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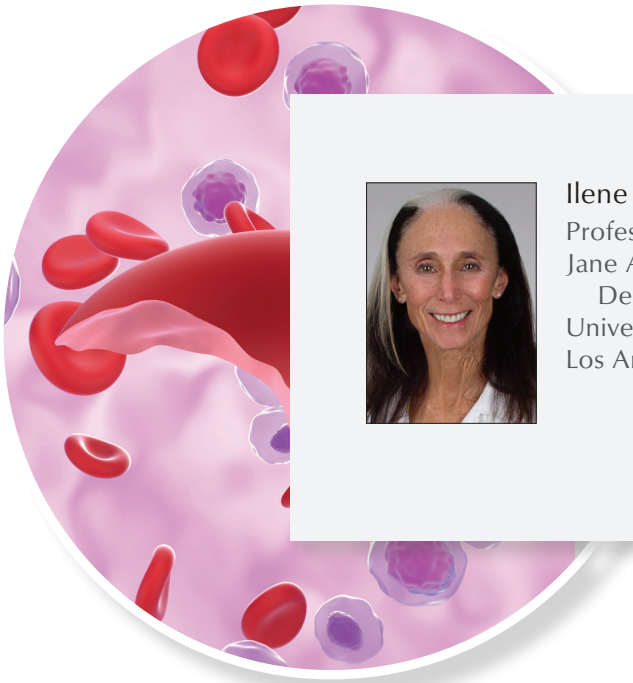
PNH Management: A Clinical Case of Ravulizumab–Danicopan Combination Therapy



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PNH Management: A Clinical Case of Ravulizumab–Danicopan Combination Therapy

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About the Patient

Patient EW is a 56-year-old woman who was diagnosed with paroxysmal nocturnal hemoglobinuria (PNH) 9 years ago, at the age of 47. At diagnosis, she presented with significant fatigue, symptomatic anemia, intermittent dark urine, and laboratory evidence of intravascular hemolysis. Given the extent of her symptoms and active hemolysis, EW was initiated on treatment with the complement inhibitor eculizumab.

EW initially experienced good disease control with eculizumab. However, approximately 3 years ago, she began experiencing recurrent fatigue and breakthrough hemolytic symptoms, particularly toward the end of the eculizumab dosing interval. Her treatment was subsequently transitioned to ravulizumab. Although her overall symptoms and control of intravascular hemolysis improved with ravulizumab, EW continued to have persistent anemia despite excellent adherence to therapy. Her hemoglobin (Hgb) remained approximately 9.2 g/dL, raising concern for residual extravascular hemolysis despite adequate terminal complement inhibition.

EW's hematologist was an investigator in the ALPHA trial and discussed with her the opportunity to participate in the study evaluating danicopan, an add-on therapy to ongoing ravulizumab or eculizumab treatment. EW enrolled in the trial and received danicopan in addition to ravulizumab. She experienced a rapid hematologic response, with progressive improvement in anemia and an increase in Hgb to approximately 12 g/dL within the first 3 months of treatment. Following completion of the study and commercial availability of danicopan, EW elected to continue combination therapy.

EW is a citizen of the European Union and frequently travels to Los Angeles to visit her daughter. She is diligent about maintaining her PNH treatment schedule while abroad, and her hematologist has previously helped coordinate administration of ravulizumab through a hospital in Los Angeles.

During her most recent trip to the United States, however, EW encountered unexpected logistical difficulties obtaining her scheduled ravulizumab infusion and ultimately was unable to receive the dose before returning home. She nevertheless continued taking oral danicopan as prescribed. By the time she returned to the European Union and received her next ravulizumab infusion, approximately 10 weeks had elapsed since her previous dose.

Despite this prolonged interval between ravulizumab infusions, EW remained clinically stable while continuing danicopan, without recurrence of her prior symptoms or clinical evidence of breakthrough hemolysis.

Brief Overview of PNH

PNH is a rare, acquired clonal hematopoietic stem cell disorder characterized by uncontrolled complement activation, causing hemolysis, bone marrow failure, and thrombosis.[1] PNH most frequently presents in adults between 30 and 40 years, but it can be diagnosed at any age. In an analysis of 1610 patients enrolled in the International PNH Registry, the median age was 42 years, with patients ranging from 3 to 99 years.[2]

PNH arises from the expansion of a hematopoietic stem cell clone carrying a somatic mutation in the X-linked *PIGA* gene. A functional *PIGA* gene is required for synthesis of

On the Cover
Illustration of red blood cells affected by hemolytic anemia.

Credit: Nemes Laszlo/Science Source

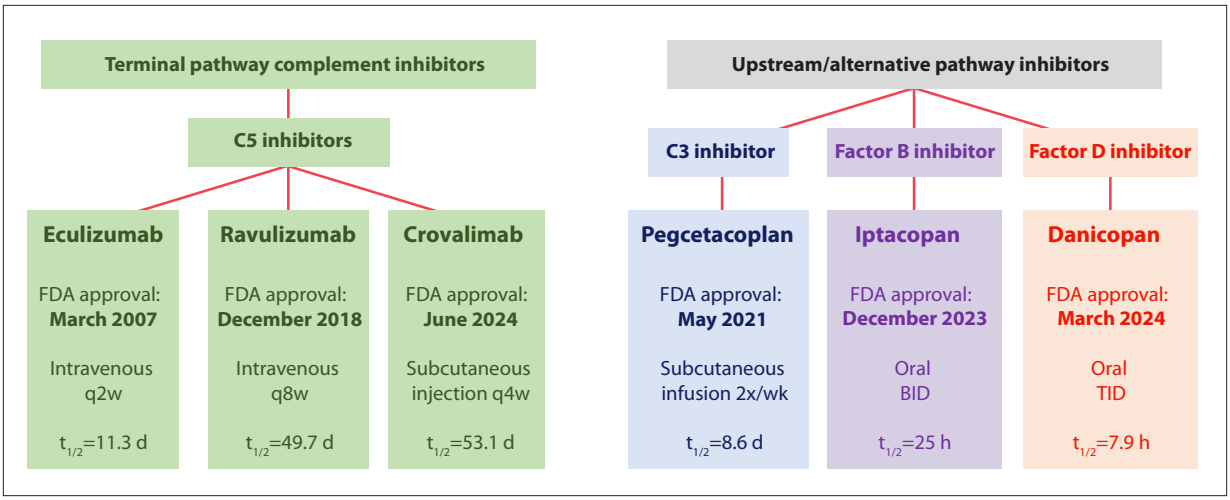

Figure 1. FDA-approved agents for the management of PNH.[14-19]
BID, twice daily; d, days; FDA, US Food and Drug Administration; h, hours; PNH, paroxysmal nocturnal hemoglobinuria; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; $t_{1/2}$, half-life; TID, 3 times daily; wk, week.

glycosylphosphatidylinositol (GPI), a glycolipid that anchors proteins to the cell surface. In red blood cells (RBCs), GPI deficiency results in loss from the cell surface of the GPI-anchored complement regulatory proteins CD55 and CD59. Normally, CD55 regulates the formation and stability of C3 and C5 convertases, whereas CD59 inhibits formation of the membrane attack complex (MAC).[3] Without these protective proteins, PNH blood cells become highly susceptible to complement-mediated injury.

The complement system, an important component of innate immunity, is activated through the classical, lectin, or alternative pathways. All 3 pathways converge at the step of C3 activation and subsequently proceed through the terminal complement pathway, including C5 activation and formation of the MAC.[3] In PNH, persistent low-level activation of the alternative pathway, combined with loss of CD55 and CD59, allows uncontrolled terminal complement activity and chronic intravascular hemolysis. Consequently, the release of free Hgb may contribute to nitric oxide depletion–driven vascular dysfunction. White cell activation of both granulocytes and monocytes can lead to inflammation and cytokine release. Monocyte activation with tissue factor exposure induces pronounced hypercoagulability.[4,5] Complement-amplifying conditions, including infection, surgery, pregnancy, vaccination, and other inflammatory events, may further increase complement activation and precipitate severe hemolytic or thrombotic episodes.

Diagnosis of PNH is based on identification and quantification of GPI-deficient blood cells by flow cytometry. Testing typically evaluates the absence of GPI-linked markers, such as CD59 on erythrocytes, together with fluorescein-labeled proaerolysin (a molecule that binds to GPI anchors on the surface of white blood cells) testing of leukocytes. Assessment of at least 2 GPI-associated markers across 2 cell lineages is generally recommended to establish the diagnosis of PNH.[6]

In general, PNH is diagnosed in the third or fourth decade of life, and is slightly more common in females than males. A retrospective analysis of a US claims database reported a mean age at diagnosis of 41.3 years, with females accounting for 55.3% of cases.[7] PNH has an estimated prevalence of approximately 12 cases per million people and an incidence of 1 to 10 cases per million person-years, although its true frequency may be underestimated because of underrecognition and delayed diagnosis.[8-11] A recent systematic literature review attempted to define the global epidemiology of PNH, finding that annual incidence estimates appeared to be slightly higher than previous reports (0.17 to 0.35 per 100,000 population).[12] This analysis also found marked variability in epidemiologic literature on PNH.

PNH is a chronic disease that requires ongoing monitoring and, for many patients, lifelong therapy. Historically, management was largely supportive, including blood transfusions and treatment of complications. Complement inhibitors have transformed PNH care by substantially reducing complement-mediated hemolysis and thromboembolic complications and improving clinical outcomes and life expectancy.[6] Nevertheless, patients may continue to experience residual symptoms, treatment burden, breakthrough or extravascular hemolysis, and the need for long-term disease management even when PNH is otherwise well controlled.[13]

Managing PNH: The Advent of Complement Inhibitors

Prior to the introduction of complement inhibitors, PNH

In the Clinic...

Educate your patients with PNH on clinical scenarios that should cause them to reach out to you:

- New or worsening fatigue, weakness, shortness of breath, dizziness, or reduced ability to perform usual activities: may indicate worsening anemia or hemolysis
- Dark or reddish urine: may reflect increased intravascular hemolysis
- Symptoms concerning for a blood clot, such as unexplained swelling or pain in an extremity, chest discomfort, difficulty breathing, or new neurologic symptoms; thrombosis is an important complication of PNH and requires immediate evaluation
- Signs or symptoms of infection or another significant inflammatory illness: may increase complement activation and potentially precipitate worsening hemolysis
- Return or worsening of PNH symptoms between treatment doses: may suggest inadequate control of complement activity
- Persistent symptoms despite treatment: may indicate breakthrough hemolysis
- A missed, delayed, or interrupted dose of complement inhibitor therapy
- Prior to surgery or another major medical procedure
- When planning or becoming pregnant

treatment was largely supportive and complication-focused, as there was no effective strategy to target the underlying complement-mediated hemolysis. The PNH therapeutic landscape then changed in 2007 with the first approval in PNH of the complement inhibitor eculizumab. Because they target the underlying cause of PNH (complement-mediated destruction of PNH RBCs) instead of simply treating the resulting complications, complement inhibitors have become transformative as a treatment strategy. Only since their introduction have patients been able to achieve significant reductions in hemolysis, transfusion requirements, and thrombosis with some patients able to completely reverse their transfusion dependence, and marked improvements in symptoms and quality of life.

Complement inhibitors can be subdivided according to where they act on the complement pathway (Figure 1). The US Food and Drug Administration (FDA) has approved 3 terminal pathway complement inhibitors, as well as C5 biosimilars, and 3 proximal pathway complement inhibitors for the treatment of PNH.[14-19] Notably, significant extravascular hemolysis occurs as a consequence of C5 inhibition in up to 20% to 30% of patients, clinically manifesting as symptomatic anemia and transfusion dependence.[20-22]

Terminal Pathway Complement Inhibitors

The humanized monoclonal antibody eculizumab was approved in March 2007 as the first treatment for PNH.[14] It is administered intravenously weekly for the first 4 weeks, followed by a fifth dose 1 week later, then every 2 weeks thereafter. Ravulizumab was approved in December 2018, and is administered intravenously every 8 weeks starting 2 weeks after the initial loading dose.[15] Crovalimab was approved in June 2024; it is administered subcutaneously every 4 weeks after the completion of 4 weekly intravenously administered loading doses.[16]

Proximal Pathway Complement Inhibitors

Although each of the 3 approved proximal pathway inhibitors has a unique mechanism of action within the proximal pathway, they all inhibit complement activation before the step of C3 activation, thus preventing C3b production and decreasing the opsonization and clearance of RBCs. Pegcetacoplan, a C3 inhibitor approved in May 2021, is administered subcutaneously twice weekly (or every 3 days in patients with lactate dehydrogenase [LDH] levels >2 × upper limit of normal).[17] The first orally administered complement inhibitor, iptacopan, a factor B inhibitor approved in December 2023,[18] is administered twice daily. Most recently, in March 2024, the factor D inhibitor danicopan was approved as an add-on therapy to ravulizumab or eculizumab for the treatment of extravascular hemolysis in adults with PNH.[19] Danicopan is administered orally, 3 times daily.

Pivotal Trials With Complement Inhibitors

The C5 inhibitors eculizumab, ravulizumab, and crovalimab were each evaluated as treatments for PNH over 6 months in randomized phase 3 trials. Eculizumab, the first of these agents to enter clinical development, was compared with placebo in the double-blind study TRIUMPH.[23] Subsequently, ravulizumab was compared with eculizumab in 2 open-label noninferiority trials, Study 301 (in complement inhibitor–naive patients) and Study 302 (in patients who were clinically stable on eculizumab).[24,25] Most recently, crovalimab was investigated also against eculizumab in the 2 open-label noninferiority studies COMMODORE 1 (which included complement inhibitor–experienced patients who were receiving eculizumab) and COMMODORE 2 (complement inhibitor–naive patients).[26,27]

The C3 inhibitor pegcetacoplan was compared with eculizumab in the 16-week open-label PEGASUS trial among patients with PNH who experienced persistent

Table 1. Data from the Pivotal Phase 3 Trials of Complement Inhibitors in PNH

Agent/trial/design	Efficacy endpoints	Safety findings
C5 inhibitor: Eculizumab		
TRIUMPH[23] Double-blind, randomized trial in 87 transfusion-dependent adult patients with PNH; eculizumab vs placebo; 26 weeks of treatment	**Primary (at week 26)** • Patients with stabilized Hgb levels in absence of transfusions: 49% vs 0% (P<.001) • PRBC units transfused (median number): 0 vs 10 (P<.001) **Secondary** • Transfusion independence: 51% vs 0% (P<.001) • Hemolysis (median AUC for LDH plotted against time): 58,587 vs 411,822 U/L (P<.001) • FACIT-Fatigue (mean change): 6.4 vs –4.0 points; difference 10.4 • Reduction in thromboembolic events	No deaths on study Serious AEs: 4 vs 9 Most common AEs[a]: headache (44% vs 27%), nasopharyngitis (23% vs 18%), back pain (19% vs 9%)
C5 inhibitor: Ravulizumab		
Study 301[24] Open-label, randomized trial in 246 complement inhibitor–naive adult patients with PNH; ravulizumab vs eculizumab; 26 weeks of treatment	**Primary (at week 26)** • Transfusion avoidance (transfusion-free and no transfusion requirement)[b]: 73.6% vs 66.1%; difference 6.8% (P_{inf}<.0001) • Hemolysis (LDH normalization)[b]: 53.6% vs 49.4%; OR 1.19 (P_{inf} <.0001) **Secondary** • LDH (LSM % change): –76.84 vs –76.02 • FACIT-Fatigue (LSM change): 7.07 vs 6.40 points • Breakthrough hemolysis: 4.0% vs 10.7% • Hgb stabilization: 68.0% vs 64.5% • Median time to first occurrence of LDH normalization: 24 vs 29 days • PRBCs transfused (mean number): 4.8 vs 5.6 • EORTC QLQ-C30 (mean change): 13.2 vs 12.9 • MAVE: 1.6% vs 0.8% • FACIT-Fatigue (LSM change): 7.07 vs 6.40 points • Transfusion avoidance: 73.6% vs 66.1%	1 death on study in eculizumab arm Serious AEs: 11 vs 9 Most common AEs[a]: headache (36.0% vs 33.1%), URTI (10.4% vs 5.8%), nasopharyngitis (8.8% vs 14.9%), nausea (8.8% vs 8.3%)
Study 302[25] Open-label, randomized trial in 197 adult patients with PNH who were clinically stable on eculizumab; ravulizumab vs eculizumab; 26 weeks of treatment	**Primary (baseline to week 26)** LDH[b] (LSM % change): –0.82% vs 8.39%; difference 9.21% (P_{inf} <.0006) **Secondary** • Breakthrough hemolysis: 0% vs 5.1% • MAVE: 0% vs 0% • FACIT-Fatigue (LSM change): 2.0 vs 0.54 points • Transfusion avoidance: 87.6% vs 82.7% • Hgb stabilization: 76.3% vs 75.5% • PRBCs transfused (mean number): 4.3 vs 3.4 • Proportion of patients with normal LDH: 66.0% vs 59.2% • EORTC QLQ-C30 (mean change from baseline): 1.15 vs –1.93	No deaths on study Serious AEs: 4 vs 8 Most common AEs[a]: headache (26.8% vs 17.3%), nasopharyngitis (21.6% vs 20.4%), URTI (18.6% vs 10.2%)
C5 inhibitor: Crovalimab		
COMMODORE 1[26] Open-label, randomized trial in 89 C5 inhibitor–experienced adult patients with PNH who were receiving eculizumab; crovalimab vs eculizumab; 24 weeks of treatment	Primary objective of study was safety and tolerability **Secondary (through week 25)** • Hemolysis control (assessed by LDH)[c]: 92.9% vs 93.7%; OR 0.88 • Transfusion avoidance[c]: 79.5% vs 78.4%; weighted difference 1.8 • Breakthrough hemolysis[c]: 10.3% vs 13.5%; weighted difference –3.5 • Hgb stabilization[c]: 59.0% vs 70.3%; weighted difference –10.8 • FACIT-Fatigue[c] (mean change): 1.1 points vs –2.6 points; difference 3.7	No deaths on study Serious AEs: 6 vs 1 Most common AEs[a]: transient immune complex reaction (16% vs 2%; rash, 7% vs 0%), pyrexia (16% vs 2%), COVID-19 (14% vs 17%), infusion-related reactions (14% vs 0%)[d]

Continued on next page

Table 1. Data from the Pivotal Phase 3 Trials of Complement Inhibitors in PNH (continued)

Agent/trial/design	Efficacy endpoints	Safety findings
C5 inhibitor: Crovalimab (continued)		
COMMODORE 2[27] Open-label, randomized trial in 204 complement inhibitor–naive adult patients with PNH; crovalimab vs eculizumab; 24 weeks of treatment	**Primary (through week 25)** • Hemolysis control (assessed by LDH)[b]: 79.3% vs 79.0%; OR 1.0 • Transfusion avoidance[b]: 65.7% vs 68.1% **Secondary** • Breakthrough hemolysis: 10.4% vs 14.5%; difference –3.9 • Hgb stabilization: 63.4% vs 60.9%; difference 2.2 • FACIT-Fatigue (mean change): 7.8 vs 5.2; difference 2.6	3 deaths on study (2 vs 1) Serious AEs: 14 vs 9 Most common AEs[a]: infusion-related reactions (15.6% vs 13.0%)[d], neutrophil count decreased (12.6% vs 10.1%), WBC count decreased (11.9% vs 10.1%)
C3 inhibitor: Pegcetacoplan		
PEGASUS[28] Open-label, randomized trial in 80 adult patients with PNH with persistent anemia despite eculizumab; pegcetacoplan vs eculizumab; 16 weeks of treatment	**Primary (baseline to week 16)** Hgb (LSM change): 2.37 g/dL vs –1.47 g/dL; difference 3.84 g/dL (P<.001) **Secondary** • Transfusion avoidance: 85% vs 15% (P<.001) • ARC (LSM change): –136 × 10^9/L vs 28 × 10^9/L • LDH (LSM change): –15 vs –10 • FACIT-Fatigue (LSM change): 9.2 points vs –2.7 points; difference 11.9	No deaths on study Serious AEs: 7 vs 6 Most common AEs[a]: diarrhea (22% vs 3%), injection-site erythema (17% vs 0%), abdominal pain (12% vs 10%), injection-site reaction (12% vs 0%)
PRINCE[29] Open-label, randomized trial in 53 complement inhibitor–naive adult patients with PNH; pegcetacoplan vs supportive care only; 26 weeks of treatment	**Primary** • Hgb stabilization: 85.7% vs 0% (P<.0001) • LDH (LSM change): –1870.5 U/L vs –400.1 U/L; difference –1470.4 U/L (P<.0001) **Secondary** • Increase in Hgb of ≥1 g/dL: 71.4% vs 5.6%; difference 54.1 (P<.0001) • ARC (LSM change): –123.3 × 10^9/L vs –19.4 × 10^9/L; difference –103.8 (P=.0002) • Hgb (LSM change): 2.9 vs 0.3; difference 2.7 (P=.0019) • Patients who received transfusion and/or had a >2 g/dL decrease in Hgb level: 11.4% vs 100% (P<.0001) • Transfusion avoidance: 91.4% vs 5.6%; difference 72.4 (P<.0001) • Transfused units[e] (median number): 21 vs 59 (P<.0001) • FACIT-Fatigue (LSM change): 7.8 points vs 3.3 points; difference 4.5 (P=.0610) • EORTC QLQ-C30 (LSM change): 18.9 points vs –2.9 points; difference 21.8 (nominal P=.0006) • ARC normalization: 60.0% vs 5.6%; difference 46.4 (nominal P=.0002) • Hgb normalization: 45.7% vs 0% (nominal P=.0010) • LDH normalization: 65.7% vs 0% (nominal P<.0001)	2 deaths on study (1 vs 1) Serious AEs: 4 vs 3 Most common AEs[a]: hypokalemia (13.0% vs 11.1%), dizziness (10.9% vs 0%), fever/pyrexia (8.7% vs 0%)

Continued on next page

anemia despite eculizumab.[28] In the 26-week open-label phase 3 study PRINCE, patients who were complement inhibitor–naive were randomized to receive either pegcetacoplan or best supportive care.[29]

The factor B inhibitor iptacopan was evaluated in the 6-month, open-label, randomized, phase 3 study APPLY-PNH, where it was compared with continued anti-C5 therapy in patients with PNH who experienced persistent anemia despite anti-C5 treatment.[30] A smaller open-label, single-group study, APPOINT-PNH, also evaluated iptacopan in patients with PNH who were complement inhibitor–naive.[30]

The factor D inhibitor danicopan was investigated as part of a combination regimen in the phase 3 ALPHA study.[31]

Table 1. Data from the Pivotal Phase 3 Trials of Complement Inhibitors in PNH (continued)

Agent/trial/design	Efficacy endpoints	Safety findings
Factor B inhibitor: Iptacopan		
APPLY-PNH[30] Open-label, randomized trial in 97 adult patients with PNH with persistent anemia despite anti-C5 treatment; iptacopan vs continued anti-C5 therapy; 24 weeks of treatment	**Primary** • Increase in Hgb level of ≥2 g/dL from baseline without RBC transfusion[e]: 82% vs 2%; difference 80% (*P*<.001) • Hgb level of ≥12 g/dL without RBC transfusion[f]: 69% vs 2%; difference 67% (*P*<.001) **Secondary** • Transfusion avoidance: 95% vs 26%; difference 69% (*P*<.001) • FACIT-Fatigue (LSM change): 8.6 points vs 0.3 points; difference 8.3 (*P*<.001) • ARC (LSM change): –115.8 × 10^9/L vs 0.3 × 10^9/L (*P*<.001) • LDH (mean % change): –3.5% vs –2.4% • Adjusted annual rate of clinical breakthrough hemolysis: 0.1 vs 0.7; ARR 0.1 (*P*=.006) • MAVE: 1 vs 0 events	No deaths on study Serious AEs: 6 vs 5 Most common AEs[a]: headache (16% vs 3%), diarrhea (15% vs 6%), nasopharyngitis (11% vs 6%)
APPOINT-PNH[30] Open-label, single group trial in 40 complement inhibitor–naive adult patients with PNH; iptacopan; 24 weeks of treatment	**Primary** Increase in Hgb level of ≥2 g/dL from baseline without RBC transfusion[e]: 92% **Secondary** • Hgb level of ≥12 g/dL without RBC transfusion: 63% • Transfusion avoidance: 98% • FACIT-Fatigue (LSM change): 10.8 points • ARC (LSM change): –82.5 × 10^9/L • LDH level (mean % change): –83.6% • Adjusted annual rate of clinical breakthrough hemolysis: 0 events • MAVE: 0 events	No deaths on study Serious AEs: 4 Most common AEs: headache (28%), COVID-19 (15%), URTI (12%)
Factor D inhibitor: Danicopan		
ALPHA[31] Double-blind, randomized trial in 73 adult patients with PNH and clinically significant extravascular hemolysis despite ravulizumab or eculizumab; danicopan vs placebo, both added to ravulizumab or eculizumab; 12 weeks of treatment	**Primary (baseline to week 12)** Hgb (LSM change): 2.94 g/dL vs 0.50 g/dL; difference 2.44 g/dL (*P*<.0001) **Secondary** • Hgb increase of ≥2 g/dL in absence of transfusion: 60% vs 0%; difference 47 (*P*<.0001) • Transfusion avoidance: 83% vs 38%; difference 42 (*P*=.0004) • FACIT-Fatigue (LSM change): 8.0 vs 1.9; difference 6.1 (*P*=.0021) • ARC (LSM change): –83.8 vs 3.5 × 10^9/L; difference –87.2 (*P*<.0001) • PRBC units transfused (LSMD in number): –1.22 (*P*=.0092) • Transfusions (LSMD in number): –0.67 (*P*=.026) • Bilirubin (LSMD): Total: –7.62 (P=.010); Direct: –3.18 (*P*<.0001) • PNH RBC clone size (LSMD): 27.63 (*P*=.0010) • C3 fragment disposition on PNH RBCs (LSMD): –16.20 (*P*=.0044) • LDH (LSMD change): –20.57 U/L • Hgb normalization: 29% vs 0% (*P*=.0080)	No deaths on study Serious AEs: 2 vs 1 Most common AEs[a]: headache (10% vs 4%), diarrhea (8% vs 13%), COVID-19 (4% vs 0%), increased ALT (4% vs 0%), increased AST (4% vs 8%), neutropenia (4% vs 0%)

[a]Top 3 most frequent AEs reported in the test arm. [b]Noninferiority endpoints; if present, post hoc *P* values were calculated for testing of noninferiority (P_{inf}). [c]Exploratory efficacy analysis. [d]Infusion-related reactions are less likely to occur in patients already stabilized on eculizumab. [e]Defined as any transfusion of RBCs, leukocyte-depleted PRBCs, leukocyte-poor PRBCs, leukocyte-poor blood, or whole blood. [f]Measured on at least 3 of 4 assessments between days 126 and 168.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ARC, absolute reticulocyte count; ARR, annualized rate ratio; COVID-19, coronavirus 2019; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; Hgb, hemoglobin; LDH, lactate dehydrogenase; LSM, least squares mean; LSMD, least squares mean difference; MAVE, major adverse vascular event; OR, odds ratio; PNH, paroxysmal nocturnal hemoglobinuria; PRBC, packed red blood cell; RBC, red blood cell; URTI, upper respiratory tract infection; WBC, white blood cell.

The design of these trials, and the efficacy and safety data reported from their primary analyses, are reported in Table 1. As danicopan was used to treat the patient EW, the ALPHA study is described in greater detail in the following section.

The ALPHA Trial

The phase 3 ALPHA study was a double-blind, international, randomized, and placebo-controlled superiority trial conducted in patients with PNH who also showed clinically significant extravascular hemolysis despite ongoing treatment with either ravulizumab or eculizumab.[31] In ALPHA, the oral factor D inhibitor danicopan was compared with placebo as an add-on treatment to intravenous eculizumab or ravulizumab.

Adult patients with PNH were eligible for enrollment if they had clinically significant extravascular hemolysis, defined as a Hgb level less than or equal to 9.5 g/dL and an absolute reticulocyte count of at least 120 × 10^9/L. Patients were required to have received either ravulizumab or eculizumab for a minimum of 6 months prior to beginning study treatment. Other eligibility criteria included platelets of at least 30,000/µL without platelet transfusion and an ANC of at least 500/µL. Patients were required to have been vaccinated against *Neisseria meningitidis* in the 3 years prior to the study.

Patients were excluded from enrollment if they had a history of a major organ transplant or a hematopoietic stem cell transplant (HSCT), or they had currently or previously had relevant comorbidities, aplastic anemia, or other bone marrow failure requiring HSCT or other therapies. Other exclusion criteria included complement deficiency, underlying bleeding disorders, or other non-PNH conditions causing anemia. Patients were also excluded if they had biliary cholestasis, untreated hepatitis B or hepatitis C virus infection, or HIV.

Between December 2020 and August 2022, patients were randomized (2:1) to treatment with either danicopan (n=49) or placebo (n=24), both administered in addition to their background therapy (either ravulizumab or eculizumab). At randomization, patients were stratified according to transfusion history in the 6 months prior (>2 vs ≤2), hemoglobin (<8.5 g/dL vs ≥8.5 g/dL), and whether the patient was enrolled from Japan (yes vs no; this latter factor was implemented to address Japanese drug submission regulatory requirements). Danicopan was administered orally (150 mg 3 times daily); dose escalation to 200 mg 3 times daily was permitted at weeks 6, 12, and 18 according to clinical response and per investigator discretion. The double-blind portion of the study comprised a 12-week treatment period, after which the study was unblinded and patients in the placebo arm were switched to treatment with danicopan in addition to ravulizumab or eculizumab, while patients in the danicopan arm continued danicopan treatment in addition to background therapy. This second treatment phase lasted an additional 12 weeks.

Overall, patient demographics and clinical characteristics were similar between the 2 treatment arms at baseline—median age (57.0 years and 55.0 years), females (57% and 63%), White (43% and 42%) or Asian (43% and 38%), baseline Hgb level (7.61 g/dL and 7.87 g/dL), mean absolute reticulocyte count (ARC; 251.98 × 10^9/L and 229.61 × 10^9/L), and mean LDH (299.25 U/L and 275.83 U/L) in the danicopan and placebo arms, respectively. In the 6 months prior to screening, 100% of patients in both arms had received an infusion (43% and 38%, respectively, had received >2 transfusions). At baseline, more patients in both arms were receiving ravulizumab (65% and 54%) than eculizumab.

The primary endpoint, change from baseline to week 12 in Hgb concentration, was met; patients in the danicopan arm showed a significantly larger increase in the least squares mean (LSM) change compared with the placebo arm (2.94 g/dL vs 0.50 g/dL; difference of 2.44 g/dL, *P*<.0001). The study authors noted that a mean difference of at least 2 g/dL was considered clinically meaningful. Mean Hgb differences in Hgb levels were observed as early as week 1 in the danicopan arm (1.19 g/dL; *P*<.0001), becoming clinically meaningful by week 2.

Danicopan was associated with significantly improved outcomes across all 4 key secondary endpoints assessed at week 12 compared with placebo—Hgb increase of at least 2 g/dL in the absence of transfusion (60% and 0%; adjusted difference, 47%, *P*<.0001), transfusion avoidance (83% and 38%; adjusted difference, 42%, *P*=.0004), improvement in LSM change in Functional Assessment of Chronic Illness Therapy–Fatigue scale (8.0 points vs 1.9 points; adjusted difference, 6.1, *P*=.0021), and LSM change in ARC from baseline (–83.8 × 10^9/L and 3.5 × 10^9/L; adjusted difference, –87.2 × 10^9/L, *P*<.0001).

Danicopan was also associated with improved outcomes across other secondary efficacy endpoints, also assessed at week 12, vs placebo—reduced transfusion requirements, demonstrated both by a significantly larger reduction in the number of RBC units transfused from baseline to week 12 (LSMD, –1.22; *P*=.0092) as well as by the number of transfusions performed between the 2 treatment arms (LSMD, –0.67; *P*=.026); increase in PNH RBC clone size (LSMD, 27.63; *P*=.0010); reduced magnitude of C3 fragment deposition (LSMD, –16.20; *P*=.0044); better control of intravascular hemolysis, evidenced by greater reductions in LDH compared with placebo (LSMD, –20.57 U/L); lowered bilirubin levels measured as both total bilirubin (LSMD, –7.62; *P*=.010) and direct bilirubin (LSMD, –3.18; *P*<.0001); and Hgb stabilization (29% vs 0%; *P*=.0080).

An exploratory analysis of quality of life demonstrated

Table 2. Long-Term Studies of Complement Inhibitors in PNH

Study description	Efficacy findings/Safety findings
Eculizumab	
Participants from 1 of 3 trials (TRIUMPH, SHEPHERD, or a phase 2 study)[34]; 36-month cutoff	Patients treated with eculizumab ≥26 weeks (n=195): 36-month estimated survival, 97.6%; LDH (median), 279 U/L (86.9% reduction from baseline); Hgb (mean in last 3 months of treatment), 10.6 g/dL; transfusion independence (last 6 months of treatment), 82.1%; PRBCs transfused (mean units in last 3 months of treatment), 2.4 Most frequently reported TEAEs in all patients: headache (54.9%), nasopharyngitis (49.7%), URTI (41.0%), diarrhea (34.9%), nausea (32.3%)
International PNH registry data analysis[39]; ≥14 years of overall follow-up	Patients treated with eculizumab ≥35 continuous days (n=1613): 49% increase in survival compared with untreated patients; HR 0.51 (95% CI, 0.41 to 0.64)
Retrospective real-world study[40]; mean follow-up 5.6 years	Patients treated with eculizumab ≥24 weeks (n=76); all values for final 24-week period of follow-up: complete/major hematologic response[a] rate, 22.9%/5.7%; transfusion avoidance, 69.4%; LDH <1.0 × ULN, 27.3%; Hgb ≥12 g/dL, 30.3%; ARC <1.0 × ULN, 19.3% Infections reported in 58% of patients; overall infection rate of 28.7 per 100 PY; 4 deaths reported
Ravulizumab (Longest study data published with complement inhibitors in PNH)	
OLE periods of Study 1 and Study 2 pivotal trials[33]; up to 6 years of follow-up	C5 inhibitor–naive patients (n=243) and eculizumab-experienced patients (n=191): 4-year survival rate, 97.7% and 98.4%; MAVE rate, 1.4 per 100 PY and 0.7 per 100 PY; mean LDH, 290.3 U/L (85.4% reduction from baseline) and 243.9 U/L; breakthrough IVH rate, 1.0 per 10 PY and 1.0 per 30 PY; transfusion avoidance, 53.9% and 70.7% Most frequently reported TEAEs in all patients: headache (29.8%), URTI (25.9%), nasopharyngitis (23.9%), pyrexia (20.2%), fatigue (14.0%)
Crovalimab	
OLE period of phase 1/2 COMPOSER trial[35]; median treatment duration of 3 years	Crovalimab-treated patients (n=43): LDH ≤1.5 × ULN across 24-week intervals, 80% to 100%; transfusion avoidance across 24-week intervals, 83% to 92%; Hgb stabilization across 24-week intervals, 79% to 88%; breakthrough hemolysis, 0.05 events per PY Any-grade TRAE: 32%; serious TRAE: 5%; most frequently reported TEAEs: headache (7%), urticaria (5%), viral infection (5%)
OLE period of COMMODORE 2 pivotal trial[41]; up to 2 years of follow-up	Crovalimab-treated patients who were originally C5 inhibitor–naive (n=197): LDH ≤1.5 × ULN across 24-week intervals, 74% to 88%; transfusion avoidance across 24-week intervals, 68% to 82%; Hgb stabilization across 24-week intervals, 62% to 73%; breakthrough hemolysis across 24-week intervals, 5% to 16% Treatment-related AEs: 68.4 per 100 PY; grade ≥3 AEs: 55.9 per 100 PY; serious AEs: 29.8 per 100 PY
C3 inhibitor: Pegcetacoplan	
OLE periods of PEGASUS and PRINCE pivotal trials[36]; up to 3 years of follow-up	Transfusion avoidance: C5 inhibitor–experienced patients (n=80), 71.2% to 79.2%; C5 inhibitor–naive patients (n=52), 79.5% to 86.4% Both groups: mean Hgb concentrations and durable reductions in median LDH concentrations close to the LLN; mean ARC and mean indirect bilirubin levels reached below the ULN Reported in all patients: hemolysis (49.2%), COVID-19 (25.0%), diarrhea (18.9%), headache (17.4%), nasopharyngitis (16.7%)
OLE study included patients from PHAROAH and PADDOCK (phase 1), PALOMINO (phase 2), and PEGASUS and PRINCE (phase 3)[42]; 48-week cutoff	Patients treated with pegcetacoplan (n=137): transfusion avoidance, 83.2%; Hgb >12 g/dL, 40.2%; LDH normalization, 67.0% Most common TEAEs reported in all patients: hemolysis (16.8%), fatigue (5.8%), URTI (5.1%), UTI (5.1%), nasopharyngitis (5.1%), headache (5.1%), anemia (5.1%), injection-site erythema (5.1%)

Continued on next page

Table 2. Long-Term Studies of Complement Inhibitors in PNH (continued)

Study description	Efficacy findings/Safety findings
Factor B inhibitor: Iptacopan	
Final results and OLE of APPLY-PNH and APPOINT-PNH pivotal trials[37]; 48-week cutoff	Patients treated with iptacopan (n=137): Hgb (mean), 12.1 g/dL to 13.2 g/dL; LDH (mean), 293.8 U/L to 358.3 U/L; ARC (mean), 78.5 × 10^9/L to 80.8 × 10^9/L Most common TEAEs reported in iptacopan-treated patients (not including those who switched from an anti-C5 therapy): COVID-19 (23% to 29%), headache (19% to 30%), nasopharyngitis or URTI (18%), diarrhea (15% to 16%)
Factor D inhibitor: Danicopan	
Final results of the ALPHA pivotal trial[38]; 72-week cutoff	Patients treated with add-on danicopan (n=57) and patients treated with add-on placebo then switched to danicopan (n=29): Hgb (change from baseline), 2.8 g/dL and 2.3 g/dL; ARC (change from baseline), –80 × 10^9/L and –55 × 10^9/L; LDH (mean), 274 U/L and 299 U/L; transfusion avoidance (weeks 48 to 72), 80.0% and 79.2% Overall: breakthrough hemolysis, 6 events per 100 PY Most common TEAEs reported in all patients: COVID-19 (31.0%), pyrexia (26.2%), headache (21.4%), nausea (15.5%), diarrhea (14.3%)

[a]Complete response defined as no transfusions required, stable Hgb in the normal range, and no evidence of hemolysis (ie, LDH ≤1.5 × ULN, ARC ≤150,000/μL). Major response was defined as no transfusion, normal Hgb, but with evidence of hemolysis (LDH >1.5 × ULN and/or ARC >150,000/μL).
ARC, absolute reticulocyte count; Hgb, hemoglobin; HR, hazard ratio; IVH, intravascular hemolysis; MAVE, major adverse vascular event; LDH, lactate dehydrogenase; LLN, lower limit of normal; OLE, open-label extension; PNH, paroxysmal nocturnal hemoglobinuria; PY, patient-years; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; ULN, upper limit of normal; URTI, upper respiratory tract infection; UTI, urinary tract infection.

significant improvements in change from baseline to week 12 with danicopan vs placebo in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 subscales of physical functioning (LSMD, 10.94; *P*=.0067); social functioning (LSMD, 14.13, *P*=.017); and fatigue symptoms (LSMD, –14.60, *P*=.019).

Among the treatment-emergent adverse events (TEAEs) reported in at least 5% of danicopan-treated patients, headache (10% vs 4% in placebo-treated patients) and diarrhea (8% vs 13%) were the most common. Grade 3 TEAEs occurred in 14% vs 13% of patients in the danicopan and placebo arms, respectively; no grade 4 or grade 5 TEAEs occurred. Two patients in the danicopan arm discontinued treatment owing to a TEAE considered study drug-related: 1 patient did and 1 patient did not recover from increased liver enzyme concentrations.

Long-Term Data With Complement Inhibitors

Long-term data with complement inhibitors demonstrate sustained efficacy in controlling PNH, with durable transfusion avoidance, stable Hgb levels, and low LDH levels. This was shown in a systematic review and meta-analysis, which analyzed data from 27 studies and stratified findings according to duration of therapy.[32] Among a total of 917 treatment-naive patients with PNH who initiated therapy with a complement inhibitor, treatment with any complement inhibitor was associated with transfusion avoidance in at least 50% of patients with PNH (pooled estimate for transfusion avoidance was 0.61 [95% CI, 0.50 to 0.70] for patients treated for 26 weeks or less, and 0.65 [95% CI, 0.48 to 0.79] for patients treated for more than 26 weeks). Mean Hgb levels were increased by 1.4 g/dL in patients who had been treated for 26 weeks or less, and were increased by 1.9 g/dL in those treated longer than 26 weeks. LDH levels (pooled estimates) were lowered from baseline by –1462.0 U/L in those treated for 26 weeks or less and by –1696.5 U/L among patients treated for longer than 26 weeks.

The long-term efficacy and safety of complement inhibitors has also been reported for the individual agents (Table 2).[33-42]

The longest available long-term data is with ravulizumab.[33] Over a 6-year follow-up period, patients receiving ravulizumab experienced durable control of both terminal complement activity and intravascular hemolysis. These outcomes were demonstrated in both eculizumab-experienced and C5 inhibitor–naive patients, with a mean LDH level at 6 years of 243.9 U/L and 290.3 U/L, respectively. The 4-year survival rate reached 98.4% in eculizumab-experienced patients, and 97.7% in C5 inhibitor–naive patients. These high survival rates were accompanied by a low incidence of major adverse vascular events (0.7 and 1.4 events per 100 patient-years, respectively) and a low rate of breakthrough intravascular hemolysis (1.0 events per 30 patient-years and 1.0 events per 10 patient-years, respectively). These breakthrough events were primarily associated with complement-amplifying conditions; just 2 events were associated with suboptimal C5 inhibition.

Long-term efficacy and safety results (72-week follow-up of the phase 3 ALPHA trial) with danicopan as add-on therapy to ravulizumab or eculizumab in patients with PNH with clinically significant extravascular hemolysis[38] included patients who received only add-on danicopan and also patients who switched from add-on placebo to add-on danicopan after week 12. Overall, add-on danicopan was associated with sustained improvements in Hgb levels, ARC levels, and LDH levels. Breakthrough hemolysis events occurred at a rate of 6 events per 100 patient-years and no new safety signals were observed.

Monotherapy vs Combination Therapy Considerations

Although complement inhibitors can provide effective initial disease control in PNH, some patients may subsequently experience recurrence of signs and symptoms associated with intravascular hemolysis. This clinical situation, referred to as breakthrough hemolysis, can occur through several mechanisms. It is important to identify the mechanistic cause of a breakthrough hemolysis event in a patient, as this drives the appropriate treatment response.[43]

Pharmacokinetic breakthrough hemolysis may develop when circulating concentrations of a C5 inhibitor fall below the threshold level required for adequate complement suppression. The result is transient loss of control of intravascular hemolysis. The size of the GPI-deficient RBC clone may impact the risk of this mechanism for breakthrough hemolysis, owing to the large reservoir of RBCs that forms even during treatment with clinically effective complement inhibition.[43] Classically, this form of breakthrough hemolysis is associated with eculizumab, owing to its fixed every-2-week dosing, wherein it typically presents near the end of a dosing interval.[44] Management of this form of breakthrough hemolysis involves either dose escalation or shortening of the interval duration.[43]

In contrast, pharmacodynamic breakthrough hemolysis may occur when a complement-amplifying event (such as infection, inflammation, surgery, or pregnancy) induces complement activation to a degree that exceeds the inhibitory capacity of otherwise therapeutic levels of circulating C5 inhibitor agents. Pharmacodynamic breakthrough overwhelms the proximal monotherapy inhibition, clinically manifesting as intravascular hemolysis owing to the lack of terminal pathway blockade. Clinically, these episodes may be particularly severe, requiring intensive management.[45] Pharmacodynamic-driven breakthrough hemolysis is considered a class-wide risk of both terminal and proximal complement inhibitors.[43]

Patients with PNH may also experience extravascular hemolysis as a mechanistic consequence of C5 inhibition.[46] Although terminal complement blockade prevents formation of the MAC and protects GPI-deficient RBCs from intravascular destruction, upstream complement activity may persist. Continued deposition of C3 fragments on surviving GPI-deficient RBCs can promote their opsonization and the subsequent lysis and clearance of these cells through extravascular mechanisms.[47] Clinically, extravascular hemolysis may present as persistent anemia or continued transfusion requirements, often accompanied by low hemoglobin and elevated reticulocyte counts after other potential causes of anemia have been excluded. Breakthrough hemolysis owing to this mechanism is often clinically conspicuous, because of the large number of sensitized RBCs that have accumulated under seemingly effective treatment.[43]

There is a risk for breakthrough hemolysis across all complement inhibitors, but to a varying degree. Breakthrough hemolysis occurs with a frequency of 10% to 15% over 6 months with eculizumab, crovalimab, or pegcetacoplan, and in fewer than 5% of patients treated with ravulizumab, iptacopan, or danicopan plus eculizumab or ravulizumab.[48] Breakthrough hemolysis may also have important clinical consequences, including pronounced fatigue that can negatively affect patient functioning and quality of life. It also markedly increases the risk of adverse vascular outcomes (such as thrombosis) or organ damage.[48]

Another scenario that may induce breakthrough

In the Clinic...

Potential clinical scenarios when combination therapy may be preferred:

- Persistent anemia despite adequate control of intravascular hemolysis with a C5 inhibitor, particularly when laboratory findings are consistent with ongoing extravascular hemolysis
- Continued transfusion requirements during C5 inhibitor therapy, suggesting that terminal complement blockade alone is not providing sufficient control of RBC loss
- Evidence of C3-mediated extravascular hemolysis; added proximal inhibition can reduce C3 deposition that occurs upstream of C5 blockade
- Clinically meaningful residual PNH symptoms associated with persistent anemia, such as fatigue, weakness, or reduced functional capacity, despite otherwise effective terminal complement inhibition
- Suboptimal hematologic response to C5 inhibitor monotherapy, where hemolysis control has improved but Hgb normalization or transfusion independence is not present

hemolysis is when switching from one complement inhibitor to another. Notably, pegcetacoplan monotherapy switching was associated with severe breakthrough hemolysis in about 24% of patients in the PEGASUS study.[48] As a result, switch protocol must be carefully considered and require mandatory overlap. For example, when switching a patient from eculizumab to pegcetacoplan, the latter agent must be initiated while continuing eculizumab, discontinuing the eculizumab after 4 weeks of pegcetacoplan.

Delayed or missed administration of complement inhibitor therapy is an important situation in which monotherapy may fail to provide continuous protection from hemolysis. The efficacy of terminal C5 inhibition depends on maintaining adequate drug trough concentrations throughout the dosing interval to fully sustain suppression of MAC formation. Even relatively brief interruptions in therapy may permit complement activity to reemerge, particularly when accompanied by infection, inflammation, physiologic stress, or other complement-amplifying conditions. When drug concentrations fall below the inhibitory threshold, GPI-deficient RBCs once again become susceptible to complement-mediated destruction.

Dual complement inhibition targeting both the early (proximal) and late (terminal) components of the complement cascade may provide broader control of hemolysis. Terminal inhibition can prevent MAC-mediated intravascular hemolysis, whereas proximal inhibition can reduce the upstream C3 fragment deposition driving extravascular hemolysis. By addressing both pathways, combined complement inhibition has the potential to provide more comprehensive control of hemolysis, reduce breakthrough events and ongoing extravascular hemolysis, increase the likelihood of transfusion independence, and ultimately improve clinical outcomes for patients with PNH.

Add-on strategies, such as danicopan added to eculizumab or ravulizumab, maintains continuous terminal complement protection and prevents the breakthrough hemolysis that might develop if the patient were simply switched from one of these agents. This scenario is exemplified in a case report of 2 patients who remained anemic despite ravulizumab monotherapy.[49] Both patients showed high reticulocyte counts and experienced significant fatigue. The first patient, a 70-year-old female, had been diagnosed more than a decade earlier with PNH and an associated refractory anemia myelodysplastic syndrome. In the 12 months prior to this case report, this patient had required 16 PRBC transfusions. After initiating danicopan add-on therapy in addition to ravulizumab, this patient's Hgb level rapidly increased while the reticulocyte counts markedly decreased over the first few weeks. The PNH RBC clone increased in size from 38% before starting danicopan to 100% within 15 weeks of starting danicopan. The second patient, a 23-year-old female, was diagnosed with both PNH and Budd-Chiari syndrome. Despite initiating treatment with eculizumab and then switching to ravulizumab, in the 12 months prior to the case report she had received 2 PRBC transfusion. After beginning add-on therapy with danicopan, the patient's haptoglobin levels normalized, while her bilirubin and LDH levels decreased and Hgb levels increased.

Back to the Patient

This patient case highlights several important considerations in the long-term management of PNH. First, effective control of intravascular hemolysis with a terminal C5 inhibitor does not necessarily eliminate all clinically meaningful disease manifestations. Despite improvement on ravulizumab, EW continued to have persistent anemia, illustrating how residual extravascular hemolysis can contribute to an incomplete hematologic response during otherwise effective C5 inhibition.

Second, the case demonstrates the potential value of targeting multiple points in the complement cascade. While receiving ravulizumab monotherapy, EW's hemoglobin level was 9.2 g/dL—not requiring transfusion, but low enough to be anemic and symptomatic. The addition of danicopan to ravulizumab was associated with a substantial improvement in EW's hemoglobin, up to 12 g/dL within 3 months. This response illustrates how the addition of proximal complement inhibition can address mechanisms of ongoing hemolysis that may persist despite terminal complement blockade.

Third, EW's experience emphasizes the importance of individualized, longitudinal PNH management. Treatment goals extend beyond suppression of intravascular hemolysis and should include assessment of anemia, transfusion requirements, residual symptoms, quality of life, and evidence of extravascular hemolysis.

Lastly, the difficulties EW encountered obtaining ravulizumab while traveling illustrate the practical challenges associated with lifelong complement inhibitor therapy and the importance of planning for continuity of treatment. Despite this prolonged interval between ravulizumab infusions, EW remained clinically stable while continuing danicopan, without recurrence of her prior symptoms or clinical evidence of breakthrough hemolysis. Her experience illustrates the importance of sustained complement control in a chronic disease such as PNH and provides an example of the clinical stability that may be observed with complementary targeting of proximal and terminal components of the complement pathway.

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References

1. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124(18):2804-2811.
2. Schrezenmeier H, Muus P, Socié G, et al. Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. *Haematologica*. 2014;99(5):922-929.
3. Gavriilaki E, de Latour RP, Risitano AM. Advancing therapeutic complement inhibition in hematologic diseases: PNH and beyond. *Blood*. 2022;139(25):3571-3582.
4. Luzzatto L. Control of hemolysis in patients with PNH. *Blood*. 2021;138(20):1908-1910.
5. Gerber GF, Broome CM, Weitz IC. Navigating the paroxysmal nocturnal hemoglobinuria (PNH) landscape. *Clin Adv Hematol Oncol*. 2025;23(4 suppl 8):1-19.
6. Panse JP, Höchsmann B, Schubert J. Paroxysmal nocturnal hemoglobinuria: pathophysiology, diagnostics, and treatment. *Transfus Med Hemother*. 2024;51(5):310-320.
7. Tantravahi SK, Latremouille-Viau D, Desai R, et al. Real-world prevalence and outcomes of patients with paroxysmal nocturnal hemoglobinuria treated with C5 inhibitors in the US: a retrospective claims database analysis. *J Health Econ Outcomes Res*. 2025;12(2):66-74.
8. Jalbert JJ, Chaudhari U, Zhang H, Weyne J, Shammo JM. Epidemiology of PNH and real-world treatment patterns following an incident PNH diagnosis in the US [ASH abstract 3407]. *Blood*. 2019;134(suppl 1).
9. Gulbis B, Eleftheriou A, Angastiniotis M, et al. Epidemiology of rare anaemias in Europe. *Adv Exp Med Biol*. 2010;686:375-396.
10. Gediz F, Payzin BK, Cakmak OZ, Uzum Y, Ernur D, Sahin F. Paroxysmal nocturnal hemoglobinuria in the differential diagnosis of thrombocytopenia. *Hematol Rep*. 2017;9(1):6862.
11. Sahin F, Akay OM, Ayer M, et al. PESG PNH diagnosis, follow-up and treatment guidelines. *Am J Blood Res*. 2016;6(2):19-27.
12. Zorina O, Beiki O, Holt M, et al. Global epidemiology of paroxysmal nocturnal hemoglobinuria: a systematic literature review. *J Epidemiol Glob Health*. 2026;16(1):99.
13. Dingli D, Matos JE, Lehrhaupt K, et al. The burden of illness in patients with paroxysmal nocturnal hemoglobinuria receiving treatment with the C5-inhibitors eculizumab or ravulizumab: results from a US patient survey. *Ann Hematol*. 2022;101(2):251-263.
14. Soliris (eculizumab) [prescribing information]. Boston, MA: Alexion Pharmaceuticals, Inc.; Revised June 2026.
15. Ultomiris (ravulizumab-cwvz) [prescribing information]. Boston, MA: Alexion Pharmaceuticals, Inc.; September 2025.
16. PiaSky (crovalimab-akkz) [prescribing information]. South San Francisco, CA: Genentech, Inc.; June 2024.
17. Empaveli (pegcetacoplan) [prescribing information]. Waltham, MA: Apellis Pharmaceuticals, Inc.; July 2025.
18. Fabhalta (iptacopan) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; July 2026.
19. Voydeya (danicopan) [prescribing information]. Boston, MA: Alexion Pharmaceuticals, Inc.; May 2026.
20. Debureaux PE, Kulasekararaj AG, Cacace F, et al; Severe Aplastic Anemia Working Party of the European Group for Bone Marrow Transplantation. Categorizing hematological response to eculizumab in paroxysmal nocturnal hemoglobinuria: a multicenter real-life study. *Bone Marrow Transplant*. 2021;56(10):2600-2602.
21. Kulasekararaj A, Schrezenmeier H, Usuki K, et al. Ravulizumab provides durable control of intravascular hemolysis and improves survival in patients with paroxysmal nocturnal hemoglobinuria: long-term follow-up of study 301 and comparisons with patients of the international PNH registry. *Blood*. 2023;142(suppl 1):2714.
22. Kulasekararaj AG, Lee JW, Patriquin CJ, et al. Characterizing clinically significant extravascular hemolysis in adults with PNH on ravulizumab or eculizumab treatment. *Blood Adv*. 2025;9(19):4936-4945.
23. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2006;355(12):1233-1243.
24. Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood*. 2019;133(6):530-539.
25. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood*. 2019;133(6):540-549.
26. Scheinberg P, Clé DV, Kim JS, et al. Phase 3 randomized COMMODORE 1 trial: crovalimab versus eculizumab in complement inhibitor-experienced patients with paroxysmal nocturnal hemoglobinuria. *Am J Hematol*. 2024;99(9):1757-1767.
27. Röth A, He G, Tong H, et al. Phase 3 randomized COMMODORE 2 trial: crovalimab versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibition. *Am J Hematol*. 2024;99(9):1768-1777.
28. Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2021;384(11):1028-1037.
29. Wong RSM, Navarro-Cabrera JR, Comia NS, et al. Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria. *Blood Adv*. 2023;7(11):2468-2478.
30. Peffault de Latour R, Röth A, Kulasekararaj AG, et al. Oral iptacopan monotherapy in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2024;390(11):994-1008.
31. Lee JW, Griffin M, Kim JS, et al. Addition of danicopan to ravulizumab or eculizumab in patients with paroxysmal nocturnal haemoglobinuria and clinically significant extravascular haemolysis (ALPHA): a double-blind, randomised, phase 3 trial. *Lancet Haematol*. 2023;10(12):e955-e965.
32. Lee J, Lee H, Kim S, Suh HS. Efficacy of complement inhibitors for patients with paroxysmal nocturnal hemoglobinuria: a systematic review and meta-analysis. *Ther Adv Hematol*. 2023;14:20406207231216080.
33. Kulasekararaj A, Brodsky R, Schrezenmeier H, et al. Ravulizumab demonstrates long-term efficacy, safety and favorable patient survival in patients with paroxysmal nocturnal hemoglobinuria. *Ann Hematol*. 2025;104(1):81-94.
34. Hillmen P, Muus P, Röth A, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2013;162(1):62-73.
35. Röth A, Ichikawa S, Ito Y, et al. Crovalimab treatment in patients with paroxysmal nocturnal haemoglobinuria: long-term results from the phase I/II COMPOSER trial. *Eur J Haematol*. 2023;111(2):300-310.
36. de Castro C, Kelly RJ, Griffin M, et al. Efficacy and safety maintained up to 3 years in adults with paroxysmal nocturnal hemoglobinuria receiving pegcetacoplan. *Adv Ther*. 2025;42(9):4641-4658.
37. Risitano AM, Kulasekararaj AG, Scheinberg P, et al. Oral iptacopan monotherapy in paroxysmal nocturnal haemoglobinuria: final 48-week results from the open-label, randomised, phase 3 APPLY-PNH trial in anti-C5-treated patients and the open-label, single-arm, phase 3 APPOINT-PNH trial in patients previously untreated with complement inhibitors. *Lancet Haematol*. 2025;12(6):e414-e430.
38. Kulasekararaj A, Griffin M, Piatek C, et al. Long-term efficacy and safety of danicopan as add-on therapy to ravulizumab or eculizumab in PNH with significant EVH. *Blood*. 2025;145(8):811-822.
39. Terriou L, Lee JW, Forsyth C, et al. Long-term effectiveness of eculizumab: data from the International PNH Registry. *Eur J Haematol*. 2023;111(5):796-804.
40. Versmold K, Alashkar F, Raiser C, et al. Long-term outcomes of patients with paroxysmal nocturnal hemoglobinuria treated with eculizumab in a real-world setting. *Eur J Haematol*. 2023;111(1):84-95.
41. Röth A, He G, Brodsky A, et al. Phase III randomized COMMODORE 2 trial: 2-year efficacy and safety of crovalimab in patients with paroxysmal nocturnal hemoglobinuria (PNH) naive to complement inhibition. *Blood*. 2024;144(suppl 1):2687.
42. Patriquin CJ, Bogdanovic A, Griffin M, et al. Safety and efficacy of pegcetacoplan in adult patients with paroxysmal nocturnal hemoglobinuria over 48 weeks: 307 open-label extension study. *Adv Ther*. 2024;41(5):2050-2069.
43. Chen C, Zhong J, Xiong D. Beyond terminal blockade: a mechanism-based approach to complement inhibitor selection in paroxysmal nocturnal hemoglobinuria. *Drug Des Devel Ther*. 2026;20:624829.
44. Brodsky RA, Peffault de Latour R, et al. Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. *Haematologica*. 2021;106(1):230-237.
45. Griffin M, Kelly RJ, Panse J, et al. Management of acute breakthrough hemolysis with intensive pegcetacoplan dosing in patients with PNH. *Blood Adv*. 2024;8(7):1776-1786.
46. Notaro R, Luzzatto L. Breakthrough hemolysis in PNH with proximal or terminal complement inhibition. *N Engl J Med*. 2022;387:160-166.
47. Sica M, Barone F, Nannelli C, et al. The long-acting anti-C5 ravulizumab results in C3 binding to PNH red cells similar to its parental molecule eculizumab. *Br J Haematol*. 2023;201:e1-e4.
48. Fattizzo B, Versino F, Barcellini W. Breakthrough hemolysis in paroxysmal nocturnal hemoglobinuria throughout clinical trials: from definition to clinical practice. *Blood*. 2025;146(4):411-421.
49. Füreder W, Valent P. Stable responses to danicopan as add-on to ravulizumab in two patients with paroxysmal nocturnal hemoglobinuria. *Ann Hematol*. 2024;103(8):3235-3238.