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EXPERT OPINION

Optimizing Care in Patients with Paroxysmal Nocturnal Hemoglobinuria: Managing Suboptimal Response and Uncontrolled Disease

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Abstract: The treatment of patients with PNH has been revolutionized by terminal complement C5 inhibitors, which control intravascular hemolysis and thrombosis, reduce morbidity and mortality, and improve life expectancy to that approaching people without PNH. In recent years, approval of proximal inhibitors provides clinicians and patients with additional treatment options such that patients who have residual anemia, ongoing symptoms affecting quality of life, or are intolerant to terminal C5 inhibition now have options to optimize treatment. Here, we provide five questions to guide clinicians involved in the care of patients with PNH in assessing treatment response on terminal inhibitors and identifying patients who might benefit from therapy adjustments. We also provide insights into additional treatment options.

Keywords: proximal complement inhibitor, C5 inhibitor, intravascular hemolysis, extravascular hemolysis, breakthrough hemolysis, treatment response

Introduction

Complement inhibitor treatment has revolutionized the care of patients with paroxysmal nocturnal hemoglobinuria (PNH). Historically, the 10-year mortality rate with best supportive treatment was approximately 35%.[1] Survival rates have, however, improved dramatically since the approval of the complement component 5 (C5) inhibitor, eculizumab.[2] A 20-year longitudinal study involving 509 patients treated primarily with eculizumab demonstrated survival rates comparable to age- and sex-matched controls without PNH, excluding those receiving treatment for bone marrow failure.[3] Along with improved survival, use of C5 inhibitors like eculizumab, and the more recent ravulizumab and crovalimab, has enhanced quality of life (QoL), reduced transfusion requirements, alleviated symptoms, and significantly lowered thrombotic risk.[4–6] Despite these advances, some patients continue to experience PNH-related symptoms and incomplete responses to C5 inhibitors. This awareness, coupled with an expanded understanding of the complement system, has spurred the development of treatments with unique complement targets and various modes of delivery. In the context of the availability of these new treatments, clinicians must identify patients with inadequate responses to first-line therapy, recognize the place in therapy of newer agents, and optimize treatment strategies. This paper provides guidance to clinicians on optimizing the care of patients with PNH receiving complement inhibitor therapy. It outlines approaches to evaluating treatment response, determining when and how to switch between C5 inhibitors and proximal inhibitors, and identifying when to consider add-on therapy. This guidance document adopts a Canadian perspective, which predominantly places C5 inhibitors as first line therapy.

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Pathophysiology

PNH occurs when a somatic mutation in the phosphatidylinositol glycan-A (*PIGA*) gene in hematopoietic cells prevents expression of glycosylphosphatidylinositol (GPI) anchor proteins, which are required to tether certain complement regulatory proteins to cell surfaces.[7] The resulting absence of two such GPI-dependent proteins, CD55 (decay accelerating factor, DAF) and CD59 (membrane inhibitor of reactive lysis, MIRL), leaves hematopoietic cells vulnerable to the unregulated activity of the complement alternative pathway.[7] This vulnerability results from the spontaneous activation of complement component 3 (C3), known as "C3 tickover", and the subsequent formation of C3 and C5 convertases on the cell surface. As a result, complement-mediated damage occurs through the membrane attack complex (MAC) and other mechanisms.[8–10] Unchecked complement activation on the red blood cell (RBC) surface leads to intravascular hemolysis (IVH).[9–11] The consequences of IVH include anemia, fatigue, renal dysfunction, and smooth muscle dystonic symptoms due to nitric oxide depletion, such as dysphagia, abdominal pain, pulmonary hypertension, and erectile dysfunction. Additionally, patients with PNH are at increased risk of thromboembolic events through multiple mechanisms.[12] Before the availability of complement inhibitors, thromboses affected up to 40% of patients, often occurring in atypical locations like intra-abdominal, cerebral, or dermal veins. More than 50% of PNH-related deaths were attributed to thrombotic events. With C5 inhibition, the risk of thrombosis and death now appears to be similar to that of age-matched controls without PNH.[13]

Diagnosis

PNH often affects individuals in the third or fourth decade of life, at a time when they are balancing demands of work and family. Timely diagnosis and effective management are important for maintaining QoL and preventing catastrophic outcomes related to the disease. However, diagnosis of PNH is often delayed due to its diverse, non-specific symptoms, leading patients to consult multiple healthcare providers without receiving a diagnosis. In one study, 24% of patients experienced a diagnostic delay of over 5 years, 79% consulted more than one physician, and 38% saw 5 or more physicians before being diagnosed.[14] A recent Canadian paper similarly noted that patients saw a median of 4 healthcare providers before diagnosis, and experienced a median delay of 168 months from initial symptom onset to referral and eventual diagnosis.[15]

The Canadian PNH Network recommends considering a diagnosis of PNH in 5 clinical scenarios, summarized by the acronym CATCH (Figure 1): unexplained cytopenia, aplastic anemia / myelodysplasia, unexplained thromboembolism, Coombs' (direct antiglobulin test, DAT)-negative hemolysis, and hemoglobinuria.[16] The presence of multiple aspects of the CATCH acronym in a same patient may further increase the pre-test probability of PNH.[17] The initial evaluation

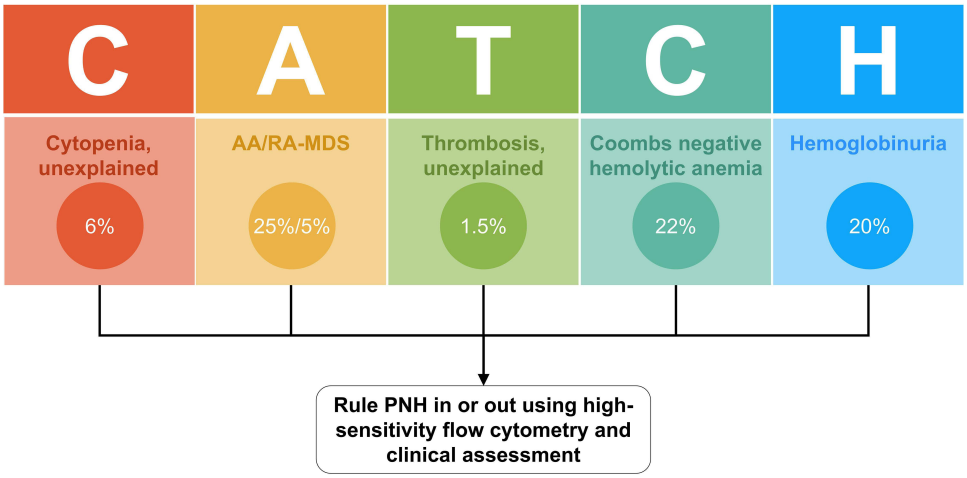

Figure 1 Clinical scenarios warranting the consideration of PNH.[16] Percentages represent the proportion of PNH cases attributable to the clinical scenario.[18]
Abbreviations: AA, aplastic anemia; RA-MDS, refractory anemia myelodysplastic syndromes.

involves detailed history taking, physical examination, and laboratory evaluation to assess the extent and severity of disease. Imaging may be indicated for certain patients.[16,18]

Definitive testing for PNH relies on high-sensitivity flow cytometry of peripheral blood to confirm the loss of GPI-anchored proteins on erythrocytes and leukocytes (granulocytes and monocytes), and to quantify the PNH clone size. The larger clone between neutrophils and monocytes should be used to define the PNH clone size.[16,19] Due to the shorter life span of hemolyzing PNH RBCs relative to granulocytes and the dilutional effect of transfusions, the apparent clone size in RBCs is often underestimated.[19] To address this limitation, an assay incorporating CD71 testing has been developed to improve the assessment of PNH clones in more immature erythroid cells (which are less prone to hemolysis), preventing potentially misleading results from mature RBCs alone.[20] However, CD71 testing is not widely utilized, as immature red cell markers were not taken into account by the 2018 International Clinical Cytometry Society Consensus Guidelines for the detection of PNH by flow cytometry.[21]

Patients at the highest risk of thrombosis are those who have a history of thrombosis, 30% or more GPI-negative granulocytes, or a lactate dehydrogenase (LDH) ratio of at least 1.5 times the upper limit of normal (ULN) along with two or more high disease activity (HDA) clinical criteria (hemoglobin Hb<100 g/L, abdominal pain, dyspnea, dysphagia, fatigue, hemoglobinuria, or male erectile dysfunction).[22]

Treatment Goals

The primary treatment goal for patients with PNH is the blockade of terminal complement activation and control of IVH, thereby preventing thrombosis, the leading cause of death and a major source of morbidity. Controlling IVH is also essential to reduce complications such as anemia, hemoglobinuria, impaired renal function, pulmonary hypertension, and other manifestations. Improvement of overall survival has been achieved with C5 blockade and remains a central goal of novel therapeutics. Additional treatment goals include transfusion-independence, improvement of hemoglobin, and alleviating fatigue and residual symptoms related to nitric oxide depletion. Patient preferences related to treatment tolerability and minimizing treatment burden must also be considered.

Current Standard of Care for Treatment of PNH

Supportive care is crucial for all patients with PNH; this includes hematinic supplementation with folic acid, as well as correction of vitamin B12 and iron deficiencies. Patients with severe anemia may need blood transfusions, and iron chelation may eventually be required to address transfusion-associated iron overload. Other supportive treatments include analgesics to manage abdominal pain and anticoagulants at prophylactic or therapeutic doses for patients at high risk of thrombosis if they cannot promptly begin complement-directed therapy. Although practices vary, anticoagulation use as primary prevention is often considered in patients with a granulocyte clone >30%, those meeting two or more HDA criteria with an LDH ≥1.5 times the ULN, or those with a history of thrombotic events.[22] Some experts, however, rely solely on a granulocyte clone threshold of ≥50%.[23] Select patients with smaller clones who appear to be at higher risk of thrombosis could also be considered for prophylactic anticoagulation. Shared-care decision-making is important to weigh the potential benefits against the risks of bleeding on a case-by-case basis.

As in many countries, complement inhibition is the standard of care in Canada for the treatment of patients with hemolytic PNH.[11] First-line treatment options include the intravenously administered C5 inhibitors eculizumab and ravulizumab, as well as crovalimab, which is administered subcutaneously following an initial intravenous (IV) loading dose (see Treatment Algorithm, Figure 2). These therapies specifically and effectively inhibit IVH, thereby reducing the risk of complications such as thrombotic events and end-organ damage, and ultimately improving survival.[2–4]

As treatment with C5 inhibitors blocks MAC-mediated membrane damage, PNH erythrocytes are then able to circulate without being intravascularly hemolyzed. The lack of CD55 on the surface permits membrane accumulation of C3b and its split products, driving receptor-mediated extravascular hemolysis (EVH) in the reticuloendothelial system, including the liver and spleen.[9,10] Quantification of C3d opsonization on RBCs by flow cytometry is being evaluated as a surrogate marker for EVH, but is not universally available.[24–26] In a retrospective analysis of 56 patients with PNH receiving eculizumab, 73% had significant C3 deposition on RBCs, measured by flow cytometry. Optimal responders to C5 inhibition had the lowest proportion of C3-coated RBCs.[27] Up to 35% of patients treated with C5 inhibitors remain

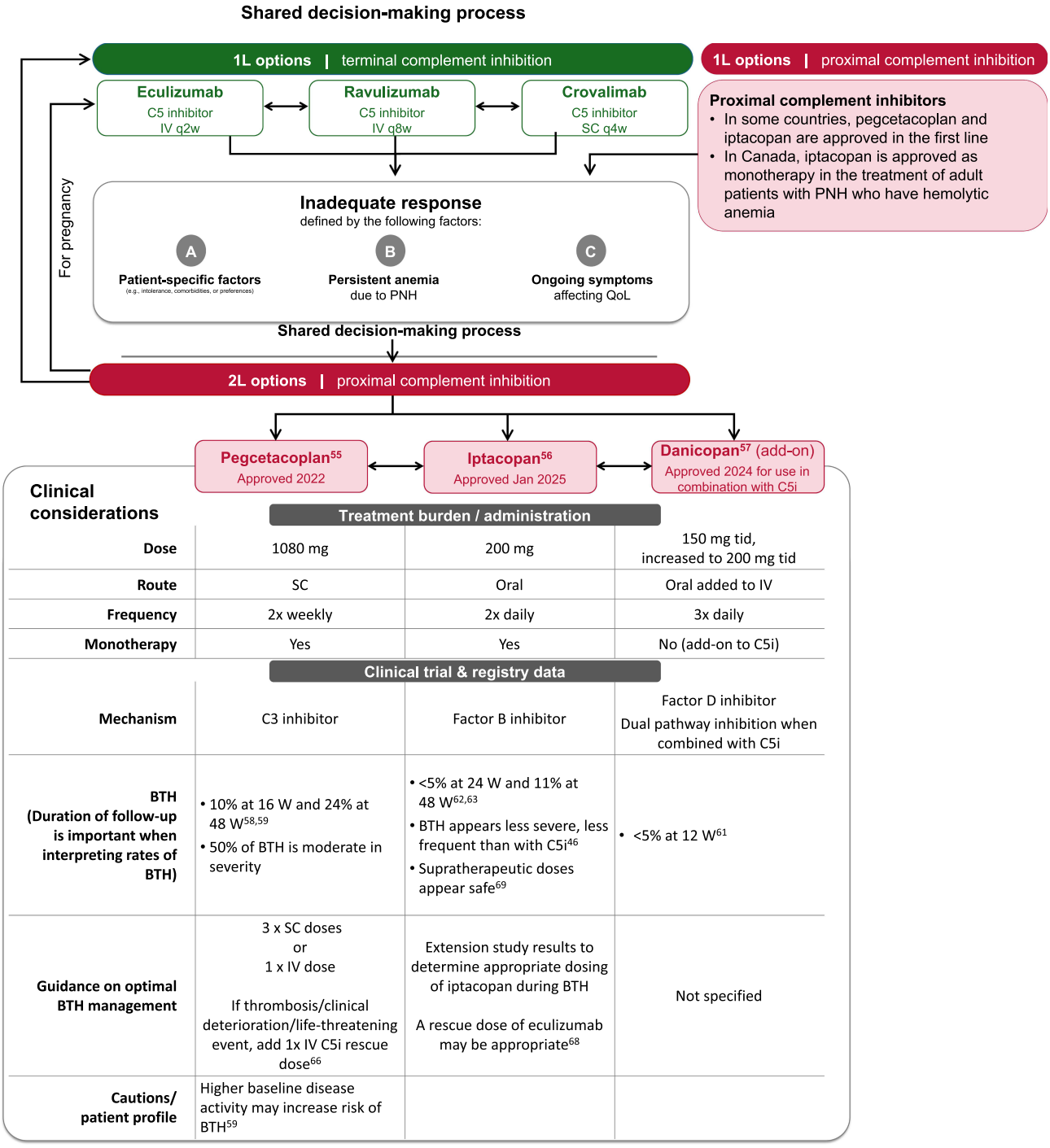

Figure 2 Treatment algorithm to guide management of patients with PNH.
Abbreviations: 1L, first line; 2L, second line; BTH, breakthrough hemolysis; C5i, complement factor 5 inhibitor; IV, intravenous, PNH, paroxysmal nocturnal hemoglobinuria; QoL, quality of life; SC, subcutaneous; tid, three times daily; W, week.

transfusion-dependent, partly due to iatrogenic EVH,[10,28] and approximately 40% have been shown to have either a minor or partial hematologic response to eculizumab, leaving a considerable proportion of patients on C5 inhibitors who may benefit from optimized treatment.[28]

For patients who have an inadequate response to C5 inhibitors (see Section on Evaluating treatment response to C5 inhibitors), consideration is given to either switching to a proximal inhibitor (pegcetacoplan or iptacopan) or, for those on

ravulizumab or eculizumab, adding a factor D inhibitor. The reimbursement landscape for proximal inhibitors is evolving, and in some countries, the proximal complement inhibitors pegcetacoplan and iptacopan are approved as first-line therapy.

The only curative therapy for PNH is allogeneic stem cell transplant. Given the significant risk of transplant-related morbidity and mortality, however, as well as the availability of complement inhibitors in many countries, transplant is not generally considered except when indicated for progressive marrow failure or in countries without access to complement inhibitors.[11]

Since terminal complement function is crucial for immune defense against encapsulated bacteria, patients on complement-directed therapy are at risk of severe infections, notably life-threatening meningococcal infections. Patients with PNH must be vaccinated at the time of initiating treatment with complement inhibitors against meningococcus, with regular boosters every three to five years. Prophylactic antibiotics should also be given for at least 14 days following the initial vaccine doses, with extended coverage considered based on individual risk factors and tolerance. With the use of proximal inhibitors (discussed later), protective measures have broadened to include vaccination against pneumococcus and *H. influenzae* as well. All patients should be given "pill-in-pocket" antibiotics to keep with them to take at the first onset of meningitis symptoms, with instructions to then seek urgent medical attention at their closest emergency department.

C5 Inhibitors for First-Line Treatment

The Canadian PNH Network recommends initiating therapy with a C5 inhibitor in patients with a leukocyte PNH clone >10%, laboratory evidence of significant IVH (LDH ≥1.5 x ULN) and at least one of: symptomatic anemia (regardless of transfusion dependence status), thrombosis, renal insufficiency, pulmonary hypertension or insufficiency (NYHA criteria grade III), or severe abdominal pain.[16] Hemoglobin is a variable parameter from patient to patient and its value does not always correlate with disease severity or symptom burden. Treatment decisions should be guided by a comprehensive clinical assessment, including LDH levels, transfusion requirements, thrombotic risk, and symptom burden.

Eculizumab

Eculizumab was the first targeted therapy to demonstrate efficacy in treating PNH and is reviewed in detailed elsewhere.[16] In the pivotal phase-3 trials, TRIUMPH and SHEPHERD, eculizumab reduced hemolysis and transfusion-dependence, improved QoL, and extended overall survival.[2,29–32] The standard induction regimen for eculizumab in adults involves weekly dosing of 600 mg IV for the first four weeks, followed by an increased dose of 900 mg IV in the fifth week, and every two weeks thereafter.[30,32,33] Long-term safety investigations revealed that eculizumab was well tolerated, toxicities were not cumulative, and occurrence of adverse events decreased over time.[34] As with all C5 inhibitors, there is a risk of *Neisseria meningitidis* infection, with an incidence rate of 0.42 per 100 patient-years, necessitating appropriate vaccination and antibiotic use as appropriate.[34]

Ravulizumab

Ravulizumab is a second-generation C5 inhibitor; it is an analog of eculizumab, binding to the same epitope on C5.[35] It differs from eculizumab by the substitution of four amino acids, resulting in an ability to offload C5 in acidifying endosomes and greater recirculation via the neonatal Fc receptor (FcRn). The latter allows for an extended terminal half-life, with a dosing interval of every 8 weeks (or every 4 weeks if weight is <20kg) compared to every 2 weeks for eculizumab.[36–38] Its efficacy was demonstrated in two phase 3 trials (Study 301 and Study 302). The trials found that ravulizumab was non-inferior to eculizumab in terms of LDH improvement or normalization and transfusion avoidance, with results numerically favoring ravulizumab.[36,37] Overall survival rates for patients receiving ravulizumab are comparable to those for patients on eculizumab.[4] A post hoc analysis of these studies showed that ravulizumab was associated with a lower risk of pharmacokinetic breakthrough hemolysis (BTH) compared to eculizumab. Suboptimal C5 inhibition as measured by elevated free C5 (≥5 μg/mL) was associated with 50% (11 of 22) of the BTH events occurring in patients treated with eculizumab and none of the 5 BTH events occurring in patients treated with ravulizumab.[39]

Crovalimab

Crovalimab is a next-generation C5 inhibitor which, like ravulizumab, is designed to have an extended half-life allowing for every-4-week subcutaneous dosing through recirculation via the FcRn.[40] Crovalimab strongly binds C5 in the neutral pH environment of the blood and then rapidly offloads it in the acidic pH of endosomes.[41] Crovalimab targets a unique C5 epitope, resulting in efficacy regardless of C5 R885H polymorphism, a genetic variant seen in some patients of Asian ethnicity, associated with refractoriness to eculizumab and ravulizumab.[41]

In COMMODORE-1, a phase 3, multicenter, open-label, randomized trial, patients aged ≥18 years with LDH ≤1.5 x ULN and receiving eculizumab for ≥24 weeks were randomized 1:1 to receive crovalimab (weight-based tiered dosing; weekly subcutaneous doses for 4 weeks followed by dosing every 4 week thereafter) or continue their treatment with eculizumab.[42] The primary objective was to evaluate safety and tolerability of crovalimab. Exploratory efficacy endpoints (insufficient statistical power for significance to be established) included maintenance of hemolysis control, transfusion avoidance, episodes of BTH, and hemoglobin stabilization. Rates of all-grade and serious adverse events were numerically higher with crovalimab than with eculizumab. Crovalimab was non-inferior to eculizumab in achieving exploratory outcomes. Four of 39 patients (10.3%) receiving crovalimab and 5 of 37 (13.5%) receiving eculizumab experienced a BTH event, most of which were attributed to a complement-amplifying condition (CAC). Transient type III immune complex reactions occurred in 7 patients in the crovalimab arm as a result of switching from another C5 inhibitor that binds a different C5 epitope; all were deemed mild or moderate except for one patient who experienced a severe event.

COMMODORE-2 was a phase 3, open-label, multicenter trial consisting of two parts: a randomized arm of crovalimab versus eculizumab in complement inhibitor-naïve patients ≥18 years of age with clone size ≥10%, LDH ≥2 x ULN, and one or more PNH-related sign or symptom in the past 3 months; and a descriptive, non-randomized arm exploring crovalimab in pediatric patients <18 years of age.[43] Patients received crovalimab (n=134) as per a weight-based, tiered dosing regimen. The loading doses comprised of one weight-based IV infusion (weight 40 to <100 kg: 1000 mg; weight ≥100 kg: 1500 mg) on day 1, followed by 4 once-weekly subcutaneous injections on day 2 through week 4 (340 mg for all weights). Subcutaneous maintenance dosing (weight 40 to <100 kg: 680 mg; weight ≥100 kg: 1020 mg) was given every 4 weeks starting at week 5, and until week 25. The co-primary endpoints were hemolysis control (LDH ≤1.5 x ULN) from week 5 to week 25 and transfusion avoidance from baseline to week 25. Crovalimab was non-inferior to eculizumab for both co-primary endpoints. Hemolysis control occurred in 79.3% and 79.0% of patients treated with crovalimab and eculizumab, respectively, and transfusion avoidance was achieved in 65.7% and 68.1% of patients, respectively. Non-inferiority of crovalimab to eculizumab was also reported for the secondary endpoints of BTH and hemoglobin stabilization. Fourteen of 134 patients (10.4%) receiving crovalimab and 10 of 69 (14.5%) receiving eculizumab experienced a BTH event. The proportions of patients with stabilized hemoglobin (defined as avoidance of a ≥20 g/L decrease in hemoglobin from baseline in the absence of transfusion) were 63.4% with crovalimab and 60.9% with eculizumab. Both groups reported clinically meaningful improvements in fatigue. Infusion-related reactions were the most commonly reported adverse events with crovalimab (15.6%) and eculizumab (13.0%). The rates of treatment-related serious adverse events were low, reported in 3.0% of patients treated with crovalimab and 1.4% of patients treated with eculizumab.

Evaluating Treatment Response to C5 Inhibitors

Control of IVH is the main goal of anticomplement treatment for patients with PNH, assessed based on LDH levels, improvement in PNH symptoms, reduced transfusion needs, and protection from thrombosis. Once initial IVH control is achieved, monitoring for BTH and clinically significant anemia is critical. Additionally, it is important to consider the treatment burden (eg route of administration and adverse event profile) and potential impact of treatment scheduling on the patient's QoL.[9]

Response to anticomplement treatment with a C5 inhibitor can be evaluated based on the algorithm proposed by Kulasekararaj et al.[24] The overall approach is summarized in Figure 2. In addition, we propose the following 5 questions as a practical and comprehensive approach to evaluate treatment response in patients on C5 inhibitor therapy:

1. Is the patient tolerating treatment well and are they adherent?
2. Is there remaining IVH after initiating C5 inhibitor therapy?
3. Are there episodes of pharmacokinetic (PK) or pharmacodynamic (PD) BTH?
4. Is there evidence of EVH?
5. Are there concomitant causes of anemia?

Is the Patient Tolerating Treatment Well and Are They Adherent?

Patient preferences and intolerance of certain side effects are always important considerations when evaluating treatment response, as both may affect adherence. Biweekly IV dosing of eculizumab imparts a high treatment burden on patients. In the Study 302 extension, 93% of patients preferred ravulizumab over eculizumab, citing infusion frequency, ability to plan activities, and overall QoL as the most important factors in their decision.[44] Burden of illness despite treatment is also an important consideration. A United States (US) patient survey reported that most patients treated with eculizumab (88.6%; n=31/35) or ravulizumab (74.7%; n=65/87) still reported fatigue.[9] Some patients are affected by needle phobia and are therefore intolerant of treatments involving injections; this could be of particular concern with self-administration. Support to ensure proper self-administration of subcutaneous therapies is important for adherence and disease control. Oral agents may be preferred over parenteral agents in selected patients. With oral therapies, consideration should be given to the effects of twice-daily- or three-times-daily dosing frequency on adherence.

Is There Remaining IVH After Initiating C5 Inhibitor Therapy?

In addition to improvement in PNH symptoms, control of IVH is generally demonstrated with LDH levels <1.5 x ULN drawn just prior to the next dose. If the LDH is <1.5 x ULN after 6 weeks, therapy is continued and LDH can be regularly assessed thereafter to ensure that IVH remains controlled.[24] Typically, in presence of ongoing IVH, haptoglobin levels remain undetectable. Reticulocytosis commonly persists, assuming that the patient does not have bone marrow failure. Increased bilirubin (predominantly unconjugated) may remain elevated.[26]

If LDH remains ≥1.5 x ULN after 6 weeks of treatment, a 50% hemolytic complement assay (CH50) should be used, where available, to measure terminal complement activity. Low CH50 activity (ie <10%) indicates effective terminal complement blockade, suggesting that the elevated LDH may indicate something other than IVH and warrants investigation. If available, testing for LDH isoenzymes can help pinpoint the source of elevation.[24]

If LDH is ≥1.5 x ULN and the CH50 assay indicates incomplete terminal complement blockade, C5 inhibitor dosage should be increased. Approximately 20% of patients receiving eculizumab require dose increases beyond the product label recommendation.[24] Where available, switching from eculizumab to ravulizumab can achieve more consistent C5 blockade.[36]

Truly uncontrolled PNH despite C5 inhibitor treatment is rare. In a minority of people of Asian descent (3.2% among Japanese patients with PNH and <0.01% worldwide), a C5 polymorphism—p.Arg885His—renders them refractory to C5 inhibition with eculizumab or ravulizumab.[24] A patient should be assessed for C5 polymorphism if LDH is unchanged after 6 weeks with persistent incomplete terminal complement blockade, as demonstrated by a CH50 >10%. These patients are candidates for crovalimab, due to its distinct C5 binding site, or a complement inhibitor with an alternative target.[11,41]

Are There Episodes of PK or PD BTH?

BTH refers to a return of IVH after a period of control during which LDH was maintained <1.5 x ULN. It can be pharmacokinetic (ie due to inadequate complement inhibition) or pharmacodynamic (ie due to a CAC).[45]

PK BTH typically occurs near the end of each dosing interval and is identified by cyclical return of symptoms along with increasing LDH (≥1.5 x ULN) and CH50. If available, measurement of free C5 would show elevation above 0.5 μg/mL.[39] Increasing the dose or shortening the dosing interval can address PK BTH.[10,12] Switching from eculizumab to ravulizumab may also address this.[6] Bodó et al published European consensus recommendations for switching from C5 anticomplement inhibitors in special patient populations. In the patients who experience recurrent PK BTH after ≥3 months of C5 inhibitor

treatment, they recommend increasing the dose or shortening the dose interval of eculizumab, switching to ravulizumab, or switching to a proximal inhibitor.[6]

There is no standardized definition of BTH, though it is often a safety outcome in clinical trials.[46] A phase 3 trial comparing eculizumab and ravulizumab defined BTH as "one or more new or worsening symptoms or signs of IVH (fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia [hemoglobin <100 g/L], major adverse vascular event including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥2 x ULN after prior LDH reduction to <1.5 x ULN while on therapy".[39] More recently, an expert panel defined PD BTH as "an acute drop of hemoglobin of ≥15 g/L compared to the patient's latest assessment in the presence of newly elevated LDH ≥1.5 x ULN, caused by a known CAC (eg infection, vaccination, or surgery)".[47] The expert panel further agreed on a severity classification of BTH events (mild, moderate, severe) using both symptoms and extent of hemoglobin drop.[47] The consensus management of PD BTH due to a CAC included shortening the dosing interval of eculizumab or ravulizumab if the patient experiences symptoms or more severe decreases in hemoglobin (ie ≥25 g/L) during the second half of the standard dosing interval (ie second week with eculizumab, or the last four weeks with ravulizumab). Efforts to mitigate the risk of the CAC should be undertaken. After resolution of the event, a return to the original dosing is recommended.[47] Fattizzo et al recently reviewed the definition and rate of BTH from clinical trials.[46] The authors emphasized the importance of the duration of follow-up when evaluating the rate of BTH.[46]

Is There Evidence of EVH?

In the presence of persistent anemia with or without transfusion dependence and despite LDH <1.5 x ULN and suppressed CH50, iatrogenic EVH induced by C5 inhibition must be considered.[11,24] Provided there is effective hematopoiesis, patients with EVH will often have an elevated absolute reticulocyte count.[28] Elevated bilirubin (particularly unconjugated) and decreased haptoglobin will also be observed.[26] A positive DAT for C3d is a clear indicator of EVH, though it is not always present.[24] Typical changes in monitoring parameters used to differentiate IVH and EVH are summarized in Table 1.

Table 1 Treatment Evaluation and Response Parameters to Differentiate IVH, EVH, and BTH.[24,26]

Typical Monitoring Parameters	**IVH**	**EVH**	**BTH (PK)**	**BTH (PD)**
LDH	≥1.5 x ULN	<1.5 x ULN	Symptoms / monitoring parameters consistent with IVH Cyclical - occurs toward end of dosing period	Symptoms / monitoring parameters consistent with IVH Coincides with CAC (eg pregnancy, infection, vaccination, surgery, physical trauma)
DAT	Negative	DAT with anti-C3d: ±		
Hb	↓↓	↓		
Bilirubin	↑	↑↑ (higher in EVH usually)		
Haptoglobin	↓	↓		
Reticulocyte count (in absence of concomitant bone marrow failure)	↑↑	>150 x 10^9/L		
Other	PNH symptoms Hemoglobinuria detected by urinalysis	Symptoms from anemia (ie fatigue, malaise)		

Notes: ↓, Reduced; ↓↓, Markedly Reduced; ↑, Elevated; ↑↑, Markedly Elevated.

Abbreviations: BTH, breakthrough hemolysis; CAC, complement-amplifying condition; DAT, direct antiglobulin test; EVH, extravascular hemolysis; Hb, hemoglobin; IVH, intravascular hemolysis; LDH, lactate dehydrogenase; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal.

For those with clinically significant EVH (eg with symptomatic anemia ± transfusion-dependence), consideration should be given to switching to a proximal inhibitor.[10,11] Proximal complement inhibitors can significantly improve hematologic response by preventing the activation of C3 on RBCs, thereby blocking both IVH and EVH.[10]

Debureaux et al presented a revised classification of hematologic response to anticomplement therapies based on evidence from 160 patients with PNH receiving eculizumab (55% had classic PNH, 67% were receiving blood transfusions before starting therapy, and median eculizumab treatment duration was 5.8 years [range, 0.5–14.5]) (see Figure 3).[28] During the last 6 months of follow-up on eculizumab, 21% of patients had achieved complete response (ie transfusion independence and no anemia). However, despite achieving complete response, 11% experienced BTH and 17% had evidence of EVH, demonstrating the importance of continued monitoring and treatment optimization. A good response, defined as transfusion independence with mild anemia (hemoglobin 100–120 g/L), was achieved in 40%. Partial response, defined as persistent anemia (80–100 g/L) with occasional transfusions (≤2 in 6 months), occurred in 27% of patients, and minor response (transfusion-dependent anemia) was seen in 12%. In general, the lower the response category, the more both BTH and EVH appeared to contribute (see Figure 3). The authors suggested that patients with minor or partial response are candidates for treatment optimization to normalize hemoglobin, improve QoL, and achieve transfusion-independence.

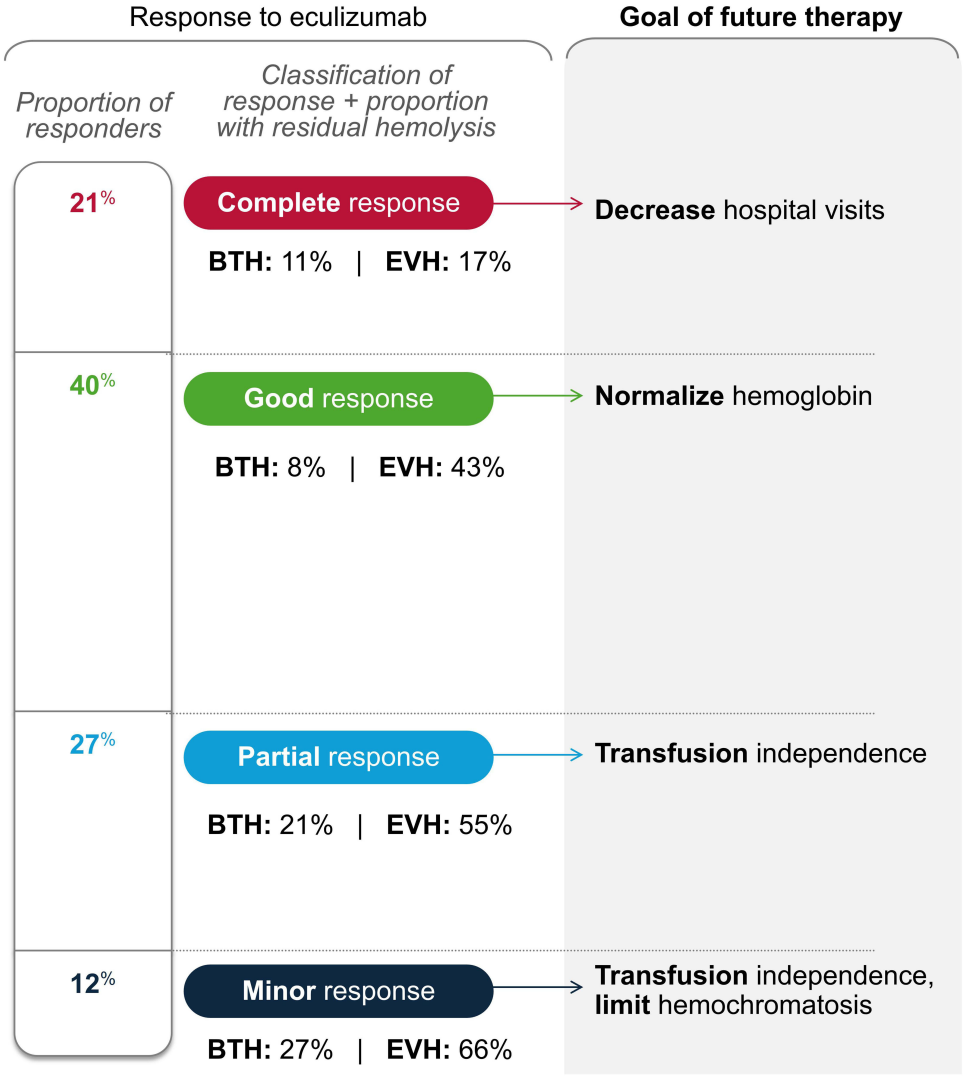

Figure 3 Classification of response to eculizumab with proportion of patients with BTH and EVH and proposed goal for future therapy. Adapted from Debureaux PE et al. Bone Marrow Transplant. 2021;56(10):2600–2602.[28]
Abbreviations: BTH, breakthrough hemolysis; EVH, extravascular hemolysis.

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Patients with a good response may also be candidates for treatment optimization depending on symptoms, patient preference, and local reimbursement criteria, provided that control of IVH is maintained.[28,48,49]

Are There Confounding Factors for Symptomatic Anemia?

In a patient with PNH who has otherwise been optimized on treatment, the presence of persistent anemia requires further investigation beyond that related to hemolysis. In those with low or inappropriately normal reticulocyte count, assessment for bone marrow failure syndromes (eg aplastic anemia, MDS, or acute myeloid leukemia) is required.[50] Hematinic deficiencies (eg folate, vitamin B12, iron) can be addressed with supplementations. Relative erythropoietin deficiency may occur in patients with chronic kidney disease and can be addressed with exogenous erythropoietin.[6,24] Patients with anemia and elevated reticulocytes must also be assessed for the possibility of bleeding (particularly if on anticoagulation or with concomitant thrombocytopenia), hypersplenism, or ineffective erythropoiesis.[24]

In summary, patients with PNH are complex and evaluating treatment response to C5 inhibitors is multifactorial. It is often difficult to pinpoint a clear source of residual signs and symptoms despite evidence of terminal complement blockade and optimized therapy. Individualized treatment is essential. Consideration is given to switching to second-line therapy in patients who have persistent fatigue, need either episodic or chronic transfusions, or are otherwise symptomatic such that it affects their activities of daily living.

Proximal Complement Inhibitors

More than half of patients with PNH treated with C5 inhibitors still have mild to moderate symptoms, most do not achieve a normal hemoglobin, and 39% remain transfusion-dependent.[28,51,52] In a cross-sectional survey of 122 patients with PNH in the US who had been receiving C5-targeted therapy for ≥3 months, 87.5% of those on eculizumab and 82.9% of those on ravulizumab had anemia (hemoglobin ≤120 g/L).[9] Notably, 88.6% and 74.7% of patients in these respective groups continued to report symptoms of fatigue. Transfusions were required in 52.5% of patients receiving eculizumab and 22.6% of those receiving ravulizumab.[9] Healthcare resource utilization and cost for patients with PNH receiving eculizumab remains high.[53,54] One claims study of 151 patients receiving eculizumab for PNH in the US demonstrated that patients who are transfusion dependent had 3 times as many PNH-related hospitalizations, higher medical costs, and more absenteeism compared to non-transfusion-dependent patients.[54]

Patients with PNH who are treated with C5 inhibitors and have persistent anemia, inadequate response, ongoing symptoms, or reduced QoL, or who are intolerant to C5 inhibitors, may benefit from switching treatment to proximal inhibitors. There are currently three proximal inhibitors approved for use in Canada, each with a different target: pegcetacoplan, a C3 inhibitor; iptacopan, a Factor B inhibitor; and danicopan, a Factor D inhibitor. Pegcetacoplan, given as a subcutaneous infusion twice weekly (starting dose), is approved for patients who have an inadequate response to or are intolerant of C5 inhibitors.[55] Iptacopan, a twice-daily oral agent, is approved for use as monotherapy in the treatment of adult patients with PNH who have hemolytic anemia.[56] Danicopan, a thrice-daily oral agent, is approved as an add-on to C5 blockade (eculizumab or ravulizumab) for patients with signs and symptoms of EVH.[57]

Proximal inhibitors are intended to prevent both IVH and EVH, the latter by preventing C3 deposition on erythrocytes.[10] As reviewed below, all three proximal inhibitor strategies have shown superiority in terms of hemoglobin improvement compared to C5 inhibition alone. Findings from the pivotal trials of pegcetacoplan, iptacopan, and danicopan are summarized in Table 2. Although not unique to proximal inhibitors, the issue of BTH has become a central focus with these agents. BTH might be more severe with proximal complement inhibitors than with C5 inhibitors partly due to downstream amplification of incomplete complement inhibition and a larger surviving RBC population from the PNH clone susceptible to IVH;[10,47] though this was not universally seen in clinical trials. Six-month BTH rates have been reported to be 10%–15% for eculizumab, crovalimab, and pegcetacoplan, and <5% for ravulizumab, iptacopan, and danicopan combined with anti-C5 therapy.[46] With longer follow-up, however, the rates of BTH may change; the 3-year rate of BTH with pegcetacoplan is reported to be 28%.[46] More experience is needed to understand the long-term incidence and event severity of BTH for proximal inhibitors in the real-world setting.

Table 2 Pivotal Trials of Proximal Complement Inhibitors

Clinical Trial	Patient Population and Intervention	Definition of Suboptimal Response for Inclusion	Primary Outcome(s), Intervention vs Control	BTH Rates and Severity, Intervention vs Control
PEGASUS (NCT03500549) Pegcetacoplan Phase 3, multicenter, RCT[58]	Adults with PNH on stable doses of eculizumab for ≥3 months before screening Subcutaneous pegcetacoplan vs eculizumab monotherapy for 16 weeks	Hb <105 g/L	Change in Hb level from baseline to week 16: 23.7 g/L vs -14.7 g/L (mean difference, 38.4 g/L; 95% CI 23.3–53.3 g/L; $p<0.001$)	10% (4/41) vs 23% (9/39) at 16 weeks 3 of 4 patients with BTH on pegcetacoplan discontinued (severity: n=1 severe, n=2 moderate) vs none with eculizumab
PEGASUS Pegcetacoplan post hoc analysis of hemolysis events[59]	Adverse events of hemolysis reported by investigators in patients treated with pegcetacoplan during the 16-week randomized controlled period of the PEGASUS trial and the 32-week open-label period	N/A	N/A	19 patients (24%) experienced 26 hemolysis adverse events during pegcetacoplan therapy at 48 weeks 14 of 26 hemolysis events (54%) were moderate in severity and 17 of 26 (65%) were manageable without pegcetacoplan discontinuation
PRINCE (NCT04085601) Pegcetacoplan Phase 3, multicenter, RCT[60]	Complement inhibitor-naïve adults with PNH Subcutaneous pegcetacoplan vs continued supportive care only for 26 weeks (open label)	Hb <105 g/L	Coprimary endpoints: Hb stabilization from baseline to week 26: 85.7% vs 0% (difference, 73.1%; 95% CI, 57.2–89.0; $p<0.0001$) Change from baseline to week 26 in LDH levels: −1870.5 vs 400.1 (difference, −1407.4 U/L; 95% CI −2113.4 to −827.3; $p<0.0001$)	No BTH reported in either arm at 26 weeks
ALPHA (NCT04469465) Danicopan Phase 3, randomized, double-blind RCT[61]	Patients with PNH with clinically significant EVH despite treatment with C5 inhibitors (eg eculizumab) for ≥6 months Oral danicopan vs placebo, added on to ravulizumab or eculizumab, for 12 weeks	Hb <95 g/L	Change in Hb from baseline to week 12: 29.4 g/L vs 5.0 g/L (LSM difference, 24.4 g/L; 95% CI, 16.9–32.0; $p<0.0001$)	4% (2/49) vs 0 at 12 weeks Both cases of BTH were nonserious, mild to moderate in severity, and resolved without dose changes or RBC transfusions
APPLY-PNH (NCT04558918) Iptacopan Phase 3, open-label RCT[62,63]	PNH patients with residual anemia despite anti-C5 therapy (eculizumab or ravulizumab) for ≥6 months; included patients with a history of transfusion dependence and those with BTH Oral iptacopan monotherapy vs continued anti-C5 therapy for 24 weeks	Hb <100 g/L	Coprimary endpoints: Increase in Hb >20 g/L from baseline[a]: 82% vs 2% (difference, 80%; 95% CI, 71–88; $p<0.001$) Hb level ≥120 g/L[a]: estimated percentages, 82% vs 2% (difference, 80%; 95% CI, 71–88; $p<0.001$)	3.2% (2/62) vs 17.1% (6/35) at 24 weeks Annualized RR of iptacopan vs anti-C5 at 24 weeks: 0.1 (95% CI, 0.0–0.6; $p=0.006$) Iptacopan severity (2 events): 1 mild, 1 moderate Anti-C5 severity (11 events): 2 mild, 8 moderate, 1 severe Rate of BTH for iptacopan at 48 weeks: 7%

(*Continued*)

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Table 2 (Continued).

Clinical Trial	Patient Population and Intervention	Definition of Suboptimal Response for Inclusion	Primary Outcome(s), Intervention vs Control	BTH Rates and Severity, Intervention vs Control
APPOINT-PNH (NCT04820530) Iptacopan Phase 3, open-label, single-arm trial[62,63]	PNH patients naive to C5 inhibitors; included patients with a history of transfusion dependence and/or with BTH Iptacopan monotherapy for 24 weeks	Hb <100 g/L	Increase in Hb >20 g/L from baseline without RBC transfusion: 92% (95% CI, 82–100; exceeding 15% threshold)	No BTH reported in either arm at 24 weeks; 2 (5%) at 48 weeks

Note: [a]On ≥3/4 assessments between days 126–168.
Abbreviations: BTH, breakthrough hemolysis; CI, confidence interval; EVH, extravascular hemolysis; Hb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; RCT, randomized controlled trial; RR, rate ratio; ULN, upper limit of normal.

Pegcetacoplan

Pegcetacoplan, a pegylated anti-C3 cyclic peptide, is a C3-targeted therapy for PNH.[55] The safety and efficacy of pegcetacoplan was evaluated in PEGASUS and PRINCE, two phase 3, randomized, multicenter, open-label, controlled trials.[58,60] PEGASUS enrolled patients ≥18 years of age diagnosed with PNH with persistent anemia (hemoglobin <105 g/L) despite receiving eculizumab for ≥3 months. After a 4-week run-in phase during which patients took both therapies, they were randomized 1:1 to pegcetacoplan (n=41) or eculizumab (n=39) monotherapy for 16 weeks. The primary endpoint was hemoglobin change from baseline to week 16. Key secondary endpoints included transfusion avoidance and change from baseline to week 16 in absolute reticulocyte count and LDH.

Pegcetacoplan demonstrated superiority to eculizumab in hemoglobin change from baseline (+23.7 g/L vs −14.7 g/L; mean difference, 38.4 g/L; 95% CI 23.3–53.3; $p<0.001$). Over the 16-week randomized period, 35 patients (85%) in the pegcetacoplan group were transfusion-free vs 6 (15%) in the eculizumab group ($p<0.001$). The absolute reticulocyte count decreased with pegcetacoplan and slightly increased with eculizumab (adjusted mean ±SE changes, −136±7 x 10^9 per liter and 28±12 × 10^9 per liter, respectively), demonstrating noninferiority of pegcetacoplan to eculizumab. Noninferiority was not shown for LDH change from baseline. BTH was reported in 4 patients (10%) receiving pegcetacoplan and in 9 patients (23%) receiving eculizumab. All four pegcetacoplan-treated patients who had BTH had LDH elevation >3 x ULN. These BTH events occurred without identifiable triggers or detectable anti-pegcetacoplan antibodies and resulted in 3 patients discontinuing pegcetacoplan and switching back to eculizumab. BTH events were moderate to severe.[58]

In a post hoc analysis of the PEGASUS trial, including a 32-week open-label period, 26 hemolysis adverse events occurred in 19 patients.[59] In 16 (62%) of the events, a CAC was identified. Of the 26 events, 14 (54%) were considered moderate in severity. Hemolysis adverse events led to discontinuation in 5 patients. Notably, patients with a hemolytic adverse event tended to have higher baseline disease activity (ie higher-than-label eculizumab dose, detectable CH50, and ≥4 transfusions in the previous 12 months) than patients without a hemolysis adverse event.[59]

PRINCE enrolled patients ≥18 years of age diagnosed with PNH, with hemoglobin levels below the lower limit of normal (LLN; male <136 g/L and female <120 g/L) and LDH levels ≥1.5 x ULN.[60] Patients treated with eculizumab or ravulizumab within 3 months of screening were excluded. Patients were randomized 2:1 to twice-weekly treatment with pegcetacoplan 1080 mg (n=35) or supportive care only (n=18) for 26 weeks. Coprimary endpoints were hemoglobin stabilization (avoidance of >10 g/L decrease in hemoglobin from baseline to week 26) and LDH change from baseline to week 26. Both co-primary endpoints were met. Most patients treated with pegcetacoplan (85.7%) achieved hemoglobin stabilization at week 26 vs none with supportive care ($p<0.0001$). Pegcetacoplan significantly improved LDH change from baseline vs supportive care (difference, −1407.4 U/L; 95% CI −2113.4 to −827.3 U/L; $p<0.0001$). There was no PNH-related hemolytic event or thrombosis.

A post hoc analysis of patients with baseline hemoglobin ≥100 g/L and who were C5i-naïve (Phase 1 PADDOCK, n=6 and PRINCE, n=8) or had suboptimal response despite treatment with eculizumab (PEGASUS, n=11) showed that mean hemoglobin increased by ≥20 g/L after starting or switching to pegcetacoplan.[49] After 16 weeks, most patients had hemoglobin ≥120 g/L in PADDOCK (60%), PRINCE (87.5%), and PEGASUS (72.7%) and this coincided with improved FACIT-Fatigue scores.

The open-label extension (Study 307) reported on the long-term safety and efficacy of pegcetacoplan from five completed clinical trials (phases 1, 2, and 3).[64] Hemolysis serious adverse events occurred in 11 patients (8%). Treatment-emergent adverse events (TEAEs) occurred in 22 patients (16%) with 25 events. Sixteen events were associated with a CAC and 10 events required transfusions. Fifteen events were treated with an increase in pegcetacoplan dose and 3 patients received ravulizumab or eculizumab during the hemolysis event. Three of the 22 patients with hemolysis events discontinued the study.

The open-label extension also investigated the management of BTH using an intensive regimen of pegcetacoplan. A treatment algorithm was developed whereby an acute BTH episode is treated with either a single 1080 mg IV dose of pegcetacoplan or a daily 1080 mg SC dose for 3 consecutive days followed by maintenance dosing of pegcetacoplan at the next higher dosing frequency as before the acute event.[65] This algorithm has been adopted into Canadian practice with a preference for the 3 SC doses due to easier access and no apparent inferiority to a single IV dose. C5 inhibitor rescue should be considered for hemolytic episodes complicated by thrombosis, clinical deterioration, or life-threatening event.[66]

Real world experience with BTH has been reported for pegcetacoplan among patients being treated in the UK and France.[66] Six patients experienced 18 acute BTH episodes outside of the clinical trial. Seven of the 18 episodes were associated with a CAC. The mean LDH rose from 1.1 x ULN to 5.4 x ULN and in 16 of the 18 episodes there was a reduction in hemoglobin (mean reduction 22 g/L). Three patients had multiple episodes of BTH. Because half the patients who had BTH had repeated events, the authors noted the challenge in identifying such patients as an area for future research. A real-world study from Italy reported that 6 of 22 patients (27%) treated with pegcetacoplan experienced a BTH event.[67] Among them, 1 patient was hospitalized, 4 required blood transfusions, and 2 received additional therapy – either anticomplement treatment with pegcetacoplan for 3 days + 2 eculizumab doses, or erythropoietin.

Iptacopan

Iptacopan is an oral Factor B inhibitor approved for use as monotherapy in the treatment of adult patients with PNH who have hemolytic anemia.[56] The safety and efficacy of iptacopan was evaluated in two phase 3, open-label trials (APPLY-PNH and APPOINT-PNH) over a 24-week period in patients ≥18 years of age with PNH, mean hemoglobin <100 g/L, and no laboratory evidence of bone marrow failure.[62] In APPLY-PNH, patients who had received eculizumab or ravulizumab for ≥6 months were randomized 8:5 to twice-daily iptacopan 200 mg monotherapy or to continue their anti-C5 therapy. Patients who were on eculizumab prior to randomization received their first dose of iptacopan 7 or 8 days after eculizumab infusion. In the case of ravulizumab, iptacopan dosing started 41 to 43 days after the ravulizumab infusion.

Iptacopan was superior to C5 inhibitors for both coprimary endpoints (increase in hemoglobin ≥20 g/L from baseline and a hemoglobin level ≥120 g/L on ≥3/4 assessments between days 126–168) each without RBC transfusion. A total of 51/60 iptacopan-treated patients achieved an increase in hemoglobin ≥20 g/L from baseline without transfusions, compared to none of the 35 patients treated with C5 inhibitors (estimated percentages, 82% vs 2%; difference, 80%; 95% CI, 71–88; $p<0.001$). A total of 42/60 patients who received iptacopan had hemoglobin levels that reached ≥120 g/L without transfusions, compared to none of the patients treated with anti-C5 therapy (estimated percentages, 69% vs 2%; difference, 67%; 95% CI, 56–77; $p<0.001$). Two iptacopan-treated patients had clinical BTH events (1 mild and 1 moderate event), defined as one of either a decrease in hemoglobin of ≥20 g/L or PNH symptoms in addition to an increase in LDH >1.5 x ULN, compared to 6 out of 35 patients who received C5 inhibitors (11 events; 2 mild, 8 moderate, and 1 severe; $p=0.006$).

After 24 weeks, patients in APPLY-PNH were eligible for an optional 24-week treatment extension period where patients from the iptacopan group continued with the same dosing and patients in the anti-C5 arm switched to iptacopan 200 mg twice daily. At 48 weeks, the patients who had received iptacopan throughout continued to have a sustained improvement from baseline in hematologic and clinical outcomes, including normalization of hemoglobin levels, transfusion avoidance, and decreased fatigue.[63] Patients who switched to iptacopan achieved a mean hemoglobin level of 120 g/L at 48 weeks, a 29 g/L improvement from week 24. Additionally, these patients experienced a mean 10-point increase in the FACIT-Fatigue score between 24 and 48 weeks, indicating a meaningful improvement in fatigue.[63] The safety profile after 48 weeks of treatment was consistent with the 24-week data; there were no reports of serious TEAEs of hemolysis, serious infections, or TEAE-related discontinuations.[63]

APPOINT-PNH was a single-group trial. Patients who had not received complement inhibitor therapy and had LDH levels 1.5 x ULN received iptacopan 200 mg twice daily for 24 weeks. The primary endpoint was an increase in hemoglobin ≥20 g/L from baseline without transfusion, and a secondary endpoint was a hemoglobin level ≥120 g/L without transfusion. A total of 31 of the 33 evaluable patients had an increase in hemoglobin ≥20 g/L from baseline without transfusion (92%; 95% CI 82–100) and 19 of 33 evaluable patients had hemoglobin levels that reached ≥120 g/L without transfusion (63%; 95% CI 48–78). No patient had BTH or a major adverse vascular event.[62] Patients in APPOINT-PNH were offered an optional 24-week treatment extension. The benefits achieved during the first 24-week period were sustained throughout this extension period.[63] The safety profile after 48 weeks of treatment was consistent with the 24-week data; there were no TEAE-related discontinuations and low rates of serious TEAEs. A serious BTH event was reported in one patient.[63]

APPULSE-PNH, a phase 3b study in patients with PNH on a C5 inhibitor and hemoglobin levels >100 g/L showed that switching to iptacopan increased mean hemoglobin by 20 g/L to 138.8 g/L at week 24 ($p<0.0001$).[48] Findings from this study show it is feasible to further normalize hemoglobin and possibly improve QoL in suitable patients, including those with evidence of ongoing EVH, anemia according to WHO guidelines, or those who require hospital visits.

Results of a post hoc analysis of APPLY-PNH and APPOINT-PNH demonstrated that of 102 patients treated with iptacopan, 10 clinical BTH events occurred in 9 patients over a 48-week period. Most events were associated with a CAC, particularly infections. No patient discontinued iptacopan due to clinical BTH and in most cases transfusions were given to manage the BTH event, although one patient was treated with a dose of eculizumab (900 mg).[68] In the ongoing rollover extension program (NCT04747613), BTH events associated with CAC can be managed with temporary increases of iptacopan to 400 mg twice daily for up to 14 days. The results of this approach are eagerly awaited. Of note, supratherapeutic doses of iptacopan were well tolerated in a phase 1 study in healthy individuals.[69] Some clinicians have proposed a rescue dose of eculizumab to manage severe BTH occurring in patients being treated with iptacopan.[46] Real-world data from the UK showed that one BTH event occurred (following a urinary tract infection) out of 20 patients treated with iptacopan (5%). The patient was managed with an additional dose of eculizumab.[70]

Danicopan

Danicopan is an orally-administered Factor D inhibitor. Although the safety and efficacy of danicopan monotherapy was demonstrated in a phase 2 trial, some patients experienced IVH.[71] This led to its evaluation as a dual target inhibition strategy, ie C5 inhibition to block IVH and proximal inhibition with danicopan add-on to address EVH. In a multicenter, open-label, multiple-dose, single-arm phase 2 study in patients with PNH with inadequate response to eculizumab (≥1 transfusion within 12 weeks of screening), 12 patients received oral danicopan thrice daily (100–150 mg for the first 4 weeks, then up to 200 mg) for 24 weeks in addition to eculizumab at their usual dose and schedule.[72] The primary endpoint was hemoglobin increase at week 24 relative to baseline. Secondary endpoints included reductions in transfusions and in LDH levels at week 24 vs baseline.

There was a significant increase in mean hemoglobin from baseline (79 g/L) to week 24 (103 g/L; 24 g/L increase; $p=0.0001$). Significant improvement first appeared at week 2 and was maintained throughout the study. A clinically meaningful reduction in transfusion needs was demonstrated over the 24-week treatment period. Although there were decreases in mean absolute reticulocyte counts between baseline and week 24, there was no significant change in mean LDH level (1.06 x ULN at baseline and 1.04 x ULN at week 24). One patient had a non-serious grade 3 episode of

anemia that resolved and was considered unrelated to danicopan. One patient experienced a non-serious grade 3 direct bilirubin increase with a grade 1 increase in alanine aminotransferase (day 70), which was considered unrelated to danicopan and believed to be caused by BTH due to the associated doubling of LDH and hemoglobin decrease of 8 g/L. Both adverse events resolved. Danicopan treatment was not interrupted; the dose of danicopan was temporarily reduced and re-escalated after the event resolved.

The same combination was evaluated in ALPHA, a phase 3, multisite, double-blind, placebo-controlled randomized trial evaluating danicopan as add-on therapy to ravulizumab or eculizumab in patients aged ≥18 years with PNH and clinically significant EVH (hemoglobin ≤95 g/L; absolute reticulocyte count ≥120 x 10^9/L) despite treatment with ravulizumab or eculizumab for ≥6 months. This trial is unique in that it enrolled based on EVH. Patients were randomly assigned (2:1) to danicopan 150–200 mg thrice daily (n=49) or placebo (n=24) added to ravulizumab 3000–3600 mg every 8 weeks or eculizumab 900–1500 mg every 2 weeks for 12 weeks.[61] The primary endpoint was hemoglobin change from baseline to week 12. The primary endpoint was met; at week 12, danicopan + ravulizumab or eculizumab increased hemoglobin vs placebo + ravulizumab or eculizumab (least squares mean [LSM] change from baseline: danicopan, 29.4 g/L [95% CI 25.2–33.6]; placebo, 5.0 g/L [−1.3–11.2]; LSM difference, 24.4 g/L [16.9–32.0]; $p<0.0001$).[61]

A long-term safety analysis of danicopan as add-on therapy to ravulizumab or eculizumab in patients with significant EVH reported the rate of BTH as 6 events per 100 patient-years. BTH events were investigator-assessed based on clinical decision and not according to defined parameters.[73] All BTH events resolved rapidly without trial discontinuation or dose adjustments.

Proximal Inhibitors' Place in Therapy and Treatment Decisions

In treating patients with PNH, control of IVH is paramount, and has led to important outcomes of reduced thrombotic burden and improved overall survival. With additional therapeutic options, we can now optimize treatment in patients who have an inadequate response to initial therapy. As previously noted, second-line therapy may be considered for patients who have persistent anemia, ongoing symptoms leading to reduced QoL, or are intolerant to C5 inhibitors. Patient preference is also an important consideration.

There are three proximal inhibitor treatment options, each with their own clinical considerations (see Figure 4). In evaluating the treatment options, one should consider safety and efficacy data in trials, maturing real-world evidence, route of administration and its acceptance, and other patient-specific factors, including comorbidities and patient preferences.

Pegcetacoplan has been Health Canada approved for the treatment of PNH since 2022,[55] thus, we have some real-world experience outside of the clinical trial setting. Guidance is also available for the management of BTH associated with pegcetacoplan, enabling treatment of episodes regardless of geographic location and often without the need for additional C5 inhibition.[65] However, there is evidence to suggest that patients with higher disease activity at baseline may be more at risk of BTH and thus warrant close monitoring.[59]

Iptacopan received Health Canada approval in January 2025 for treatment of adults with PNH who have hemolytic anemia.[56] As such, clinical experience with iptacopan in Canada is still emerging. The clinical trial comparing iptacopan to C5 inhibitors demonstrated that the rate of BTH was comparatively low and mild or moderate in severity with no severe episodes reported.[62] As yet, we do not have guidance on how best to manage episodes of BTH with iptacopan. A single dose of a C5 inhibitor may be indicated. Supratherapeutic doses of iptacopan (400 mg twice daily for 14 days) were shown to be well tolerated in healthy participants, but the additional therapeutic benefit in the context of BTH has yet to be confirmed.[69]

Danicopan is an add-on therapy to C5 inhibition.[57] While the use of both proximal and terminal complement inhibition is attractive, its use may be limited by financial burden on the healthcare system and by requirements for thrice-daily oral dosing in addition to IV administration. Dual blockade may be particularly helpful in patients with recurrent BTH on proximal anticomplement monotherapy despite optimization attempts and for those with significant thrombotic history, while we await data maturation of the other therapies with respect to thromboembolic control. Oral agents such as iptacopan and danicopan may be preferred in selected patients after consideration of their individual preferences and attributes (eg suitability for oral therapy).

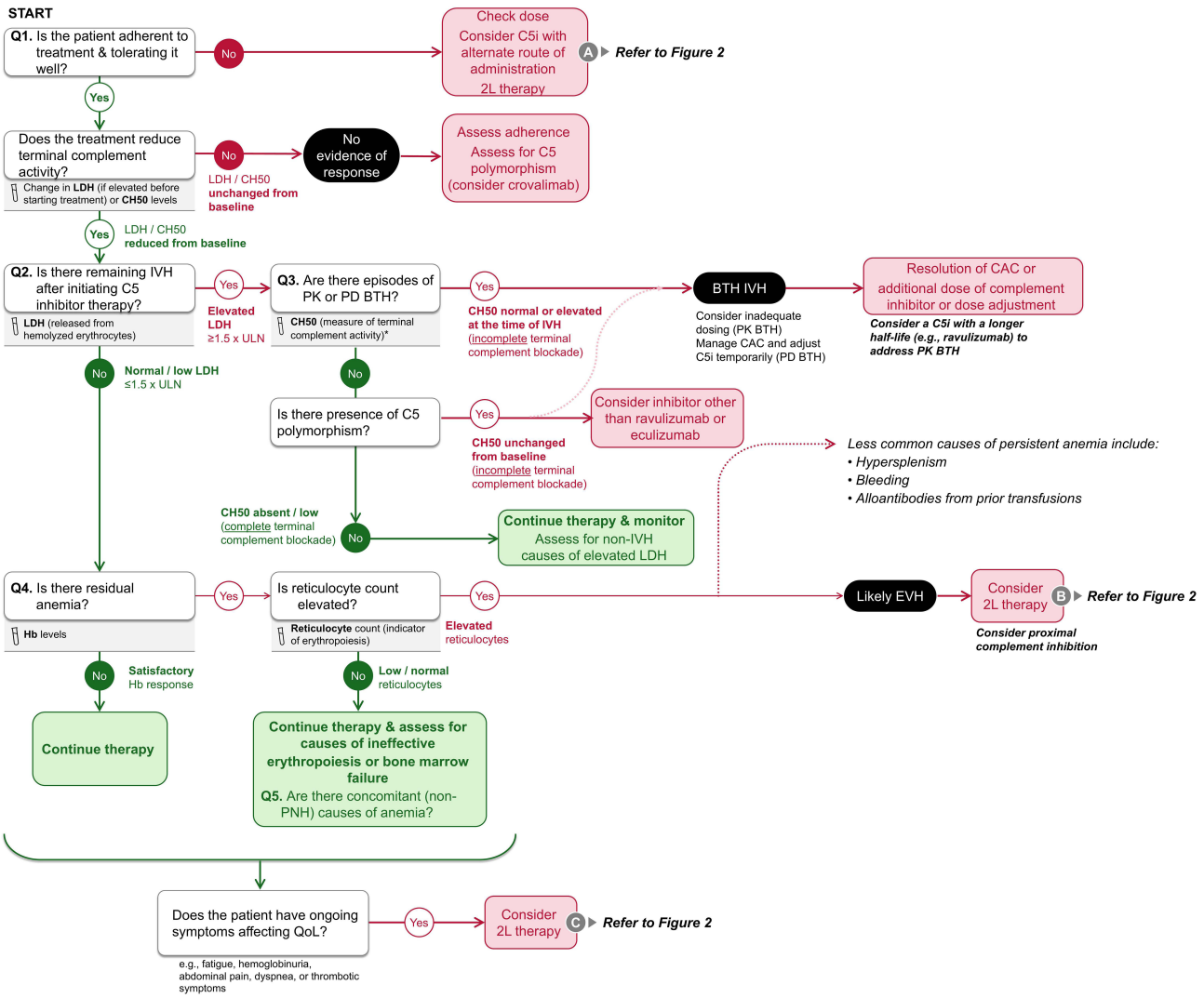

Figure 4 Monitoring response to C5-targeted anticomplement treatment. Q1, Q2, Q3, Q4, and Q5 represent key clinical decision points and correspond to the questions presented in the main text. Grey circles with letters (A, B, and C) indicate inadequate response as defined by the factors described in Figure 2. Green denotes continue first-line therapy. Red denotes consider second-line therapy. *Caution! Interpret results in the context of known assay limitations. Adapted from: Kulasekararaj AG et al. Am J Hematol. 2021;96(7):E232–E235.[24]

Abbreviations: 2L, second line; BTH, breakthrough hemolysis; C5i, complement factor 5 inhibitor; CAC, complement-amplifying condition; CH50, 50% hemolytic complement assay; EVH, extravascular hemolysis; Hb, hemoglobin; IVH, intravascular hemolysis; LDH, lactate dehydrogenase; PD, pharmacodynamic; PK, pharmacokinetic; PNH, paroxysmal nocturnal hemoglobinuria; QoL, quality of life; RBC, red blood cell; ULN, upper limit of normal.

BTH remains a major challenge for some patients with PNH, even with advances in complement inhibitor therapies.[46] In situations when there is acute hemolysis while on optimized dosing of complement inhibitors, a rescue dose of eculizumab may be necessary. However, access to a rescue dose of eculizumab for BTH treatment varies across Canada, thereby creating barriers to timely and effective care for patients. Furthermore, in cases of severe BTH considered to be a medical emergency, delaying access to treatment can significantly worsen outcomes. Thus, it is essential to standardize access to a rescue dose of eculizumab across the country to manage BTH in patients with PNH.

Patients who may benefit from proximal complement inhibition based on clinical assessment may not meet the criteria for access to public reimbursement, which is expected to limit the use of these agents to patients with persistent anemia (eg hemoglobin <105 g/L) despite C5 inhibition. As stated earlier, hemoglobin is a variable parameter from patient to patient, and its value does not always correlate with disease severity or symptom burden. As the management of PNH evolves and more patients are treated with newer complement inhibitors, clinicians may encounter situations

where switching from one proximal inhibitor to another may be appropriate, whether to address recurrent episodes of BTH or to improve adherence and accommodate patient preference. In some cases, a transition from proximal inhibition to C5 blockade may be necessary, such as during pregnancy. Flexibility in moving between therapies will be essential. Although experience with such transitions is limited, they represent an important aspect of PNH management that warrants close monitoring and continued learning.

Conclusion

Optimal care of patients with PNH relies on timely and thorough evaluation of treatment response to first-line C5 inhibitor therapy. For patients with PNH who have an inadequate response to first-line complement inhibition, second-line treatment options are available. We have proposed an algorithm to evaluate response to C5 inhibitors and offered direction on switching to proximal inhibitors or add-on therapy. Pegcetacoplan, iptacopan, and danicopan have all demonstrated efficacy and safety in clinical trials, although real-world experience remains limited. Self-administered options represent an important advancement toward individualizing treatment for patients in line with their preferences and lifestyle. Ongoing registry data and real-world evidence will provide further evidence on how second-line therapies address residual hemolysis, persistent symptoms, and improve patient QoL, and better our understanding of the frequency, severity, and management of BTH associated with proximal inhibitors. Access and funding to complement inhibitors regardless of hemoglobin thresholds in patients with inadequate response and symptomatic anemia, fluidity to switch between proximal inhibitors, and access to rescue dose of eculizumab for BTH management will further allow clinicians to improve and optimize care for their patients with PNH.

Ethics / Consent Statement

All experts whose perspectives are included in this manuscript have provided informed consent for publication of their views. Signed consent forms have been obtained and are available upon request from the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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