Literature review

How to appropriately manage patients with paroxysmal nocturnal hemoglobinuria

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Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematologic disorder, with a reported worldwide prevalence ranging from 1 to 1.5 cases per million people to 3.81 cases per 100,000 individuals.[1] It can occur at any age but is most commonly diagnosed in the third decade of life. The pathogenesis of PNH involves a somatic mutation in the *PIGA* gene, an X-linked gene responsible for the biosynthesis of glycosylphosphatidylinositol (GPI) anchors. This defect results in a deficiency of GPI-anchored proteins, particularly the complement regulatory proteins CD55 (decay-accelerating factor, DAF) and CD59 (membrane inhibitor of reactive lysis, MIRL). Under normal physiological conditions, the alternative complement pathway is continuously activated at a low level to provide immune surveillance against pathogenic organisms. In the absence of complement regulatory proteins, uncontrolled complement activation leads to excessive formation of membrane attack complexes (MACs).[2,3] These MACs cause red blood cell (RBC) membrane lysis and intravascular hemolysis, thereby predisposing patients to significant morbidities such as chronic kidney disease, pulmonary hypertension, and both arterial and venous thrombosis, ultimately increasing mortality. Before the advent of complement inhibitors, approximately 20% to 35% of patients with PNH died within five to ten years of diagnosis.[4]

The diagnosis of PNH is challenging. Its rarity often leads to a lack of awareness among physicians, resulting in low specialist referral rates, with only one-third of patients being referred to a hematologist.[5] Differentiating PNH from other hemolytic anemias is essential; for instance, a positive family history suggests hereditary hemolytic anemia, while RBC autoagglutination or the presence of schistocytes indicate autoimmune hemolytic anemia or microangiopathic hemolytic anemia, respectively. PNH symptoms are varied and non-specific, including fatigue, weakness, dyspnea, abdominal or back pain, and up to 40% of patients lack a history of the classic dark urine. Consequently, diagnosis is often delayed, with approximately 40% of patients experiencing delays in treatment of more than two years.[5] Furthermore, some cases of PNH are associated with bone marrow failure syndromes and may present with anemia accompanied by an inappropriate reticulocyte response, leukopenia and/or thrombocytopenia, adding to the diagnostic complexity for both general practitioners and hematologists unfamiliar with the disease.[6]

The only curative treatment for PNH is allogeneic hematopoietic stem cell transplantation (HSCT). However, this therapy is associated with substantial treatment-related morbidity and mortality and is therefore reserved for patients with additional indications, such as concurrent severe aplastic anemia (AA). Studies have shown that patients with PNH who undergo HSCT in the presence of thrombosis have significantly lower overall survival than those without thrombosis.[7]

Currently, complement inhibitors are the treatment of choice for patients with PNH presenting with hemolysis or thrombosis. The first such agent approved

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by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2007 was eculizumab, a monoclonal antibody targeting complement component C5. Treatment with eculizumab leads to sustained improvements in intravascular hemolysis, transfusion independence, reduced thrombotic events, improved quality of life, and prolonged survival. However, because the drug requires intravenous infusion every two weeks indefinitely, it imposes a considerable treatment burden on patients.[8] Approximately 40% of patients treated with eculizumab continue to have hemoglobin (Hb) levels below 10 g/dL, and around 30% remain transfusion-dependent. This has led to the development of novel anti-C5 inhibitors with longer half-lives, more consistent C5 inhibition, and comparable efficacy, thereby improving patient convenience.[9] In addition, proximal complement inhibitors have been developed to address the issue of C3-mediated extravascular hemolysis (EVH) that occurs in some patients receiving C5 inhibitors[4] (Table 1).

This article presents three illustrative cases of PNH, highlighting key clinical insights into diagnosis, management of thrombotic complications, and the development of anemia and iron overload following treatment with C5 inhibitor.

Case Scenario 1: A 23-year-old woman with aplastic anemia progressing to PNH

A 23-year-old woman presented with recurrent bruising, gum bleeding, fatigue and dizziness for approximately one year. She was unable to donate blood because of anemia. Physical examination revealed mild pallor without jaundice, hepatosplenomegaly or lymphadenopathy. Laboratory investigations showed: Hb 9.1 g/dL, hematocrit (Hct) 26.6%, mean corpuscular volume (MCV) 105 fL, white blood cell (WBC) count 3,860/μL (neutrophils 39%, lymphocytes 50%; absolute neutrophil count 1,505/μL), platelet (PLT) count 31,000/μL and reticulocyte count 1.1%. Bone marrow examination demonstrated hypocellularity without dysplastic morphology. Based

Table 1 Approved complement inhibitors[3,4,10]

Drugs	Target	Route and frequency of administration	Efficacy
Eculizumab	C5	Intravenous route every 2 weeks	Compared to placebo, showed improved IVH, transfusion avoidance, thrombotic events, QoL and survival
Ravulizumab	C5	Intravenous route every 8 weeks	Compared to eculizumab, showed non-inferiority efficacy with fewer BTH and better QoL
Crovalimab	C5 and C5 polymorphisms (cannot bind to eculizumab or ravulizumab)	Subcutaneous route every 4 weeks	Compared to eculizumab, showed non-inferiority efficacy in hemolysis control, transfusion avoidance and BTH with better QoL
Pegcetacoplan	C3	Subcutaneous route twice weekly	Compared to eculizumab, showed superiority efficacy in IVH, C3-mediated EVH, Hb levels, transfusion avoidance and QoL
Iptacopan	Factor B	Oral route twice daily	Compared to anti-C5, showed superiority efficacy in Hb levels, transfusion avoidance and QoL
Danicopan (combined with an anti-C5 inhibitor)	Factor D	Oral route three times daily	Compared to anti-C5 alone, showed superiority efficacy in Hb levels, transfusion avoidance and QoL

BTH, breakthrough hemolysis; EVH, extravascular; Hb, hemoglobin; IVH, intravascular hemolysis; QoL, quality of life

on these findings, she was diagnosed with non-severe AA and treated with oxymetholone 50-100 mg/day combined with prednisolone 40-60 mg orally on alternate days. Her symptoms improved, and eight months later, a complete blood count (CBC) revealed Hb 12.9 g/dL, Hct 39.4%, MCV 106 fL, WBC 3,900/μL (neutrophils 40.6%, lymphocytes 52.7%; absolute neutrophil count 1,583/μL) and PLT count 43,000/μL.

One year later, the patient developed worsening anemia and noted dark brown urine in the morning. She also occasionally experienced dysphagia. Laboratory results revealed Hb 8.5 g/dL, Hct 27.5%, MCV 115 fL, WBC 3,400/μL (neutrophils 53.9%, lymphocytes 40.2%; absolute neutrophil count 1,832/μL), PLT count 102,000/μL, reticulocyte count 10%, total bilirubin 1.5 mg/dL (0-1.2), direct bilirubin 0.4 mg/dL (0-0.3), aspartate aminotransferase (AST) 96 U/L (5-40), alanine aminotransferase (ALT) 39 U/L (5-41) and lactate dehydrogenase (LDH) 3,000 U/L (135-225). Given the clinical features suggestive of intravascular hemolysis, flow cytometric analysis for CD59 was performed, revealing deficiency of GPI-anchored proteins in 27.6% of erythrocytes and 82.5% of granulocytes. The patient was diagnosed with PNH. Furthere details of her disease progression and treatment are described and discussed in Case Scenario 2.

Discussion of Case Scenario 1

The clinical presentation of PNH is characterized by a classic triad of intravascular hemolysis, thrombosis and cytopenia. The presence of cytopenias beyond anemia suggests concomitant bone marrow failure, such as AA. The significant overlap between PNH and AA is not coincidental, given the rarity of both disorders.[11] AA is an autoimmune disorder in which autoreactive cytotoxic T lymphocytes selectively destroy hematopoietic stem cells expressing GPI anchors. Consequently, GPI-deficient clones escape immune-mediated destruction and persist within the bone marrow of patients with AA. These PNH clones may subsequently expand, potentially through the acquisition of additional somatic mutations–such as in *JAK2*, *TET2* or *STAC3*–which confer leukemogenic properties.[12,13] Patients with AA may develop PNH over time, and conversely, individuals with PNH may later develop AA.[11]

Data from the International PNH Registry–the largest global observational study of patients with PNH–collected information on 4,948 individuals diagnosed with PNH or harboring PNH clones (> 0.01%) between 2007 and 2017. Approximately 53% of these patients had a prior history of AA. This figure is likely underestimated, as patients with mild AA may remain undiagnosed and unreported.[14]

Flow cytometric testing for PNH should be performed in patients presenting with one or more of the following clinical features: intravascular hemolysis, acquired bone marrow failure syndromes or unprovoked thrombosis (Table 2).

Currently, flow cytometry is the gold standard for detecting PNH cells because of its superior sensitivity and specificity compared with traditional assays.[17,18] Two major techniques are used, as described below.

1. **Low-sensitivity assays** (gating by forward scatter and side scatter) such as flow cytometric analysis for CD59, can identify PNH clones ≥ 1%. These assays are suitable for diagnosing classical PNH with overt hemolysis, as such patients typically have mean granulocyte clone size sexceeding 70%.[19]

2. **High-sensitivity assays** (gating by forward scatter and specific antigen markers), such as fluorochrome-labeled aerolysin (FLAER), detect PNH clones on granulocytes and monocytes. In addition, high-sensitivity red blood cell assays can detect PNH clones on erythrocytes. These techniques are capable of identifying PNH clones as small as 0.01%. They are particularly valuable for detecting small PNH clones in subclinical PNH–defined by the absence of clinical and laboratory evidence of hemolysis and thrombosis–often associated with bone marrow failure syndromes. Current diagnostic recom-

Table 2 Indications for PNH flow cytometry testing[15,16]

Clinical characteristics	With any of the following
Intravascular hemolysis	- Negative direct Coombs' test without red blood cell abnormalities on peripheral blood smear - Symptoms of smooth muscle dystonia due to reduced nitric oxide (e.g., dysphagia, abdominal pain, erectile dysfunction) - Iron deficiency with evidence of urinary iron loss or without obvious causes - Renal dysfunction with hemoglobinuria/hemosiderinuria or with unexplained causes - Cytopenias involving other cell lines
Evidence of bone marrow failure	- Aplastic anemia - Hypoplastic myelodysplastic syndrome or refractory cytopenia with unilineage dysplasia - Unexplained cytopenias
Unprovoked thrombosis	- Hemolysis - Cytopenias - Thrombosis at unusual sites (e.g., intra-abdominal veins, cerebral veins, dermal veins) - Poor response to anticoagulant therapy

mendations using high-sensitivity assays require the demonstration of deficiencies in at least two different GPI-anchored proteins across two cell lineages (granulocytes, monocytes, or erythrocytes).

One study reported that 60% of patients with AA and 15% of those with low-risk myelodysplastic syndrome (MDS) have detectable PNH clones, most of which are < 1%.[20] However, other studies have reported mean granulocyte clone sizes of up to 11% in these populations.[19] Therefore, in institutions lacking high-sensitivity assays, low-sensitivity assays may still be considered.

Currently, testing for CD59 on RBCs is recommended because CD59 stains more brightly than CD55, allowing better discrimination type I (normal GPI-anchored protein expression) from type II (partial GPI-anchored protein deficiency) and type III (complete GPI-anchored protein deficiency) PNH RBCs. Accordingly, when low-sensitivity assays are used, testing for CD59 on both red and white blood cells is advised. Reliance on RBC testing alone can lead to misinterpretation, such as false positives in congenital CD55 or CD59 deficiencies on RBCs or in autoimmune diseases associated with acquired CD55 or CD59 deficiency on RBCs. Additionally, PNH clone sizes measured on RBCs are often lower than those observed on WBCs because abnormal RBCs are preferentially destroyed by hemolysis or diluted by transfused RBCs.[17]

Case Scenario 2: A 35-year-old woman with PNH who developed thrombosis

A 35-year-old woman had been diagnosed with PNH for six years earlier. At the time of diagnosis, flow cytometric analysis for CD59 revealed deficiency of GPI-anchored proteins in 27.6% of erythrocytes and 82.5% of granulocytes. Six years later, repeat testing demonstrated GPI-anchored protein deficiency in 8.75% of erythrocytes and 96.51% of granulocytes. Her Hb levels ranged from 6 to 8 g/dL, with markedly elevated LDH levels between 3,300 and 7,400 U/L (135-225). She required transfusion of two units of packed red cells every six weeks and was receiving oxymetholone 50-100 mg/day and prednisolone 40-60 mg on alternet days.

The patient was admitted with severe epigastric pain. Physical examination revealed mild epigastric tenderness, and the D-dimer level was markedly elevated at 3,486 ng/mL (< 500). Computed tomography (CT) of the abdomen showed multiple thromboses involving branches of hepatic vein, the superior and inferior mesenteric veins and long-segment small bowel wall thickening, consistent with small bowel ischemia with splanchnic venous thrombosis. She underwent emergency exploratory laparotomy for suspected bowel gangrene; however, no gangrenous bowel was identified intraoperatively. Postoperatively, she was treated with

enoxaparin, resulting in resolution of abdominal pain and normalization of the D-dimer level to 400 ng/mL. After four months of anticoagulation with enoxaparin, she was transitioned to warfarin, with a target International Normalized Ratio (INR) of 2 to 3.

One month later, she again developed severe epigastric pain. Repeat abdominal CT revealed progression of hepatic vein thrombosis, and the D-dimer level increased to > 10,000 ng/mL. Warfarin was discontinued and enoxaparin was restarted, resulting in improvement of her abdominal symptoms. Eight months later, she presented with bilateral leg edema, abdominal distension, and discomfort. Physical examination revealed hepatomegaly with ascites. Abdominal CT showed progression of hepatic vein and intrahepatic inferior vena cava thrombosis. She was diagnosed with liver decompensation secondary to progressive Budd–Chiari syndrome (BCS). Subsequently, the patient developed recurrent spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatorenal syndrome, and ultimately died of bacteremia with septic shock.

Discussion of Case Scenario 2

Before the introduction of eculizumab, thrombosis accounted for 22% to 67% of deaths in PNH,[21] with approximately 20% of patients dying from BCS.[22] Between 29% and 44% of patients with PNH experience at least one thrombotic episode, predominantly at venous sites (80% to 85%) and less frequently in arterial sites (15 to 20%). Approximately 20% of patients have multisite thromboses.[21] Common sites of venous thrombosis include the lower extremity veins, intra-abdominal veins (hepatic, portal, splenic, and mesenteric), cerebral veins, and dermal veins. Arterial thromboses most commonly involve cerebral arteries, followed by coronary arteries.[23,24] Patients with PNH have a markedly higher risk of thrombosis than the general population, even among those with mild symptoms. The risk increases substantially in patients with a granulocyte clone size > 50%, who exhibit a 10-year cumulative thrombosis incidence of 44%, compared with 5.8% in those with smaller clone sizes.[25] Other risk factors include LDH > 1.5× the upper limit of normal (ULN) and a history of prior thrombosis.[26]

It is now well established that complement activation is the major driver of thrombosis in PNH.[27,28] Activated C5 can stimulate coagulation factors, and coagulation factors can, in turn, activate complement.[29,30] Multiple mechanisms contribute to thrombosis, including platelet activation, decreased nitric oxide bioavailability, complement-mediated intravascular hemolysis and impairment of fibrinolytic system.[24] Therefore, anticoagulation alone is insufficient for managing thrombosis in PNH. Despite treatment with anticoagulants or antiplatelet agents, patients may still develop new or progressive thromboembolic events.[22,31,32]

A study comparing thrombotic events in the same patients before and after eculizumab therapy demonstrated a significant reduction in thrombosis incidence, from 10.61 events per 100 patient-years before treatment to 0.62 events per 100 patient-years after treatment ($p < 0.001$), corresponding to a relative risk reduction of 94%.[23]

Management of acute thrombosis in PNH involves initiating parenteral anticoagulation, as in patients without PNH, and starting a complement inhibitor as soon as possible to prevent further thrombotic progression. For long-term management, warfarin is an option, with a target INR of 2-3. Currently, there are no large prospective studies evaluating the use of direct oral anticoagulants (DOACs) for PNH-related thrombosis, although their use has been reported in some countries.[4,26]

For patients with thrombosis who are not treated with complement inhibitors, lifelong anticoagulation is generally recommended. In contrast, for patients receiving complement inhibitors, practice varies. Some physicians recommend indefinite anticoagulation, whereas others suggest continuing anticoagulation for three to six months in combination with complement inhibition, followed by discontinuation once thrombotic symptoms resolve and LDH levels decrease < 1.5× ULN, indicating adequate

control of intravascular hemolysis. This approach has not been standardized and should be individualized through shared decision-making with the patient.[24]

At present, no clear guidelines exist regarding primary prophylaxis of thrombosis with warfarin or antiplatelet agents in high-risk patients who are not receiving complement inhibitors. This is due to the frequent coexistence of thrombocytopenia resulting from bone marrow failure, which increases bleeding risk, as well as the recognized limitations of anticoagulation alone in preventing thrombosis in PNH. These limitations are underscored by the diseases' pathophysiology and the occurrence of thrombotic events despite therapeutic anticoagulation.[26,33] Patients receiving complement inhibitors do not require primary thrombosis prophylaxis, as complement blockade itself significantly reduces thrombotic risk.

Case Scenario 3: PNH receiving anti-C5 therapy with worsening anemia and iron overload

A 46-year-old Thai man was diagnosed with PNH eight years earlier. Flow cytometric analysis for CD59 demonstrated the absence of GPI-anchored proteins in 74% of erythrocytes and 99% of granulocytes. The patient required transfusion of one to two units of packed red cells every two to three months. Initial laboratory evaluation revealed the following: Hb 6.5 g/dL, Hct 22.4%, MCV 114 fL, WBC count 9,800/μL (neutrophils 61%, lymphocytes 30%), PLT count 279,000/μL, absolute reticulocyte count 420,000/μL, a negative direct antiglobulin test (DAT), LDH 12,000 U/L (135-225), and ferritin 230 ng/mL. He was treated with folic acid 5 mg/day, ferrous sulfate 200 mg/day, and prednisolone 50-60 mg orally on alternate days. Subsequently, ravulizumab 3,300 mg intravenously every eight weeks was initiated and continued for five years. Following initiation of anti-C5 therapy, his symptoms improved markedly: fatigue resolved, urine color normalized from dark to yellow, work performance improved, and corticosteroids were discontinued. The patient continued folic acid and ferrous sulfate supplementation.

Despite significant clinical improvement, he remained anemic, with a baseline Hb 8-10 g/dL, absolute reticulocyte count 400,000-500,000/μL. The DAT became positive (3+), with reactivity for anti-C3c and anti-C3d but negative for IgG, IgA, and IgM. LDH levels ranged from 230 to 490 U/L (135-225), and transfusion requirements decreased to one to two episodes per year. Blood transfusions were administered during periods of worsening anemia accompanied by fatigue, shortness of breath, and cola-colored urine. These episodes sometimes occurred approximately one week before the scheduled ravulizumab infusion, without an identifiable trigger (e.g., fever, vaccination, or surgery). At other times, anemia worsened during febrile illnesses or infection, with Hb decreasing to 6.1-6.5 g/dL and LDH rising to twice the ULN.

After three years of ravulizumab therapy, the patient developed transaminitis, with AST levels of 70-90 U/L (5-40) and ALT levels of 130-170 U/L (5-41), without evidence of viral hepatitis or drug-induced liver injury. Further evaluation revealed marked iron overload, with a serum ferritin level of 10,892 ng/mL, transferrin saturation 88% and MRI demonstrating hepatosplenomegaly with hepatic and splenic iron deposition. Ferrous sulfate was discontinued, and iron chelation therapy with deferiprone was initiated and continued for two years. At follow-up, serum ferritin had decreased to 1,753 ng/mL, and liver enzyme levels had normalized.

Discussion of Case Scenario 3

Complement inhibitors effectively suppress intravascular hemolysis and increase hemoglobin levels in patients with PNH. However, persistent anemia may still occur through three main mechanisms: C3-mediated EVH, pharmacokinetic breakthrough hemolysis (BTH) and pharmacodynamic BTH (Table 3).

1. C3-mediated EVH

C3-mediated EVH occurs in nearly all patients treated with C5 inhibitors such as eculizumab, ravulizumab, or crovalimab. C5 inhibition prevents cleavage of C5 into C5a and C5b, thereby blocking MAC formation. How-

Table 3 Comparison of persistent anemia mechanisms in PNH patients receiving complement inhibitors

Classification	C3-mediated EVH	Pharmacokinetic BTH	Pharmacodynamic BTH
Underlying mechanism	- Occurs with C5 Inhibitors - Upstream complement activity: leading to C3 fragment deposition on PNH RBCs	- Occurs with C5 or proximal inhibitors - Insufficient drug trough in short half-life drugs	- Occurs with C5 or proximal inhibitors - Complement-amplifying conditions (e.g., infection, vaccination, surgery, pregnancy) overcome drug blockade
Site of hemolysis	EVH	IVH	IVH
Onset	Insidious: begins 1 week after initiating C5 inhibiton	Predictable: occurs near the end of the dosing interval	Acute: occurs shortly after a complement-amplifying conditions
Laboratory Findings	- Mild to moderate anemia - Reticulocytosis - Positive DAT - LDH < 1.5×ULN	- Moderate to severe anemia - LDH ≥ 1.5-2×ULN - Subtherapeutic drug levels	- Moderate to severe anemia - LDH ≥ 1.5-2×ULN - Therapeutic drug levels
Associated Risk	Iron overload	Potential for thrombosis	- Potential for thrombosis - Organ damage from acute intravascular hemolysis
Management	- Switch to a proximal Inhibitor (pegcetacoplan, iptacopan) - Add a proximal inhibitor (danicopan) to the C5 inhibitor	- Increase dose or shorten interval (eculizumab) - Switch to a longer-acting C5 inhibitor (ravulizumab, crovalimab) - Add a C5 inhibitor to proximal Inhibitor (pegcetacoplan, iptacopan, danicopan)	- Treat the underlying trigger - Maintain scheduled complement inhibitor - Transfuse as needed

BTH, breakthrough hemolysis; DAT, direct antiglobulin test; EVH, extravascular hemolysis; IVH, intravascular hemolysis; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RBCs, red blood cells; ULN, upper limit of normal

ever, upstream complement activation persists, leading to accumulation of C3 fragments on PNH RBCs. These opsonized RBCs are subsequently cleared by hepatic and splenic macrophages, resulting in EVH.[24] C3 deposition can be detected as early as one week after treatment initiation and typically stabilizes by 10 to 12 weeks.[34,35] C3 deposition correlates inversely with Hb levels and directly with absolute reticulocyte count.[34] Clinically, patients may present with chronic mild-to-moderate anemia, reticulocytosis and a positive DAT, while LDH remains < 1.5×ULN, indicating the absence of ongoing intravascular hemolysis. As a result of residual EVH, approximately 25% to 50% of patients receiving eculizumab experience symptomatic anemia,[36] and 18% to 35% remain transfusion-dependent.[34,37-39] Only 37% of patients achieve Hb levels > 11 g/dL.[34]

To address EVH, novel proximal complement inhibitors have been developed to block C3 activation in the alternative complement pathway. These include pegcetacoplan (C3 inhibitor), iptacopan (factor B inhibitor), and danicopan (factor D inhibitor). Corticosteroids are generally ineffective,[40] with only a single case report demonstrating a favorable response.[41] In addition, three case reports involving patients who remained transfusion-dependent despite eculizumab therapy described reduced transfusion requirements or transfusion independence following selective splenic artery embolizations or splenectomy. However, these interventions carries long-term risks, including thrombosis and infection.[36]

Chronic anemia suppresses hepcidin, leading to increased intestinal iron absorption. In addition, C5 inhibition prevents urinary iron loss associated with

intravascular hemolysis. Together, these mechanisms predispose patients to iron overload, even in non-transfused patients, through a process analogous to that observed in non-transfusion-dependent thalassemia. Routine iron supplementation is therefore not recommended in patients receiving complement inhibitors. Regular monitoring of serum ferritin is advised, and iron chelation therapy should be initiated when iron overload is identified.[36,42-44] However, due to the rarity of PNH and the limited number of patients treated with C5 inhibitors, no evidence-based threshold for iron parameters have been established to guide the initiation of chelation therapy.

BTH refers to recurrent intravascular hemolysis in patients who previously achieved adequate control of hemolysis (LDH < 1.5×ULN) with terminal or proximal complement inhibitors, followed by recurrence of PNH-related hemolytic or thrombotic symptoms and an increased LDH level > 1.5-2×ULN.[45] BTH is classified into pharmacokinetic and pharmacodynamic subtypes.

2. Pharmacokinetic BTH

Pharmacokinetic BTH results from insufficient drug levels, typically near the end of the dosing interval, and is more common with shorter half-life agents such as eculizumab or certain proximal complement inhibitors. This leads to predictable hemolysis prior to the next scheduled dose (e.g., around day 10 in a 14-day eculizumab dosing cycle). In phase 3 clinical trials (ALXN301[8] and ALXN302[46]), ravulizumab demonstrated lower rates of BTH compared with eculizumab (4% vs 10.7% and 0% vs 5.1%, respectively), attribute to its approximately fourfold longer half-life and more sustained complement inhibition. Management strategies include increasing the eculizumab dose, shortening the dosing interval or switching to a longer-acting anti-C5 agent such as ravulizumab or crovalimab.[24] For patients receiving proximal complement inhibitors (pegcetacoplan, iptacopan, danicopan), the addition of an anti-C5 agent may be considered.

3. Pharmacodynamic BTH

Pharmacodynamic BTH occurs despite adequate circulating drug levels and is typically triggered by complement-amplifying conditions such as infection, vaccination, pregnancy, or major surgery. These conditions increase C3b deposition on RBCs, promoting conformational changes in C5 that resemble C5b and are no longer effectively inhibited by C5 inhibitors. Alternatively, high levels of C3b may generate high-affinity C5 convertases capable of cleaving C5 even when it is bound to a C5 inhibitor.[47,48]

Proximal complement inhibitors may also fail to prevent pharmacodynamics BTH, as certain triggers-particularly infections-can activate the classical complement pathway and bypass C3 to directly activate C5 (so-called "C3 bypass activation of C5").[49,50] Management involves prompt treatment of the underlying trigger, transfusion when clinically indicated, close monitoring for thrombotic complications, and continuation complement inhibition as scheduled. Importantly,complement inhibitor therapy must not be interrupted, even during infection-an essential counseling point for both patients and treating physicians.[45]

Compared with C5 inhibitors, proximal complement inhibitors (pegcetacoplan, iptacopan, danicopan) may be associated with more severe BTH when C3 inhibition is incomplete. This is because incomplete inhibition of a single C3 molecule can result in formation of one C5 convertase capable of generating multiple MAC complexes, whereas incomplete inhibition of one C5 molecule results in formation of only a single MAC.[51] Management of BTH in patients receiving proximal inhibitors includes increasing the dose or dosing frequency or adding a C5 inhibitor.[45]

In Case Scenario 3, the patient's persistent anemia despite treatment with ravulizumab was attributable to all three mechanisms:

- **C3-mediated EVH:** Baseline anemia with reticulocytosis and a positive DAT indicating C3-coated

RBCs, along with a marked reduction in LDH levels, consistent with well-controlled intravascular hemolysis.

- **Pharmacokinetic BTH:** Worsening symptoms occurring approximately one week before the next scheduled infusion, suggesting declining drug levels toward the end of the dosing interval.
- **Pharmacodynamic BTH:** Exacerbation of hemolysis during the episodes of infection or fever due to heightened activation of the complement cascade.

Conclusion

Although PNH is classified as a benign hematologic disorder, it can lead to devastating complications associated with substantial morbidity and mortality. Treatment with complement inhibitors has fundamentally altered the natural history of the disease by improving quality of life and significantly extending overall survival. Nevertheless, optimal patient outcomes require a comprehensive understanding of the efficacy, limitations and adverse reactions of complement inhibitors, as well as appropriate management of PNH-related complications and the provision of individualized supportive care.

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