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Ravulizumab–Danicopan Combination Therapy in PNH Management

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In the Clinic

AB presented to our clinic in 2017, at the age of 70, for a second opinion regarding management of paroxysmal nocturnal hemoglobinuria (PNH) that was diagnosed following a long history (starting in 2010) of mild self-limited thrombocytopenia without anemia.

AB's primary care physician had noted macrocytosis. A bone marrow biopsy revealed mild hypercellularity, erythroid hyperplasia, left-shifted maturation, and mild dyspoiesis. Flow cytometry confirmed PNH with a type 3 clone (83.3% in the neutrophil lineage) and a type 1 clone (13.2% in the red blood cell [RBC] lineage with 86% normal cells). AB subsequently developed worsening anemia and a pulmonary embolism, prompting initiation of treatment with the C5 inhibitor eculizumab in 2016. This resulted in a marked improvement in AB's lactate dehydrogenase (LDH) levels (from 5400 U/L at eculizumab initiation to 561 U/L) and stabilization of hemoglobin level (at 10 g/dL), with resolution of multiple PNH-related symptoms, including fatigue, myalgias, palpitations, dysphagia, abdominal pain, and darkened urine.

At her initial visit to our clinic in 2017, the hemoglobin was 10.5 g/dL, the platelet count was 249 × 10^9/L, and the white blood cell (WBC) count was 4.66 × 10^9/L. Despite hematologic stability, AB reported persistent exertional dyspnea and fatigue that significantly limited her ability to sustain her prior activity level as an avid hiker.

In 2018, AB was transitioned to ravulizumab. She remained clinically stable until April 2022, when she developed atrial fibrillation and worsening anemia (hemoglobin 8 g/dL), associated with extreme fatigue and requiring repeated cardioversions. Her ravulizumab regimen was intensified (to be delivered at the maximum dose every 7 weeks), but despite these interventions, the hemoglobin remained around 9 g/dL with elevated bilirubin (3.3 mg/dL) and reduced exercise tolerance. She underwent atrial ablation for management of the atrial fibrillation, with return to normal sinus rhythm, but despite this she continued to endorse decreased exercise tolerance with ongoing fatigue. Her hemoglobin did not improve beyond around 9 g/dL despite better control of the atrial fibrillation.

In June 2024, danicopan was added to the ravulizumab. Within 2 weeks of starting therapy, her hemoglobin improved to 12.8 g/dL, which has been maintained despite a bout of pneumonia. Additionally, the bilirubin has improved to 1.4 mg/dL and LDH remains only slightly above the upper limit of normal (ULN). Subsequently, AB was weaned to the standard interval dosing of ravulizumab every 8 weeks with sustained hemoglobin levels above

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

Credit: Nemes Laszlo/Science Source

12 g/dL. Clinically, she reported marked improvement in fatigue and dyspnea, regained functional capacity, and expressed satisfaction with her ability to resume travel and family visits.

Brief Overview of PNH

PNH is a rare acquired disorder of clonal hematopoietic stem cells in which uncontrolled terminal complement activation leads to intravascular hemolysis and other complications. The clinical manifestations of PNH include complement-mediated hemolytic anemia, bone marrow failure, and thrombosis.[1]

The prevalence of PNH is estimated at 12 per million and the incidence is estimated at 1 to 10 per million person-years.[2] However, this may be an underestimation due to underrecognition and delayed diagnoses.[3-5] Most patients with PNH present between 30 and 40 years of age, although it can also be diagnosed in children and older adults. A 2012 analysis of 1610 patients from the International PNH Registry revealed the median patient age as 42 years (with a median PNH duration of 4.6 years from disease start to registry enrollment) and an age range of 3 to 99 years.[6]

Pathophysiology

PNH can be traced to the expansion of a hematopoietic stem cell clone harboring a somatic mutation in the X-linked *PIGA* gene. *PIGA* encodes a protein required for the synthesis of the glycolipid glycosylphosphatidylinositol (GPI), which serves to anchor proteins to the cell surface. Lack of this protein expression allows *PIGA*-mutated stem cells to survive attack by autoreactive T cells in the marrow. *PIGA* mutations therefore represent a biomarker for acquired immune-mediated cytopenias and aplastic anemia that predicts responsiveness to immunosuppressive therapy. In RBCs, reduced or absent expression of GPI results in a lack of expression of the GPI-anchored complement regulatory proteins CD55 and CD59 on the cell surface.

Complement is a key component of the innate immune system, providing immediate protection against pathogens, clearance of cellular debris, and processing of immune complexes.[7] The complement system is a carefully orchestrated signaling network that signals via a cascade of enzymatic plasma proteins. Complement can be initiated through 3 pathways—the classical, lectin, or alternative pathways—all of which converge at the formation of the C3 convertase, triggering C3 activation. From there, complement signaling continues on a common terminal pathway, which includes the formation of the C5 convertase and C5 activation, culminating in the formation of the membrane attack complex (MAC). Breakdown products from the conversion of C3 and C5 to their active components drive local vasodilation and act as a chemoattractant for activation of the cellular immune response.

Normally, the expression and localization of CD55 and CD59 to the RBC cell surface regulates complement activation.[7] Specifically, CD55 regulates the formation and stability of C3 and C5 convertases, and CD59 blocks the formation of the MAC and the insertion of the complement protein C9 into the lipid bilayer. In GPI-deficient RBCs, white cells, and platelets, the lack of CD55 and CD59 expression at the cell surface allows uncontrolled complement activation and the MAC to remain active and unregulated. Patients with PNH exhibit constant, low-level activation of complement via the alternative pathway, resulting in chronic intravascular hemolysis, release of platelet microparticles, and generalized inflammation that drives vascular hyperreactivity (from free hemoglobin induced nitric oxide scavenging) as well as pronounced hypercoagulability.[8,9] Complement-amplifying events (including infection, surgery, pregnancy, vaccination, or other inflammatory triggers) can trigger further unregulated RBC lysis and increased activation of the thrombotic cascade, causing severe paroxysmal events that can become life-threatening via either direct worsening of hemolysis or due to thrombotic complications.

Diagnosis

PNH is diagnosed with evaluation of the presence and size of a PNH clone in the peripheral blood. Flow cytometry is used to quantify the proportion of cells with a lack of GPI-anchored proteins (eg, CD59 on erythrocytes) and fluorescein-labeled proaerolysin (a fluorescently-conjugated prototoxin that binds to GPI anchors on the surface of WBCs). At least 2 different GPI markers on 2 cell lines (leukocytes and erythrocytes) is generally recommended for the diagnosis of PNH.[10]

Disease Burden

PNH is a chronic disease that requires intensive management and lifelong treatment. For many years, PNH treatment was limited to supportive therapy, including transfusions. The advent of complement inhibitors has resulted in substantial clinical benefits, including improved life expectancy.[10] However, there remains a significant and lifelong treatment and symptom burden even among patients whose disease is well-controlled.[11,12]

Overview of Complement Inhibitors

Given the key role of complement in the pathophysiology of PNH, C5 inhibitors targeting the terminal pathway emerged as the first class of drugs approved for the management of PNH.

With their ability to prevent intravascular hemolysis

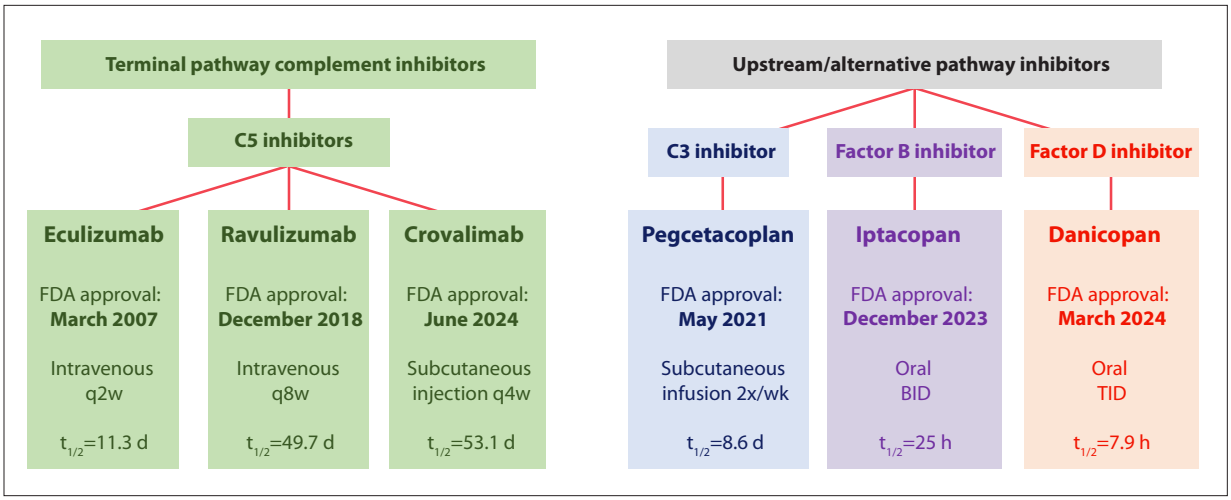

Figure 1. FDA-approved agents for the management of PNH.[9,13-18]
BID, twice daily; d, days; FDA, US Food and Drug Administration; h, hours; PNH, paroxysmal nocturnal hemoglobinuria; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; t½, half-life; TID, 3 times daily; wk, week.

and its downstream consequences, C5 inhibitors have been demonstrated to reduce thrombotic risk, increase the likelihood of transfusion avoidance, improve quality of life, and extend patient survival. Over the past 2 decades, 3 C5 inhibitors have been approved by the US Food and Drug Administration (FDA) (Figure 1).[9,13-18]

The first of these, the humanized monoclonal antibody eculizumab, was approved in March 2007. Eculizumab is administered intravenously weekly for the first 4 weeks, followed by a fifth dose 1 week later, then every 2 weeks thereafter.[13] Subsequently, a second C5 inhibitor, ravulizumab, was approved in December 2018. Ravulizumab is administered intravenously every 8 weeks starting 2 weeks after the initial loading dose.[14] The ravulizumab monoclonal antibody differs from eculizumab in that the Fc portion binds less tightly to its receptor. Following C5 binding, both molecules undergo endocytosis where C5 is displaced and degraded. Whereas eculizumab is also degraded in the endosome, ravulizumab is recycled to the cell surface, extending its half-life. Crovalimab is the most recent C5 inhibitor approved in June 2024. After an initial intravenous loading dose, crovalimab is administered subcutaneously, first as 4 weekly loading doses and then by maintenance doses every 4 weeks.[15]

Whereas intravascular hemolysis is the primary clinical feature associated with the diagnosis of PNH, a second type of hemolysis becomes more prominent in patients treated with C5 inhibitors. Even though C5 inhibition prevents MAC formation, C3 fragments (specifically C3b) are deposited on the surface of the GPI-deficient RBCs, leading to enhanced RBC opsonization. Opsonized red cells coated with C3b are targeted for destruction by immune cells in the liver and spleen, resulting in decreased red cell life expectancy, increased bilirubin levels, and anemia in patients with poor underlying bone marrow reserve (a majority of patients). Significant extravascular hemolysis occurs as a consequence of C5 inhibition in up to 20% to 30% of patients; this can manifest with symptomatic anemia and even transfusion dependence in some patients.[19-21] Newer complement inhibitors were designed to target the proximal complement pathway to prevent both intravascular and extravascular hemolysis. Three proximal complement pathway inhibitors have been approved for the management of PNH by the FDA, each with a different mechanism of action (Figure 1).

Pegcetacoplan, a C3 inhibitor approved by the FDA in May 2021, is administered subcutaneously twice weekly (or every 3 days in patients with LDH levels >2 × ULN).[16] In December 2023, a factor B inhibitor and the first oral agent, iptacopan was approved. It is administered twice daily.[17] 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. Danicopan is administered orally, 3 times daily.[18] All these proximal complement inhibitors block complement activation before enzymatic lysis of C3 and prevent the production of C3b and therefore enhanced opsonization and clearance of RBCs, enhancing the life expectancy of PNH RBCs.

Monotherapy With Complement Inhibitors

An overview of the efficacy results from the pivotal studies evaluating complement inhibitors as monotherapy in PNH is provided in Table 1.

Eculizumab

Eculizumab was evaluated in the TRIUMPH pivotal phase 3 study.[22] This double-blind, randomized 26-week trial compared 6 months of treatment with eculizumab vs placebo in 87 transfusion-dependent adult patients with PNH. There were 2 primary endpoints in this study: stabilization of hemoglobin levels in the absence of transfusions and the number of units of packed RBCs transfused. Although no patients in the placebo group achieved stabilization of hemoglobin levels above the prespecified set point (median, 7.7 g/dL for both groups), nearly half (49%) of the eculizumab group achieved this endpoint (P<.001). The median number of units of packed RBCs transfused per patient was 0 among eculizumab-treated patients and 10 among placebo-treated patients (P<.001). Mean hemoglobin levels changed from 10.0 g/dL and 9.7 g/dL in the eculizumab and placebo group, respectively, at baseline to 10.1 g/dL and 8.9 g/dL, respectively, at week 26 (P<.001). Eculizumab treatment resulted in a rapid and sustained decrease in LDH levels (a measure of intravascular hemolysis) as early as week 1; the median AUC was 85.8% lower in the eculizumab arm than in the placebo arm (58,587 vs 411,822 U/L; P<.001). Clinically significant improvements in quality of life scores were achieved by patients treated with eculizumab, as assessed by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue instrument (P<.001) and the European Organization for Research and Treatment of Cancer Quality of Life (EORTC-QoL) Questionnaire (P≤0.01). The most common adverse events reported with eculizumab that were more frequent than with placebo were headache (44% vs 27%) and back pain (19% vs 9%), although these differences were not statistically significant. No serious treatment-related adverse events were reported.

Ravulizumab

Ravulizumab was evaluated in 2 head-to-head phase 3 trials: Study 301 included 246 adult patients with PNH naive to complement inhibitor therapy, whereas Study 302 included 195 adult patients with PNH who were clinically stable during prior eculizumab therapy.[23,24] In both studies, patients were randomized to treatment with either ravulizumab or eculizumab; ravulizumab demonstrated noninferiority to eculizumab in both populations. In Study 301, coprimary efficacy endpoints were proportion of patients remaining transfusion-free (73.6% vs 66.1%; difference of 6.8%; 95% CI, –4.66 to 18.14) and achieving LDH normalization (53.6% vs 49.4%; odds ratio, 1.19; 95% CI, 0.80-1.77). Ravulizumab also showed noninferiority across key secondary endpoints, including percentage reduction in LDH, change in FACIT-Fatigue score, breakthrough hemolysis, and stabilized hemoglobin. In Study 302, the primary endpoint was percentage change in LDH from baseline to day 183, for which ravulizumab also showed noninferiority to eculizumab (difference of 9.21%; 95% CI, –0.42 to 18.84). Ravulizumab was also noninferior across all key secondary endpoints (proportion of patients with breakthrough hemolysis, change in FACIT-Fatigue score, transfusion avoidance, and stabilized hemoglobin). Headache was the most frequently reported adverse event in both studies. In Study 301 and Study 302, 11 and 4 ravulizumab-treated patients, respectively, reported a serious adverse event (vs 9 and 8 in the eculizumab arm).

Crovalimab

Crovalimab was evaluated in 2 noninferiority studies, where it was compared with eculizumab in 2 populations: 89 C5 inhibitor–experienced adult patients with PNH (COMMODORE 1) and 204 adult patients with C5 inhibitor–naive PNH (COMMODORE 2).[25,26] In COMMODORE 2, crovalimab was found to be noninferior to eculizumab in the coprimary endpoints of hemolysis control (79.3% vs 79.0%; odds ratio, 1.0; 95% CI, 0.6-1.8) and transfusion avoidance (65.7% vs 68.1%; weighted difference, –2.8; 95% CI, –15.7 to 11.1). It also showed noninferiority in the secondary endpoints of breakthrough hemolysis and hemoglobin stabilization; both arms showed a clinically meaningful improvement in FACIT-Fatigue score. Target recruitment for the COMMODORE 1 trial was not met, given the changing treatment landscape during the conduct of the trial. Therefore, safety became the new primary objective and efficacy endpoints underwent exploratory analyses that demonstrated that crovalimab-treated patients showed sustained terminal complement activity inhibition and maintained disease control. The most frequently reported (≥5% in either arm) adverse events in COMMODORE 1 were pyrexia (16% with crovalimab vs 2% with eculizumab), COVID-19 (14% vs 17%), and infusion-related reactions (14% vs 0%). It should be noted that infusion-related reactions may have been lower in the eculizumab arm as these patients were already stabilized on eculizumab.

Pegcetacoplan

Two open-label phase 3 trials were used to evaluate the C3 inhibitor pegcetacoplan. In PEGASUS, 80 patients with PNH and hemoglobin levels less than 10.5 g/dL despite eculizumab therapy were enrolled.[27] After first receiving a 4-week run-in phase with pegcetacoplan plus eculizumab, patients were randomly assigned to receive either pegcetacoplan or eculizumab. A significant improvement in the mean change in hemoglobin level from baseline to week 16, the primary endpoint, was achieved with pegcetacoplan vs eculizumab (mean difference, 3.84 g/dL; P<.001). Mean hemoglobin levels changed from 8.7 g/dL in both

Table 1. Pivotal Efficacy Data for Complement Inhibitors[22-30]

Agent	Trial details	Key efficacy findings
Terminal complement inhibitors		
Eculizumab	TRIUMPH: eculizumab vs placebo in adults with PNH (n=87)	• 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)
Ravulizumab	301 study: ravulizumab vs eculizumab in complement inhibitor–naive adults with PNH (n=246)	• Proportion of patients remaining transfusion-free at 26 weeks: 73.6% vs 66.1% • LDH normalization at 26 weeks: 53.6% vs 49.4%
	302 study: ravulizumab vs eculizumab in eculizumab-experienced patients (n=195)	Difference in percentage change in LDH from baseline to day 183: 9.21% (*P*=.058 for superiority)
Crovalimab	COMMODORE 1: crovalimab vs eculizumab in C5 inhibitor–experienced patients (n=89)	Exploratory efficacy analysis: sustained terminal complement inhibition, maintained disease control
	COMMODORE 2: crovalimab vs eculizumab in C5 inhibitor–naive patients (n=204)	• 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%
Alternative pathway inhibitors		
Pegcetacoplan	PEGASUS: pegcetacoplan vs eculizumab in patients with Hb <10.5 g/dL on eculizumab (n=80)	• 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%
	PRINCE: pegcetacoplan vs supportive care in patients with complement inhibitor–naive PNH (n=53)	• 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)
Iptacopan	APPLY-PNH: iptacopan vs continued C5 inhibitor in patients with Hb <10 g/dL despite C5 inhibitor (n=97)	• 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)
	APPOINT-PNH: iptacopan in complement inhibitor–naive patients with LDH >1.5 × ULN (n=33)	Increase in Hb ≥2 g/dL without transfusion: 92%

Hb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal.

the eculizumab and pegcetacoplan groups at baseline to 11.5 g/dL in the pegcetacoplan group and 8.6 g/dL in the eculizumab group at week 16. Patients treated with pegcetacoplan also showed improved rates of transfusion independence at week 16 and improved FACIT-Fatigue scores. The second trial, PRINCE, enrolled 53 patients with complement inhibitor–naive PNH.[28] Patients were randomized to treatment with either pegcetacoplan or continued supportive care; those treated with pegcetacoplan achieved a higher rate of hemoglobin stabilization (85.7% vs 0%; difference, 73.1%; *P*<.0001) and greater change from baseline in LDH (LS mean change, –1870.5 U/L vs –400.1 U/L; difference, –1470.4 U/L; *P*<.0001). Mean hemoglobin levels changed from 9.4 g/dL and 8.7 g/dL in the pegcetacoplan and control group, respectively, at baseline, to 12.8 g/dL and 9.6 g/dL, respectively, at week 26. Pegcetacoplan-related serious adverse events did not occur in either study; in the PEGASUS study the most common adverse events in the pegcetacoplan and eculizumab arms 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%).

Iptacopan

The factor B inhibitor iptacopan was investigated in 2 phase 3 studies, APPLY-PNH and APPOINT-PNH.[29] In APPLY-PNH, a total of 97 patients with prior exposure to a C5 inhibitor were randomly assigned to either switch to iptacopan or continue their current C5 inhibitor for 24 weeks. Compared with the C5 inhibitor, the iptacopan arm had a significantly higher proportion of patients achieving an increase in hemoglobin of at least 2 g/dL

from baseline without transfusions (82% vs 2%), and also in the proportion of patients who attained a hemoglobin level of 12 g/dL or greater without transfusions (69% vs 2%) at 24 weeks. The 24-week mean hemoglobin levels, irrespective of red-cell transfusions, were 12.6 g/dL and 9.2 g/dL in the iptacopan group and anti-C5 group, respectively. Additionally, 95% of iptacopan-treated patients achieved transfusion independence, compared with 26% receiving a C5 inhibitor. The second study, APPOINT-PNH, assessed the efficacy of iptacopan in patients with an LDH greater than 1.5 × ULN and complement inhibitor–naive disease. After 24 weeks, hemoglobin increases of 2 g/dL or greater from baseline without transfusion were reported in 31 of 33 iptacopan-treated patients, and the transfusion avoidance rate between days 14 and 168 was 98%. In APPOINT-PNH, the mean hemoglobin level was 8.2 g/dL at baseline and 12.6 g/dL at week 24. The final analysis of both trials, at 48 weeks, indicated durable hemolysis control with sustained hemoglobin levels.[30] In both studies, headache was the most frequent adverse event reported with iptacopan.

Long-Term Efficacy

There are several reports of long-term efficacy with complement inhibitor agents, with the longest study data published with ravulizumab.

Eculizumab has demonstrated durable and significant improvements in clinical outcomes, including 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.[31] However, a key safety consideration is the increased risk of meningococcal disease owing to *Neisseria* infections, with the estimated absolute risk being approximately 0.5% per 100 patient-years. Importantly, even with vaccination, the risk remains more than 1000-fold higher than in healthy controls.[31]

Over a treatment period of 6 years with ravulizumab, durable control of terminal complement activity and intravascular hemolysis was demonstrated in both C5 inhibitor–exposed and C5 inhibitor–naive patients, including a 4-year survival rate of 98.4% and 97.7%, respectively (Table 2).[32] The low incidence of major adverse vascular events (0.7-1.4 per 100 patient-years) when compared with untreated patients from the International PNH Registry reduced the risk of mortality by 5-fold. The few breakthrough intravascular hemolysis events reported were commonly associated with complement-amplifying conditions, and only 2 were associated with suboptimal inhibition of C5.

Crovalimab was associated with sustained hemoglobin control and transfusion avoidance after a median treatment duration of 3 years.[33] During the open-label extension, 32% experienced treatment-related adverse events, mean normalized LDH was generally maintained at up to 1.5 × ULN, transfusion avoidance was achieved in 83% to 92% of patients, hemoglobin stabilization in 79% to 88% of patients across each 24-week interval; and 5 breakthrough hemolysis events occurred, with none leading to withdrawal.

Three-year efficacy has also been demonstrated with the proximal inhibitor pegcetacoplan, which stabilized hemoglobin and FACIT-Fatigue at close to normal range and LDH, absolute reticulocyte count, and indirect bilirubin within normal range. Annual transfusion avoidance rates were 79.5% to 86.4% and 71.2% to 79.2% in PRINCE and PEGASUS, respectively. Thirty-seven (28.0%) patients experienced clinically significant and laboratory-confirmed breakthrough hemolysis; 4 thrombotic events occurred in 3 (2.3%) patients; no meningitis cases were reported.

Table 2. Long-Term Safety, Efficacy, and Survival Outcomes With Ravulizumab in Patients With PNH[32]

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.

Situations in Which Monotherapy Does Not Yield Optimal Results

Even when patients experience initial control on a complement inhibitor, they can experience a resurgence

Table 3. Danicopan as Add-on Therapy to Ravulizumab or Eculizumab in PNH With Significant EVH: Key Findings of the ALPHA Trial[38]

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] × 10⁹/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	
Proportion of patients avoiding transfusion, %		
Weeks 0-12	**Danicopan (n=57)**	**Placebo (n=29)**
	78.9[h]	27.6
	Danicopan-danicopan	**Placebo-danicopan**
Weeks 12-24[i]	80.0	81.5
Weeks 24-48[j]	81.5	73.1
Weeks 48-72[k]	80.0	79.2

[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.
[h]*P*≤.001.
[i]Weeks 12-24: danicopan-danicopan, n=55; placebo-danicopan, n=27.
[j]Weeks 24-48: danicopan-danicopan, n=54; placebo-danicopan, n=26.
[k]Weeks 48-72: danicopan-danicopan, n=50; placebo-danicopan, n=24.
ARC, absolute reticulocyte count; EVH, extravascular hemolysis; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; LDH, lactate dehydrogenase; LSM, least squares mean; PNH, paroxysmal nocturnal hemoglobinuria; SEM, standard error of the mean.
Adapted from: Kulasekararaj A et al. *Blood*. 2025;145(8):811-822.

of the signs and symptoms of intravascular hemolysis. This occurrence, termed breakthrough hemolysis, can be attributed to several causes. In some cases, the patient may have levels of the C5 inhibitor that are too low to be effective (pharmacokinetic breakthrough hemolysis), whereas in other cases, the patient may experience a significant event (infection, inflammation, surgery, pregnancy, etc) that triggers activation of complement above a level that can be effectively inhibited by their normally circulating levels of C5 inhibitor (pharmacodynamic breakthrough hemolysis).

An alternative form of hemolysis occurs in patients with PNH as a mechanistic consequence of inhibiting C5.[35] This extravascular hemolysis occurs as a result of ongoing C3 fragment deposition on the surface of surviving GPI-deficient RBCs, resulting in RBC opsonization and lysis.[36] This extravascular hemolysis is characterized by persistent anemia or transfusion requirement with low hemoglobin and elevated reticulocytes, when other potential causes are eliminated.

The patient described in this case experienced multiple episodes of breakthrough hemolysis, despite being on a high dose of ravulizumab. This breakthrough hemolysis was associated with the development of atrial fibrillation, a potentially inflammatory triggering event that may also further deregulate the complement cascade. As exemplified by this patient case, breakthrough hemolysis can result in marked fatigue that affects the patient's quality of life.

Delayed or missed dosing represents another scenario in which complement inhibitor monotherapy may not be sufficient to maintain complete protection against hemolysis in PNH. Optimal efficacy of the terminal C5 inhibitors is best achieved by maintaining consistent trough levels to fully suppress MAC formation. Even brief lapses in dosing can allow complement activity to reemerge, particularly in the context of underlying stress, inflammation, or other triggering events. In the case of missed dosing, drug concentrations fall below inhibitory thresholds, making GPI-deficient RBCs again vulnerable to destruction.

Dual complement inhibition targeting both the early (proximal) and late (terminal) steps of the complement cascade may prevent not only MAC-mediated intravascular hemolysis but also upstream C3 fragment deposition that drives extravascular hemolysis. By blocking both mechanisms, combined therapy can yield more complete control of hemolysis, reducing and preventing breakthrough hemolysis to increase the likelihood of transfusion independence and improved outcomes in patients.

Danicopan as Add-On Therapy to C5 Inhibitors

Danicopan was evaluated in the ALPHA trial, a double-blind, international, randomized phase 3 study conducted in adult patients with PNH and clinically significant extravascular hemolysis while being treated with either

eculizumab or ravulizumab for at least 6 months.[37] Clinically significant extravascular hemolysis was defined as a hemoglobin level of 9.5 g/dL or less and an absolute reticulocyte count of 120 × 10^9/L or greater.

After a 4-week screening period, patients were randomly assigned in a 2-to-1 ratio to receive either danicopan or placebo in addition to their background therapy (ravulizumab or eculizumab) for a 12-week treatment period. At week 12, the study was unblinded; patients who had been in the placebo arm were switched to danicopan plus ravulizumab or eculizumab, whereas patients assigned to danicopan continued danicopan while remaining on ravulizumab or eculizumab for an additional 12-week treatment period. After this second period was completed, patients could enter a 2-year extension study.

The primary efficacy endpoint, change from baseline to week 12 in hemoglobin concentration, was significantly improved in the danicopan plus ravulizumab or eculizumab arm compared with the placebo plus ravulizumab or eculizumab arm (least squares mean [LSM], 2.94 g/dL vs 0.50 g/dL; difference of 2.44 g/dL; 95% CI, 1.69 -3.20; *P*<.0001). Patients in the danicopan arm achieved clinically meaningful improvements in hemoglobin concentration as early as week 2 (difference of 2.15 g/dL; *P*<.0001).

Compared with placebo, the addition of danicopan to ravulizumab or eculizumab also resulted in significant improvements across all 4 key secondary endpoints measured. At week 12, 60% of patients in the danicopan arm compared with 0% in the placebo arm had a hemoglobin increase of at least 2 g/dL in the absence of transfusion (adjusted difference, 47%; 95% CI, 29-65; *P*<.0001). Additionally, 83% of danicopan-treated patients compared with 38% of placebo-treated patients achieved transfusion avoidance (adjusted difference, 42%; 95% CI, 23-61; *P*=.0004). Fatigue, measured by the FACIT-Fatigue score, was significantly and clinically improved with the addition of danicopan vs placebo (LSM change from baseline to week 12 was 7.97 vs 1.85; difference, 6.12; 95% CI, 2.33-9.91; *P*=.0021). Finally, the LSM change in absolute reticulocyte count at 12 weeks was –83.8 × 10^9/L with danicopan compared with 3.5 × 10^9/L with placebo (difference, –87.2 × 10^9/L; 95% CI, –117.7 to –56.7; *P*<.0001).

Treatment-emergent adverse events occurred in 71% of the danicopan plus ravulizumab or eculizumab arm, compared with 63% of the placebo plus ravulizumab or eculizumab arm; none were grade 4 or 5 in severity. Among treatment-emergent adverse events that occurred in at least 5% of the danicopan arm, headache was most frequently reported (10% in the danicopan arm and 4% in the placebo arm).

Long-Term Data with Danicopan

The ALPHA had a second treatment period (unblinded 12 weeks following the initial blinded 12 weeks), after which patients could enter a 2-year long-term extension study (Table 3).[38] Of the 86 patients who were treated in the initial blinded treatment period, 82 entered the unblinded second treatment period, and 80 subsequently entered the long-term extension study. For patients who switched from placebo to danicopan at week 12, by week 24 notable improvements were observed across multiple outcomes that were maintained through week 72, including mean hemoglobin level, the proportion of patients with a 2 g/dL increase in hemoglobin or higher, absolute reticulocyte count, the proportion of patients achieving transfusion avoidance, and FACIT-Fatigue scale scores.

Addressing Both Intravascular and Extravascular Hemolysis With Combination Therapy

In PNH, dual complement pathway therapy has the potential to address the full spectrum of complement-mediated RBC lysis, with simultaneous targeting of both proximal and terminal complement activity. Although terminal pathway inhibition via C5 inhibitors is an effective mechanism to prevent MAC-mediated intravascular hemolysis, it does not inhibit upstream complement activity, leaving patients vulnerable to C3b opsonization-driven extravascular hemolysis. Newer proximal complement inhibitors, including the C3 inhibitor pegcetacoplan, were developed with the intention of preventing both intravascular and extravascular hemolysis. Severe episodes of breakthrough hemolysis in the context of a complement activating event are rare, but have been reported in patients with PNH receiving pegcetacoplan.[35] Such reports highlight the fact that pharmacodynamic breakthrough events, particularly unexpected infections, for patients on shorter acting proximal complement inhibition can result in dramatic hemolysis due to the larger PNH clone sizes in these patients.

Dual therapy, offering combined proximal (via factor D) and terminal (via C5) inhibition, has demonstrated durable control of both intravascular and extravascular hemolysis with a low incidence of breakthrough hemolysis through 72 weeks.[38] This approach can reduce the residual hemolytic burden that persists despite monotherapy.

A potential advantage of dual therapy over either terminal pathway or proximal monotherapy lies in its ability to provide a multilayered inhibition of complement. By acting at 2 critical points in the complement cascade, dual therapy may achieve robust complement blockade thus limiting both mechanisms of RBC destruction. Specifically, combining the factor D inhibitor danicopan with

a standard C5 inhibitor (eculizumab or ravulizumab) resulted in a very low rate of breakthrough events (6 events per 100 patient-years in the long-term study), which were generally not severe and managed successfully without major complications.[38]

Thus, dual therapy may provide a mechanism to protect patients from severe hemolysis in the context of triggering events (eg, inflammation, infection, etc) that might break through single complement blockade. This was seen in our patient case, when even after an episode of pneumonia, AB's hemoglobin level was maintained. Another case at our clinic demonstrated this effect. A young woman with a history of aplastic anemia and subsequent PNH initially presented with Budd-Chiari syndrome and splenomegaly. Despite treatment with eculizumab and then ravulizumab, she continued to experience significant breakthrough hemolysis, often triggered by recurrent urinary tract infections and chronic cholecystitis, leading to repeated hospitalizations, hemoglobin drops, and episodes of acute kidney injury. Given her refractory course and ineligibility for allogeneic transplant, she was managed with dual therapy (ravulizumab plus pegcetacoplan [not FDA approved]) prior to the availability of danicopan, which provided only partial control. Following cholecystectomy and improved infection prophylaxis, her disease stabilized, and she was transitioned from pegcetacoplan to danicopan in combination with ravulizumab, which has resulted in reduced breakthrough events.

In situations where there is patient reluctance to self-inject, concern for noncompliance with self-delivered therapy, social or insurance issues that might impact drug access, or lifestyle demands travelling to remote places for extended periods of time, ravulizumab is preferred to eculizumab or pegcetacoplan. Such patients are also eligible for single-agent therapy with iptacopan, the oral factor B inhibitor. The availability of multiple complement pathway inhibitors, with both oral and parenteral modes of administration, with different dosing windows and comparable efficacy represents an enormous improvement in treatment options for patients with PNH. For many years, such patients were tied to intravenous infusions every 2 weeks; now they can select from several effective and convenient therapies all of which offer excellent likelihood of hemolysis control.

Lifestyle considerations including the freedom to travel, patient preference for one mode of administration over another, and clinical circumstances all contribute to the selection of which agent is best for an individual patient. In those with frequent complement activation events that are likely to put them at risk for breakthrough hemolysis, or in those who are at risk for therapy noncompliance, combination therapy with danicopan and ravulizumab might be an ideal solution. This approach offers improved hemoglobin levels afforded by proximal complement inhibition with backup protection against the risk for severe breakthrough hemolytic crisis.

Back to the Clinic

AB, a 70-year-old woman, first presented to our clinic in 2017 seeking a second opinion for recently diagnosed PNH. Her diagnosis followed years of mild thrombocytopenia and macrocytosis. After developing anemia and a pulmonary embolism, she began eculizumab in 2016 with substantial improvement in LDH (from 5400 to 561 U/L) and stabilization of hemoglobin around 10 g/dL. These findings indicated her intravascular hemolysis was well controlled. She also recognized that many prediagnosis symptoms—fatigue, myalgias, palpitations, dysphagia, abdominal pain, and dark urine—had resolved with treatment.

She transitioned to ravulizumab in 2018 and remained stable until April 2022, when new-onset atrial fibrillation triggered a decline in hemoglobin with marked fatigue. Despite cardioversion, dose intensification, and shortened dosing intervals, her hemoglobin remained low and bilirubin elevated, signifying significant and ongoing breakthrough extravascular hemolysis.

In June 2024, shortly after approval of the factor D inhibitor danicopan, she initiated dual therapy with ravulizumab and danicopan. Within 2 weeks, her hemoglobin rose to 12.8 g/dL and her bilirubin normalized, with sustained benefit even after pneumonia. This improvement allowed deescalation of ravulizumab dosing and significantly improved her quality of life, enabling travel and resolution of shortness of breath. Additionally, the dual inhibition with added danicopan can provide a buffer in the case of missed or delayed ravulizumab dosing, particularly in the context of her travel. The patient is still on therapy as of this publication.

Disclosures

Dr Griffiths discloses the following conflicts of interest.

- ***Advisory Boards/Honoraria (payments to EAG)**: AbbVie/Genentech Pharmaceuticals, Alexion Pharmaceuticals/AstraZeneca Rare Disease, Apellis Pharmaceuticals, Cogent Biosciences, Geron Pharmaceuticals, PicnicHealth, Servier Pharmaceuticals, Taiho Oncology*
- ***Research Funding (to Roswell Park)**: Astex Pharmaceuticals/Taiho Oncology, Alexion/AstraZeneca Rare Disease/Apellis Pharmaceuticals, Blueprint Medicines, Bristol Myers Squibb, Genentech Inc, NextCure Inc, Celldex Therapeutics*
- ***CME/Honoraria (to EAG)**: American Society of Hematology, AAMDS International Foundation, MDS Foun-*

dation, MediCom Worldwide, MedscapeLive, Physicians' Education Resource, Vera & Joseph Dresner Foundation, VJHemOnc

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