long-term outcomes with ravulizumab were reported in an analysis that included patients who received ravulizumab during the phase 3 trials and into the subsequent open-label extension period (Table 2).[12] Over a treatment period of up to 6 years, ravulizumab was associated with an incidence of major adverse vascular events of 0.7 to 1.4 per 100 patient-years. At 4 years, the risk of mortality was reduced by 5-fold compared with untreated patients from the International PNH Registry (mortality ratio, 0.2; 95% CI, 0.09-0.42). A total of 122 breakthrough intravascular hemolysis events occurred, and these were frequently associated with complement-amplifying conditions; 2 events (1.8%) were associated with suboptimal C5 inhibition. Overall, this analysis showed that ravulizumab provided durable control of terminal complement activity and intravascular hemolysis in both C5 inhibitor–exposed and C5 inhibitor–naive patients.

Table 2. Long-Term Safety, Efficacy, and Survival Outcomes With Ravulizumab in Patients With PNH[12]

Parameter	C5 inhibitor–naive patients (n=246)	Eculizumab-experienced patients (n=195)
Patients completing primary evaluation period, n	244	191
MAVEs, events per 100 PY	1.4	0.7
4-year survival rate, %	97.7	98.4
Mean LDH level at 6 years, U/L	290.3	243.9
Breakthrough IVH event rate	1.0 per 10 PY	1.0 per 30 PY
Most common TEAEs	• Headache (29.8%) • Upper respiratory infection (25.9%) • Nasopharyngitis (23.9%) • Pyrexia (20.2%) • Fatigue (14.0%)	
Meningococcal sepsis events	• n=1	

IVH, intravascular hemolysis; MAVEs, major adverse vascular events; PNH, paroxysmal nocturnal hemoglobinuria; PY, patient-years; TEAE, treatment-emergent adverse event.

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Monotherapy With Upstream or Alternative Pathway Inhibitors

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The aim of proximal complement inhibition is to target both intravascular and extravascular hemolysis. Commercially available agents that block upstream components or alternative pathway components of the complement system include the C3 inhibitor pegcetacoplan, the factor B inhibitor iptacopan, and the factor D inhibitor danicopan.

This section focuses on pegcetacoplan and iptacopan, which are used as single-agent therapies. An overview of the pivotal trials of pegcetacoplan and iptacopan is shown in Table 3.[1-3] Note that differing entry criteria and different definitions of breakthrough hemolysis among the trials limit comparisons between these agents.[4] Iptacopan does offer the benefit of oral therapy, but given the short half-life of the drug, adherence is essential, and missing doses could allow for reactivation of the alternative pathway and an increased risk for hemolysis.

Danicopan, which is used as add-on therapy to a C5 inhibitor, is discussed in the next section.

C3 Inhibition

Pegcetacoplan is a PEGylated peptide that binds to C3 and its activation fragment C3b, thus preventing the interaction between C3 and C3 convertase and inhibiting complement activity.[5] Pegcetacoplan was initially evaluated in complement inhibitor–naive patients with PNH in the open-label, phase 1b, pilot PADDOCK trial (n=22) and the phase 2a PALOMINO trial (n=4).[6] Mean hemoglobin levels were below normal at baseline (8.38 g/dL and 7.73 g/dL, respectively), increased to the normal range by day 85, and were sustained through day 365 (12.14 g/dL and 13.00 g/dL, respectively). One serious adverse event was considered study drug–related.

Pegcetacoplan was subsequently evaluated in 2 open-label, phase 3 trials. The PEGASUS trial enrolled patients with PNH and hemoglobin levels less than 10.5 g/dL despite eculizumab therapy.[1] Patients received a 4-week run-in phase with pegcetacoplan plus eculizumab, then were randomly assigned to subcutaneous pegcetacoplan (n=41) or intravenous eculizumab (n=39). The trial met its primary endpoint, demonstrating a significant improvement in the mean change in hemoglobin level from baseline to week 16 with pegcetacoplan vs eculizumab (mean difference, 3.84 g/dL; $P<.001$). Other benefits with pegcetacoplan vs eculizumab included a higher rate of transfusion independence at week 16 (85% vs 15%) and improved FACIT-Fatigue scores. Pegcetacoplan demonstrated noninferiority to eculizumab in change in absolute reticulocyte count. The most common adverse events with pegcetacoplan vs eculizumab were injection site reactions (37% vs 3%), diarrhea (22% vs 3%), breakthrough hemolysis (10% vs 23%), headache (7% vs 23%), and fatigue (5% vs 15%).

The PRINCE trial enrolled 53 patients with complement inhibitor–naive PNH who were randomly assigned to pegcetacoplan subcutaneously twice weekly (n=35) or continued supportive care (n=18).[2] Pegcetacoplan was more effective than supportive care in rates of hemoglobin stabilization (85.7% vs 0%; difference, 73.1%; $P<.0001$) and change from baseline in LDH (least square mean change, –1870.5 U/L vs –400.1 U/L; difference, –1470.4

Table 3. Key Efficacy and Safety Data for Pegcetacoplan and Iptacopan

Upstream inhibitor	Trial details	Key efficacy findings in experimental vs control arm	Key safety findings
Pegcetacoplan	**PEGASUS:** pegcetacoplan vs eculizumab in patients with Hb <10.5 g/dL on eculizumab (n=80)[1]	**Significant difference in change in mean Hb from baseline to week 16:** 3.84 g/dL (*P*<.001) **Rates of transfusion independence:** 85% vs 15%	**Common AEs with pegcetacoplan:** injection site reactions, diarrhea
	PRINCE: pegcetacoplan vs supportive care in patients with complement inhibitor–naive PNH (n=53)[2]	**Rates of Hb stabilization at week 26:** 85.7% vs 0% (*P*<.0001) **Change from baseline in LDH:** –1870.5 vs –400.1 U/L (*P*<.0001)	No serious pegcetacoplan-related AEs were reported
Iptacopan	**APPLY-PNH:** iptacopan vs continued C5 inhibitor in patients with Hb <10 g/dL despite C5 inhibitor (n=97)[3]	**Rates of Hb increase ≥2 g/dL without transfusion:** 82% vs 2% (*P*<.001) **Rate of Hb ≥12 g/dL without transfusion:** 69% vs 2% (*P*<.001)	**Rates of breakthrough hemolysis** (symptoms of IVH; Hb decrease >2 g/dL; LDH 2 × ULN): 2/62 vs 6/35 **More frequent AEs with iptacopan vs C5 inhibitor:** headache (16% vs 3%), diarrhea (15% vs 6%)
	APPOINT-PNH: iptacopan in complement inhibitor–naive patients with LDH >1.5 × ULN (n=33)[3]	**Increase in Hb ≥2 g/dL without transfusion:** 92%	No clinical breakthrough hemolysis or MAVEs **Most common AEs:** headache (28%), COVID-19 (15%), upper respiratory tract infection (13%)

AE, adverse event; Hb, hemoglobin; LDH, lactate dehydrogenase; MAVEs, major adverse vascular events; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal.

U/L; *P*<.0001). No serious treatment-related adverse events were reported.

An open-label extension of pegcetacoplan included 77 patients from the PEGASUS trial.[7] Mean hemoglobin concentrations were maintained in the pegcetacoplan group from week 16 to week 48 (11.54 vs 11.30 g/dL) and increased from week 16 to week 48 in patients switching from eculizumab to pegcetacoplan (8.58 vs 11.57 g/dL). A total of 13 patients (16%) discontinued treatment because of hemolytic events during the extension study. Pegcetacoplan may be associated with more severe breakthrough hemolysis, with LDH levels reaching 10 to 15 × ULN. It has been proposed that control of complement activation through C3 inhibition leads to increased survival of PNH RBCs, making these cells susceptible to lysis and causing subsequent anemia.[8]

In an analysis of the total clinical experience with pegcetacoplan, including 619.4 patient-years of exposure in clinical trials and the postmarketing setting, the overall rate of thrombosis was 1.13 events per 100 patient-years, which is considered comparable to previously reported rates with C5 inhibitors.[9] No cases of meningococcal infection were reported.

Factor B Inhibition

Iptacopan is an orally administered selective inhibitor of factor B, an essential component of the alternative complement pathway. In an open-label, phase 2, proof-of-concept study in treatment-naive patients with PNH (n=12), iptacopan was associated with normalization of hemolytic markers and transfusion independence in all but 1 patient at week 12.[10]

Iptacopan was subsequently evaluated in the phase 3 APPLY-PNH and APPOINT-PNH trials in patients with PNH and hemoglobin levels less than 10 g/dL.[3] In APPLY-PNH, 97 patients who had previously received a C5 inhibitor were randomly assigned to switch to iptacopan 200 mg twice daily (n=62) or to continue their C5 inhibitor (n=35) for 24 weeks. The trial met its 2 primary

endpoints, demonstrating improvements with iptacopan over a C5 inhibitor in the proportion of patients attaining an increase in hemoglobin of at least 2 g/dL from baseline without transfusions (82% vs 2%) and in the proportion of patients with a hemoglobin level of 12 g/dL or greater without transfusions (69% vs 2%) at 24 weeks. Transfusion independence was attained in 95% of patients receiving iptacopan and 26% receiving a C5 inhibitor.

The single-arm APPOINT-PNH trial evaluated iptacopan in complement inhibitor–naive patients with an LDH greater than 1.5 × ULN.[3] After 24 weeks, hemoglobin increases of 2 g/dL or greater from baseline without transfusion were reported in 31 of 33 patients receiving iptacopan, and the transfusion avoidance rate between days 14 and 168 was 98%. Iptacopan was also associated with reduced fatigue, reductions in levels of reticulocytes and bilirubin, and mean LDH levels less than 1.5 × ULN.

The most common adverse event associated with iptacopan in APPLY-PNH was headache (16% vs 3% with C5 inhibitor). Breakthrough hemolysis was reported in 2 patients (1 mild, 1 moderate) in the APPLY-PNH trial compared with 6 patients receiving a C5 inhibitor (2 mild, 8 moderate, 1 severe). Extravascular hemolysis occurred in 2 additional patients receiving a C5 inhibitor.

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Dual Therapy: Danicopan as Add-on Therapy to C5 Inhibitors

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The terminal complement C5 inhibitors eculizumab and ravulizumab have been shown to substantially reduce the risk for thrombosis, extend survival, stabilize hemoglobin levels, and improve quality of life for patients with PNH. However, some patients receiving terminal complement inhibitors develop clinically significant extravascular hemolysis owing to the opsonization of surviving PNH cells with C3 fragments.

To address the limitation of extravascular hemolysis associated with terminal complement inhibitors, agents that inhibit upstream components of the complement pathway rather than the classical pathway were developed.[1] Although these agents effectively control hemolysis under steady-state conditions, a strong complement trigger such as infection, trauma, or surgery can induce significant breakthrough hemolysis that is more severe than the breakthrough hemolysis associated with C5 inhibitors.

This has led to a more comprehensive approach to complement inhibition. Also referred to as a "belt-and-suspenders approach" by Gerber and Brodsky, this method involves the combination of a C5 inhibitor to block terminal complement and the factor D inhibitor danicopan to block the upstream alternative pathway.[1] This combination approach could provide greater control of complement dysregulation than either treatment alone.

Table 4. Week 12 Treatment Difference With Danicopan as Add-on Therapy to Ravulizumab or Eculizumab in PNH With Significant EVH (MMRM Analysis)

Change from baseline[a]	Week 12 treatment difference[b]
Hb levels,[c] g/dL	2.3 (0.4); *P*<.0001
LDH,[d] U/L	–8.7 (13.8); *P*=.5306
ARC,[e] × 10^9/L	–91.7 (14.3); *P*<.0001
Total bilirubin,[f] μmol/L	–10.1 (2.6); *P*=.0002
FACIT-Fatigue scores[g]	5.8 (1.6); *P*=.0004

ARC, absolute reticulocyte count; EVH, extravascular hemolysis; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; LDH, lactate dehydrogenase; LSM, least squares mean; MMRM, mixed model for repeated measures; PNH, paroxysmal nocturnal hemoglobinuria; SEM, standard error of the mean.
[a]All values are LSM (SEM). [b]Treatment difference (danicopan-danicopan and placebo-danicopan). After week 12, participants receiving placebo were switched to danicopan treatment. [c]Week 12: danicopan, n=57; placebo, n=28 and week 24: danicopan, n=50; placebo, n=26. [d]Week 12: danicopan, n=56; placebo, n=28 and week 24: danicopan, n=54; placebo, n=26. [e]Week 12: danicopan, n=57; placebo, n=26 and week 24: danicopan, n=50; placebo, n=26. [f]Week 12: danicopan, n=57; placebo, n=29 and week 24: danicopan, n=55; placebo, n=27. [g]Week 12: danicopan, n=56; placebo, n=28 and week 24: danicopan, n=52; placebo, n=27.
Adapted from: Kulasekararaj A et al. *Blood*. 2025;145(8):811-822.[4]

Table 5. Proportion of Patients Avoiding Transfusion With Danicopan Plus Ravulizumab/Eculizumab in PNH With Significant EVH

Time frame	Proportion of patients avoiding transfusion, %	
Weeks 0-12	**Danicopan (n=57)**	**Placebo (n=29)**
	78.9[a]	27.6
	Danicopan-danicopan	**Placebo-danicopan**
Weeks 12-24[b]	80.0	81.5
Weeks 24-48[c]	81.5	73.1
Weeks 48-72[d]	80.0	79.2

EVH, extravascular hemolysis; PNH, paroxysmal nocturnal hemoglobinuria.
[a]*P*≤.001.
[b]Weeks 12-24: danicopan-danicopan, n=55; placebo-danicopan, n=27.
[c]Weeks 24-48: danicopan-danicopan, n=54; placebo-danicopan, n=26.
[d]Weeks 48-72: danicopan-danicopan, n=50; placebo-danicopan, n=24.
Adapted from: Kulasekararaj A et al. *Blood*. 2025;145(8):811-822.[4]

Adding the factor D inhibitor to a C5 inhibitor may help control complement in the case of a triggering event, and adding the C5 inhibitor to the factor D inhibitor may provide protection against intravascular hemolysis in the event of missed doses.

ALPHA Trial

The double-blind, randomized, phase 3 ALPHA trial was undertaken to evaluate the efficacy and safety of danicopan as add-on therapy to ravulizumab or eculizumab in patients with PNH and clinically significant extravascular hemolysis.[2] The trial enrolled patients with PNH with clinically significant extravascular hemolysis, defined as a hemoglobin level of 9.5 g/dL or less and an absolute reticulocyte count of 120 × 10^9/L or greater, who had been receiving ravulizumab or eculizumab for at least 6 months. These patients account for approximately 20% of patients who receive eculizumab or ravulizumab.[3]

A total of 86 patients were randomly assigned 2:1 to oral danicopan 150 mg (n=57) or placebo (n=29) 3 times a day in addition to their background ravulizumab or eculizumab therapy. After 12 weeks, patients could enter a long-term extension in which those patients initially assigned to danicopan continued the same treatment (danicopan-danicopan) and patients in the placebo arm were switched to danicopan (placebo-danicopan).[4]

In the initial analysis, the trial met its primary efficacy endpoint, demonstrating a significant improvement in the change in hemoglobin level from baseline to week 12 in the first 63 participants (least squares mean change from baseline, 2.94 vs 0.50 g/dL; *P*<.0001).[2] A subsequent analysis confirmed the significant improvement in hemoglobin, and other secondary endpoints, with danicopan vs placebo at week 12; hemoglobin levels improved from weeks 12 to 24 in patients switching from placebo to danicopan (Table 4).

Long-Term Response With Dual Therapy

With additional follow-up, this dual therapy was associated with maintained improvements in hemoglobin, absolute reticulocyte count, FACIT-Fatigue scores, bilirubin levels, and transfusion avoidance (Table 5) out to week 72.[4] Moreover, mean percentage of C3 fragment deposition on PNH type 3 RBCs decreased with the use of danicopan and was also maintained through week 72.

Serious adverse events considered related to danicopan included 1 bilirubin increase and 1 pancreatitis event in the first 12 weeks and 1 headache event in the second 12 weeks. No treatment-related serious adverse events occurred in the long-term extension. Occurrences of breakthrough hemolysis included 7 events in 5 participants, for a rate of 6 events per 100 patient-years. No meningococcal infections or discontinuations owing to hemolysis were reported.

Dual Therapy: What We Have Learned

Overall, these findings showed that the addition of danicopan to a C5 inhibitor yielded maintained improvements in hematologic abnormalities in patients with PNH with clinically significant extravascular hemolysis. This combination approach appeared to address both intravascular and extravascular hemolysis and maintained control of terminal complement activity out to 72 weeks. However, danicopan does require oral administration 3 times a day, which could be a disadvantage. Additional information, including real-world and clinical trial experience, is needed to better understand the role of combination therapy compared with a single-agent approach.

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Practical Approach to Managing PNH: Q&A

Gloria F. Gerber, MD; Ilene C. Weitz, MD; and Catherine M. Broome, MD

H&O Is there any contingency plan for managing breakthrough events in case of missed pills, food poisoning, or severe viral gastroenteritis, especially surrounding travel?

GFG We currently lack formal guidance or standard protocol for managing these situations. Breakthrough hemolysis can occur with any complement inhibitor in the setting of a complement-amplifying condition but has the potential to be more severe with proximal complement inhibitors alone than on terminal complement inhibitors. On C5 inhibitors, only 1 membrane attack complex is formed per molecule of C5 that escapes inhibition. In contrast, incomplete C3 inhibition with alternative pathway inhibitors can cleave multiple C5 molecules, thus amplifying the breakthrough event. The PNH erythrocyte clone size also increases with use of proximal complement inhibitors, approximating the size of the WBC clone, owing to increased survival of the GPI-deficient RBCs. Thus, a larger RBC clone is vulnerable to breakthrough events. Patients on dual therapy with C5 inhibitors and danicopan are protected from potential intravascular hemolysis related to missed doses by the long half-life of the C5 inhibitor backbone.

A single missed iptacopan dose should generally not cause a severe breakthrough event owing to the drug's half-life, but multiple missed doses or complement-amplifying events like viral gastroenteritis can trigger breakthrough hemolysis. For patients unable to take oral medication, eculizumab is an option, although logistical barriers, including availability and insurance approval out of hospital, may complicate access.

Our group had a patient on pegcetacoplan who missed a week's dose because of travel and caught a viral infection. This led to severe intravascular hemolysis, renal injury, and esophageal spasms. His hemoglobin dropped to 4 g/dL and he required multiple transfusions. He was also resumed on pegcetacoplan daily for several days. In such cases, I also monitor D-dimers as a surrogate for thrombotic risk, and if there are signs or symptoms of thrombosis, I urgently give eculizumab. We do not yet know in the real world how common these severe breakthrough events will be and it is important for clinicians to identify and treat them urgently, as well as to counsel patients to call their providers in the case of missed doses.

ICW There is no established plan for managing breakthrough events. Patients on oral agents like iptacopan should make up a missed dose as soon as possible. Although a major breakthrough is unlikely within 12 hours because of iptacopan's short half-life, extended delays increase risk. In severe breakthrough cases, some providers consider eculizumab. Intravenous pegcetacoplan

has been explored in England but is not widely feasible. If stabilization fails with pegcetacoplan or a factor B inhibitor, hospitalization and rescue with a C5 inhibitor may be needed.

Taking oral medications becomes problematic in patients with gastrointestinal issues, such as food poisoning with vomiting. These patients should promptly consult their doctor and may require hospitalization.

CMB Clinical trials have not investigated an antidote for breakthrough hemolysis or the consequences of missing oral doses. Anecdotally, clinicians have employed various approaches. For patients who cannot tolerate or absorb oral therapy, intravenous C5 inhibition remains a reliable alternative to halt intravascular hemolysis. Some reports suggest administering additional doses of oral therapy to compensate for missed doses, although this may not address absorption challenges in cases of gastrointestinal complications. There is still much to learn about the optimal strategies for managing breakthrough events or temporary discontinuations of these oral therapies.

H&O Do severe breakthrough events lead to thrombosis?

CMB Predicting the threshold of intravascular hemolysis that may trigger a thrombotic event in an individual patient is challenging, as this threshold varies widely among patients. Prior to the introduction of C5 inhibition, thrombosis was one of the leading causes of mortality in individuals with PNH, making it a primary concern during treatment. This is particularly relevant when using monotherapy targeting higher levels of the complement cascade.

ICW Thromboembolic events have been reported during breakthroughs. This is particularly worrisome with pegcetacoplan and iptacopan. Thromboembolic events with danicopan are less of an issue because danicopan is an add-on to ravulizumab or eculizumab. Nevertheless, depending on the severity of the breakthrough, thromboembolic events are always a concern. I would strongly recommend following D-dimers. If very high, consider anticoagulant prophylaxis.

H&O What is the impact of several micro-breakthroughs on organs?

GFG Defining a micro-breakthrough is tough; I take this to mean low-level breakthrough intravascular hemolysis that is not clinically relevant based on symptoms or more significant laboratory changes. For example, we might not observe overt kidney injury such as a rise in creatinine, but could there still be subtle damage occurring? At this point, we do not have enough information.

CMB This remains an open question, as we have not had sufficient time to fully evaluate the long-term impact of proximal complement inhibitor monotherapies. Additionally, an appropriate method for assessing the impact of micro-breakthrough events on organs has yet to be established. As research continues to evolve, further recommendations will emerge regarding the optimal approach for monitoring patients with PNH over the long term. Ongoing investigation will help clarify the implications of these prolonged micro-breakthroughs and their effects on patient outcomes.

H&O How would you differentiate between a breakthrough event and a missed dose?

GFG Outside patient reporting, this differentiation is challenging because there are no clinically available drug levels to rely on. For eculizumab, a CH50 test can determine whether the complement activity is adequately blocked, but some data suggest that this may not apply to ravulizumab, although in my own experience I have seen CH50 suppressed. With proximal complement inhibitors, the difficulty increases. This is an ongoing need and our laboratory is currently working on developing assays to assess the effectiveness of complement-blocking activity on the different complement inhibitors.

ICW It is impossible to know definitively, as the presentation is identical in both scenarios. You have to rely on the patient's report.

CMB A trusting patient–provider relationship is essential, particularly when assessing medication adherence. When faced with a significant rise in LDH and a notable decline in hemoglobin, a thorough and diligent workup is necessary to rule out any underlying infection before attributing these changes to a missed dose. If the infectious workup is negative and there are no clinical indications of infection, the next step is to engage in an open and honest conversation with the patient regarding their medication regimen and any missed doses.

H&O Should patients continue anticoagulation therapy?

ICW With C5 inhibitors, anticoagulation is generally not necessary. Following D-dimer levels is critical—if they decrease, ongoing monitoring is sufficient. However, for patients with a history of thrombotic events, particularly life-threatening events such as Budd-Chiari

syndrome, pulmonary embolism, or cerebral thrombosis, it is worth questioning whether the event was related to PNH. If their PNH is well controlled with complement inhibition, the need for continued anticoagulation should be reassessed.

CMB Patients with a history of a thrombotic event should continue their anticoagulation treatment. I do not initiate anticoagulation therapy prophylactically in patients with PNH receiving C5 inhibitors. We do not have long-term data on thrombotic risk associated with C3 or factor B inhibitors.

H&O What is your approach to pregnant patients?

ICW C5 inhibition is the cornerstone of PNH management during pregnancy as it is the most well-documented approach associated with successful pregnancy outcomes. The decision to continue a patient on ravulizumab or transition to eculizumab is nuanced. Although the majority of available data supports eculizumab in pregnancy management, an increasing number of case reports highlight safe and positive outcomes with ravulizumab. At this time, there are no data on pregnancy management using alternative pathway inhibitors.

H&O How important is long-term safety data in PNH?

GFG Most clinical trial data for proximal inhibitors report similar endpoints, with slight variations in inclusion criteria and durations. What happens in the real world over time is very important. Patients in trials tend to be highly compliant, and adherence is often good initially. However, over time, missed doses may become more common—whether by forgetting a dose, traveling without medication, or assuming that a short lapse will not cause harm. We lack data on how long these medications can be "safely missed," and it likely varies by individual.

C5 inhibitors have available long-term safety and survival data, which newer agents lack. I do counsel my patients on this point. For some patients, having long-term data holds more value. At the same time, there are some patients who want to try something new regardless of whether they are doing well on a C5 inhibitor, especially if it could mean normalizing their hemoglobin.

CMB Long-term safety data are paramount, especially for a predominantly young patient population. Beyond ensuring sustained efficacy, patients seek reassurance about the safety profile of various therapies over many years, given that these are lifelong interventions.

H&O What is your approach when you are starting a new patient on PNH therapy?

GFG This is an exciting time in PNH management because there are now multiple FDA-approved complement inhibitors and various options for patients. As clinicians, we are figuring out what the best strategy is in the absence of head-to-head trials. Moreover, successful PNH management necessitates shared patient–provider decision-making, as every patient requires a tailored approach based on expected compliance, preferred modality of treatment, and potential for pregnancy (where only C5 inhibitors have safety data).

There will be unique considerations in some patients. For example, I would be less comfortable prescribing oral monotherapy to a patient with a history of gastrointestinal bypass surgery. Some patients may prefer an oral option based on lifestyle considerations, such as ability to come to an infusion center, or fear of needles.

In my own practice currently, if a patient does not express a preference, I often start a new patient with PNH on ravulizumab owing to its long-term safety data and the opportunity for close monitoring. This also helps assess compliance.

In patients on C5 inhibitors experiencing clinically significant extravascular hemolysis leading to symptomatic anemia or transfusion requirement, I think there are strong data supporting a switch to or adding on an alternative pathway inhibitor.

ICW The availability of long-term safety data makes both the physician and the patient feel confident about therapy, as is the case with C5 inhibitors. That said, I may consider a factor B inhibitor if the patient prefers an oral agent, provided they are reliable and consistent about taking their medication.

I had a patient who initially used eculizumab, then transitioned to pegcetacoplan as part of the trials, with excellent results. She was transfusion-dependent on eculizumab but experienced significant improvement with pegcetacoplan. However, she developed numerous hematomas over time. We eventually transitioned her to iptacopan, and she was delighted with the convenience of an oral agent.

Adherence is crucial and issues can arise when traveling or managing time zone differences.

CMB Treatment decision in PNH must be a collaborative process. Clinicians should provide patients with all available data including safety data, details on clinical studies, and duration of therapy. Ultimately, it is a shared decision, and patient preference plays a crucial role.

H&O Is there any potential advantage of dual therapy compared with alternative pathway monotherapy?

GFG Dual therapy offers distinct clinical advantages in certain situations. For patients with extravascular hemolysis and a history of severe thrombosis or concerns about compliance, the C5 backbone provides protection against severe breakthrough events as the C5 inhibitor remains present even if doses are missed. However, this approach requires taking medication multiple times a day and trips to the infusion center. In patients with autoimmune diseases or cancer, where there may be more concern for breakthrough hemolysis owing to the underlying complement-amplifying condition, or in those patients who experienced significant breakthrough hemolysis on proximal complement inhibitors, dual therapy is an appropriate option.

ICW The key advantage of dual therapy is the consistent protection from terminal complement inhibition. Breakthrough events are rare and less severe. I had an international patient, on danicopan during a trial, who had to return to her country as we could not secure treatment approval from her government. She avoided breakthrough events entirely because the long-acting ravulizumab provided sufficient coverage until she got home.

CMB The safety net of C5 inhibition provides critical protection against breakthrough intravascular hemolysis, especially when patients experience infections or miss multiple doses of oral therapy. Adherence can be challenging, particularly with regimens requiring multiple daily doses, and the reality is that everyone is susceptible to gastrointestinal or respiratory infections. Dual therapy is a valuable option—not only to address extravascular hemolysis and improve hemoglobin levels but also to serve as an additional safeguard if complement activity escalates because of illness, inflammation, or other factors.

H&O Are there any investigational strategies you are excited about?

GFG There is room for improvement with complement inhibitors, such as the development of a once-daily oral option and subcutaneous or intravenous alternative pathway inhibitors with extended half-lives, such as monthly administration. Emerging therapies with mechanisms targeting both proximal and terminal complement pathways with a single drug are exciting, and phase 2 data for these has been presented.

ICW Expansion of complement inhibition to other diseases, such as vasculitides and antiphospholipid syndrome, is interesting. There are also currently no data on the use of alternative pathway inhibitors during pregnancy, although there are some case reports from Germany involving pregnant patients treated with ravulizumab. It is important to note that ravulizumab has a prolonged half-life, so if a patient becomes pregnant while on the drug, it remains in their system throughout the first trimester. Despite efforts to switch patients to eculizumab before pregnancy, it does not always happen in time. Investigating the impact of this exposure is crucial.

CMB Ongoing research continues to explore new targets within the complement system that may offer advantages over existing therapies, such as MASP inhibition. It is becoming increasingly clear that PNH likely presents with distinct phenotypes, necessitating a more individualized approach to treatment—tailoring therapeutic interventions to each individual's lifestyle, disease presentation, and predominant manifestations.

Disclosures

Dr Gerber has served on advisory boards of and received honoraria from Alexion and Apellis.

Dr Broome is an advisor for Dianthus, Alpine, Recordati, Novartis, Alexion, Lilly, and Argenx; has received speaker honoraria from Sanofi, Recordati, Alexion, and Argenx; and her institution has received research funding from Vertex, Sanofi, Recordati, Alexion, Polaris Therapeutics, Electra Therapeutics, Hutchmed, Lilly, Argenx, Takeda, and Nexcella.

Dr Weitz is a consultant for and has received speaker honoraria from Alexion; and has received research support from Novartis.

Slide Library

PNH Pathophysiology

- An acquired clonal disorder of hematopoietic stem cells arising from a somatic mutation in *PIGA* gene
- *PIGA* gene product
  - Necessary for the first step in synthesis of GPI anchors
- CD55 and CD59
  - GPI-anchored proteins that regulate complement on cellular surfaces

Brodsky RA. *Blood*. 2021;37(10):1304-1309.

Heterogeneous PNH Symptoms

- Hemolysis
- Thromboembolic events
- Bone marrow failure
- Fatigue
- Dysphagia
- Abdominal pain
- Dyspnea
- Dark urine
- Erectile dysfunction

Patriquin CJ et al. *Eur J Haematol*. 2019;102(1):36-52.

Impacts of PNH

- Ongoing fatigue and reduced quality of life even on treatment
- Ongoing transfusion requirements on C5 inhibitors (~25% of patients)
- High costs of complement inhibitors
- Globally, access to complement inhibitors remains challenging

Cheng WY et al. *Adv Ther*. 2021;38:4461-4479.

Thrombosis: A Frequent Complication

- Occurs in up to 40% of patients
- Leading cause of death prior to complement inhibitors
- Anticoagulation alone does not prevent recurrent clots
- With C5 inhibitors, survival approaches that of age-matched controls

Kokoris S et al. *Int J Mol Sci*. 2024;25(22):12104.

Hemolysis

Intravascular hemolysis

- CD55/CD59-deficient PNH RBCs not shielded from complement activation

Extravascular hemolysis

- Patients on C5 inhibition: surviving PNH RBCs accumulate C3 fragments on their surface, resulting in recognition and phagocytosis by macrophages in the liver and spleen

Duval A, Frémeaux-Bacchi V. *Am J Hematol*. 2023;98(Suppl 4):S5-S19.

Breakthrough Intravascular Hemolysis (BTH)

Reappearance of hemolysis + PNH symptoms

Pharmacokinetic (PK) BTH

- Inadequate plasma drug level (10%-15% of patients on eculizumab)
- Incomplete complement suppression of CH50

Pharmacodynamic (PD) BTH

- Can occur in any patient on a complement inhibitor in the case of a complement-amplifying condition

Risitano AM et al. *Front Immunol*. 2019;10:1157.

Indications for Starting Complement Inhibitor Therapy

- Improve outcomes in classical PNH (one-third of patients with PNH)
- Unlikely benefit in subclinical PNH or PNH overlapping with AA/BMF (two-thirds of patients with PNH)
- May provide benefit in some patients with moderate clone sizes, clinical hemolysis, and symptoms

Babushok DV. *Hematology Am Soc Hematol Educ Program*. 2021;2021(1):143-152; DeZern AE et al. *Eur J Haematol*. 2014;92(6):467-470; Shah YB et al. *Blood Adv*. 2021;5(16):3216-3226.

PNH in Pregnancy

- High risk owing to increased complement levels in late 2nd-3rd trimester
- Start complement inhibition in previously untreated PNH patient
- Multidisciplinary care, including obstetrics and hematology, important

Kelly RJ et al. *N Engl J Med*. 2015;373(11):1032-1039; Panse J. *Am J Hematol*. 2023;98(Suppl 4):S20-S32.

PNH in Pregnancy

- Eculizumab treatment
  - Reduced maternal mortality (previously 8%-20%) and thrombosis
  - Similar fetal mortality (4%-9%) owing to premature birth
  - Levels of eculizumab that cross placenta: not high enough to affect complement and not detected in breast milk
- Ravulizumab treatment
  - Few cases but less clinical experience

Kelly RJ et al. *N Engl J Med*. 2015;373(11):1032-1039; Panse J. *Am J Hematol*. 2023;98(Suppl 4):S20-S32.

Anemia in PNH on C5 Inhibitors

- Evaluate
  - LDH
  - Reticulocytes
  - CH50
- Related etiologies
  - Bone marrow failure
  - Nutritional deficiencies
  - Bleeding
  - Renal insufficiency
  - Iron overload
  - Hypersplenism

Kulasekararaj AG et al. *Am J Hematol*. 2021;96(7):E232-E235.

Management of PNH: Key Takeaways

- Patients with smaller clone sizes (<30%), no clinical hemolysis, and no symptoms
  - Unlikely to benefit from complement inhibitors
- Thrombosis
  - An indication to start urgent complement inhibition
- Pharmacodynamic breakthrough hemolysis
  - Can occur on any complement inhibitor
- Anemia
  - Need to evaluate all potential causes, including progressive bone marrow failure

Courtesy of Gloria F. Gerber, MD.

Management of PNH: Key Takeaways

- C5 inhibitors
  - Abolish transfusion need (~80% of patients)
  - Associated with extravascular hemolysis (most patients)
- Proximal complement inhibitors
  - May block both intravascular and extravascular hemolysis
- Dual initiation with C5 inhibitor and danicopan (factor D inhibitor)
  - Combines proximal and terminal complement inhibition

Courtesy of Gloria F. Gerber, MD.

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