Complement Inhibition in Paroxysmal Nocturnal Hemoglobinuria (PNH): A Systematic Review and Expert Opinion from Central Europe on Special Patient Populations

Bodó, Imre; Amine, Ismail; Boban, Ana; Bumbea, Horia; Kulagin, Alexander; Lukina, Elena; Piekarska, Agnieszka; Preložnik Župan, Irena; Sokol, Juraj; Windyga, Jerzy; ...

Source / Izvornik: **Advances in Therapy, 2023, 40, 2752 - 2772**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.1007/s12325-023-02510-4

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:527109

Adv Ther (2023) 40:2752–2772
https://doi.org/10.1007/s12325-023-02510-4

ORIGINAL RESEARCH

Complement Inhibition in Paroxysmal Nocturnal Hemoglobinuria (PNH): A Systematic Review and Expert Opinion from Central Europe on Special Patient Populations

Imre Bodó · Ismail Amine · Ana Boban · Horia Bumbea · Alexander Kulagin · Elena Lukina · Agnieszka Piekarska · Irena Preloznik Zupan · Juraj Sokol · Jerzy Windyga · Jaroslav Cermak

Received: February 10, 2023 / Accepted: March 28, 2023 / Published online: April 18, 2023

ABSTRACT

Introduction: Hemolysis in paroxysmal nocturnal hemoglobinuria (PNH) is complement-mediated due to the lack of complement inhibitors in the hemopoietic cell membranes, making complement inhibition the best approach to manage PNH. Three complement inhibitors are approved by the European Medicines Agency as targeted therapy for PNH: eculizumab and ravulizumab, two humanized monoclonal antibodies targeting the same complement 5 (C5) epitope, approved in 2007 and 2019, respectively, and the more recently approved cyclic peptide, the complement 3 (C3) inhibitor pegcetacoplan. Although national and international PNH treatment guidelines exist, they do not take into consideration the latest clinical trial evidence. Given the lack of evi-

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-023-02510-4.

I. Bodó (✉)
Department of Internal Medicine and Hematology, Semmelweis University, 46 Szentkirályi u., Budapest 1088, Hungary
e-mail: bodoimre.md@gmail.com

I. Amine
Department of Hematology, Tokuda Hospital Sofia, Sofia, Bulgaria

A. Boban
Division of Haematology, Department of Internal Medicine, University Hospital Center Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia

H. Bumbea
Bone Marrow Transplant Unit, Department of Hematology, Emergency University Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

A. Kulagin
RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russia

E. Lukina
Department of Orphan Diseases, National Research Medical Center for Hematology, Moscow, Russia

A. Piekarska
Department of Hematology and Transplantology Medical, University of Gdansk, Gdansk, Poland

I. P. Zupan
Department of Hematology, University Medical Centre Ljubljana, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

J. Sokol
Department of Hematology and Transfusion Medicine, Jessenius Medical Faculty in Martin, Comenius University in Bratislava, Martin, Slovakia

J. Windyga
Department of Hemostasis Disorders and Internal Medicine, Institute of Hematology and Transfusion Medicine, Warsaw, Poland

dence-based data for some clinical situations encountered in real life, we identified specific populations of patients who may benefit from switching to proximal C3 from terminal C5 inhibition.
Methods: The expert recommendations presented here were created using a Delphi-like process by a group of expert PNH specialists across Central Europe. Based on an initial advisory board meeting discussion, recommendations were prepared and reviewed as part of a Delphi survey to test agreement.
Results: Using a systematic approach, literature databases were searched for relevant studies, and 50 articles were reviewed by the experts and included as supporting evidence.
Conclusion: Implementation of these recommendations uniformly across healthcare institutions will promote the best use of complement inhibition in managing PNH, and has the potential to positively impact patient outcomes in Central Europe and worldwide.

Keywords: Paroxysmal nocturnal hemoglobinuria; Complement inactivating agents; Complement C5; Complement C3; Hemolysis

Key Summary Points

Up to one-third of patients with paroxysmal nocturnal hemoglobinuria (PNH) receiving complement component 5 (C5) inhibitors may experience breakthrough hemolysis due to suboptimal inhibition of the terminal complement pathway.

Evidence-based data for managing patients who may benefit from switching to proximal complement component 3 (C3) from terminal C5 inhibition are lacking.

A Delphi-like process, systematic review, real-world experience in Central Europe, and expert opinion were used to develop recommendations for using complement Inhibitors in specific populations of patients with PNH.

Five consensus recommendations for switching from C5 to C3 anti-complement agents were developed by 11 PNH experts from Central European.

These recommendations may help physicians across Central Europe and worldwide in their treatment decisions in managing patients with PNH using complement inhibitors.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disorder characterized by the expansion of a population of hematopoietic cells deficient in glycosylphosphatidylinositol (GPI) anchored surface proteins (AP) [1]. It is a rare disease that originates from somatic mutations in the X-linked phosphatidylinositol glycan A gene within a hematopoietic stem cell [1]. Due to its rarity and heterogeneity, studies reporting the incidence and prevalence rates of PNH in Europe are scarce [2]. Moreover, because PNH remains undiagnosed in many individuals due to the rarity of the condition or because the comorbidity may mask the diagnosis, reported rates are likely to be underestimated [2]. Although the exact incidence of PNH in Europe is largely unknown, data collection from different sources estimates 1 case per 100,000 individuals [3]. The onset of clinical manifestations of PNH can occur in patients of all ages, but the median age of onset is about 30–40 years [2]. The disease is rare and often misdiagnosed in children [4], with pediatric patients accounting for approximately 5–10% of reported PNH cases [5]. Clinical symptoms and disease burden of PNH vary widely between individuals, and are heavily influenced by the proportion of GPI-AP-

J. Cermak
Institute of Hematology and Blood Transfusion, Prague, Czech Republic

deficient cells or clone size [6]. Historically, PNH mortality at 5 years with best supportive treatment is about 35% [7]. However, over the last decade, survival rates for patients with PNH have dramatically improved by at least 75% with the approval of the first terminal complement component 5 (C5) inhibitor, eculizumab [2]. In addition to its effectiveness in prolonging overall survival, eculizumab has been shown to reduce or eliminate the need for blood transfusions by diminishing hemolysis and its associated sequelae, decreasing the incidence of thrombosis and improving anemia and quality of life (QoL) in a large proportion of patients [8]. Breakthrough hemolysis, characterized by the return of intravascular hemolysis and reappearance of classic PNH symptoms, may occur due to suboptimal C5 inhibition and/or complement-amplifying conditions, such as infection, inflammation, surgery, or pregnancy, that may lead to increased complement activation [9]. In addition, heterogeneous hematological responses may be related to factors including underlying aplastic anemia (AA), frequent C3-mediated extravascular hemolysis, or the rare presence of a specific mutation in the C5 gene, which prevents eculizumab from binding to the C5 protein [10]. Terminal C5 inhibition leading to extravascular hemolysis occurs because the enlarged, CD55-deficient PNH clone becomes opsonized with C3 fragments and survives due to C5 blockade, resulting in a continued need for transfusion in this patient population [11]. Therefore, upstream inhibition of the complement cascade is a rational strategy to improve the results of terminal complement-targeted treatment, which led to the development of several molecules that inhibit the proximal complement component 3 (C3) [12]. In addition to anti-C3 agents, proximal complement inhibition strategies with anti-factor D agents and anti-factor B agents are also emerging [13]. Allogeneic hematopoietic cell transplantation (allo-HCT) remains the only curative option for PNH. Still, due to the risk of transplant-related morbidity and mortality, it should be reserved for severe patients with PNH and suboptimal response to anti-C5 therapy and no access to clinical trials with novel therapeutic agents, such as patients with PNH in the setting of another specified bone marrow disorder [1].

Several PNH-specific treatment guidelines that include complement inhibition have been published in Europe [13–21]. However, these guidelines are based on evidence from early studies with eculizumab only, and were written prior to EU approval of the C5 inhibitor ravulizumab in July 2019 and the proximal C3 inhibitor pegcetacoplan by the European Medicines Agency (EMA) in December 2021. To address this shortcoming, a systematic literature review was conducted and a consensus meeting was organized to collect clinically relevant and up-to-date recommendations from 11 Central European experts on using complement inhibitor therapies in clinically-relevant patient populations.

PNH CLASSIFICATION AND CLINICAL MANIFESTATIONS

PNH is characterized by intravascular hemolysis, bone marrow failure, and a tendency to develop thrombosis. However, not all of these clinical features are found in all patients at presentation due to individual heterogeneity [1]. PNH is classified into three main subtypes: classic PNH (including hemolytic and thrombotic patients), subclinical PNH, and PNH in the setting of another specified bone marrow disorder (e.g., AA or myelodysplastic syndrome; MDS. The classic subtype is diagnosed in approximately one-third of patients with PNH, typically those presenting with intravascular hemolysis symptoms but who have no evidence of another defined bone marrow disorder [22]. These patients have a normocellular to hypercellular bone marrow with erythroid hyperplasia, an elevated reticulocyte count, and lactate dehydrogenase (LDH) 2–10 times the upper limit of normal (ULN) [23]. Patients with PNH classic symptoms usually have a large PNH clone (mean granulocyte PNH clone size 50–70%) [6]. The absence of two GPI-APs, namely CD55 and CD59, on the surface of erythrocytes is the primary cause of complement-mediated intravascular hemolysis, consequential anemia, and associated complications in

PNH [1]. Therefore, patients with classic PNH tend to benefit the most from treatment with inhibitors of the complement pathway [6]. All patients with PNH are at an increased risk of thrombosis; however, the risk possibly increases with increasing clone size [18]. Approximately 40% of patients with PNH experience unexplained venous thrombosis during the course of their disease, often in unusual locations, such as splanchnic or cerebral venous sinus thrombosis [24]. Notably, 40–67% of PNH deaths can be attributed to a thrombotic event [25]. Other classic disease manifestations include smooth muscle dystonia (e.g., esophageal spasm and erectile dysfunction), severe fatigue (present in 80% of patients with PNH) [26], renal impairment, and pulmonary hypertension [23, 27]. Many of these complications are a consequence of nitric oxide depletion, due to the toxic effects of free circulating hemoglobin.

Subclinical patients with PNH who present with cytopenia without clinical hemolysis usually have small clone sizes ($\leq$ 10% granulocyte clone) as seen by sensitive flow cytometric analysis [6, 23]. The majority of subclinical patients are asymptomatic or exhibit limited symptomology, and probably have a much lower thromboembolic risk than classic patients [6]. Approximately 2–6% of patients with PNH will develop severe bone marrow failure by 10 years post-diagnosis, which may manifest as secondary MDS/acute myeloid leukemia [28]. PNH associated with bone marrow failure is characterized by clinical and laboratory findings of hemolysis of variable degrees with concomitant evidence of a defined bone marrow abnormality [29].

ANTI-COMPLEMENT TREATMENT OPTIONS

C5 Inhibition

Two C5 inhibitors, eculizumab and ravulizumab, are licensed for intravenous use in Europe [12]. Eculizumab, a humanized monoclonal antibody that targets complement C5, was approved by the EMA in June 2007 to treat PNH in adults and children with hemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history [12]. Approval of eculizumab was based on results from the Phase 3 double-blinded, placebo-controlled TRIUMPH study, which demonstrated that eculizumab reduced hemolysis and transfusion requirements, and improved fatigue in patients with PNH [8]. Similar benefits of eculizumab were observed in the SHEPHERD study, an open-label, safety and efficacy trial that enrolled a more heterogeneous population of patients with PNH than TRIUMPH, including those with significant thrombocytopenia and minimal transfusion requirements [30]. Results from TRIUMPH and SHEPHERD provide evidence that eculizumab therapy for PNH is effective, safe, and well-tolerated in a standardized setting with predefined outcome criteria [8, 30]. Furthermore, in an open-label extension study of patients from TRIUMPH and SHEPHERD, eculizumab treatment dramatically reduced the thromboembolism event rate from 7.4 to 1.1 events per 100 patient-years [31]. Ravulizumab is indicated for treating adults and children with a body weight of 10 kg or above with PNH, with hemolysis with clinical symptom(s) indicative of high disease activity, and who are clinically stable after being treated with eculizumab for at least the past 6 months [12]. It has a mean terminal half-life approximately four times longer than eculizumab, providing immediate, complete, and sustained terminal C5 inhibition with an 8-week dosing interval [12]. Notably, ravulizumab demonstrated non-inferior efficacy and comparable safety to eculizumab in two open-label, Phase 3 studies in patients with PNH, who were complement inhibitor-naive (Study 301) or who were previously treated with eculizumab (Study 302) [32, 33]. The key efficacy findings of the Phase 3 pivotal trials for eculizumab and ravulizumab are summarized in Table 1. Patients on eculizumab or ravulizumab may be susceptible to meningococcal infections, and should, therefore, be vaccinated 2 weeks before beginning therapy [12]. Real-life data also support the beneficial effects of C5 inhibitors in the treatment of PNH [34, 35]. Notably, the proportion of patients with PNH requiring blood transfusions was substantially reduced with

Table 1 Summary of efficacy and safety data from pivotal clinical Phase 3 trials of EU-licensed complement inhibitors

Study (ClinicaTrials.gov identifier)	Study design (population characteristics)	Trial duration	Patients, *n*; median age	Primary efficacy and safety endpoints	Key outcomes		Ref
					Efficacy and safety outcomes	Transfusion independence achieved	
Eculizumab (C5 inhibition)							
TRIUMPH (NCT00122330)	Double-blind, multicenter randomized trial of ECU vs. PBO in transfusion-dependent PNH pts (pts had undergone ≥ 4 transfusions in prior 12 months)	26 weeks	87 ($n = 43$ ECU and $n = 44$ PBO); 38 years	Coprimary efficacy endpoints: stabilization of Hb levels and no. PRBC units transfused	Efficacy: Hb stabilization: 49.0% vs. 0.0% ($p < 0.001$) for pts in the ECU and PBO groups, respectively; number of PRBC units transfused: 0 in the ECU group vs. 10 in the PBO group ($p < 0.001$)	51.0%	Hillmen et al. 2006 [8]
				Safety: AEs, laboratory findings, ECG and vital signs	Safety: no deaths; SAEs reported in 4 ECU patients and 9 PBO pts; no SAE was deemed treatment-related		
SHEPHERD (NCT00130000)	Open-label, single-arm (PNH pts with minimal transfusion requirements and with evidence of TCP)	52 weeks	97 (ITT); 41 years	Efficacy: hemolysis assessed by LDH AUC	Efficacy: hemolysis reduction: 87.0% of patients ($p < 0.001$)	51.0%	Brodsky et al. 2008 [30]
				Safety: AEs, laboratory findings, ECG and vital signs	Safety: SAEs in 44 pts, 7 were possibly drug-related, including pyrexia (2), headache (1), abdominal distension (1), viral infection (1), anxiety (1), and renal impairment (1). The majority (96.4%) of AEs were mild to moderate in intensity. TEAEs in 2 pts. Vital signs, physical examination, and ECG data did not reveal temporally associated AEs. No clinically significant laboratory abnormalities were seen		
Ravulizumab (C5 inhibition)							
301 (NCT02946463)	Active-controlled, multicenter, randomized open-label study (complement inhibitor-naïve pts)	26 weeks	246 ($n = 125$ RAV and $n = 121$ ECU); 45.5 years	Coprimary efficacy endpoints: transfusion avoidance and hemolysis assessed by LDH normalization	Efficacy: transfusion avoidance achieved for 73.6% and 66.1% of pts receiving RAV and ECU, respectively, with a between-group difference of 6.8% (95% CI, − 4.7, 18.1; $P_{inf} < 0.0001$); The adjusted prevalence of LDH normalization was 53.6% for the RAV group and 49.4% for the ECU group	NR	Lee et al. 2019 [32]
				Safety: AEs	Safety: headache occurred in 36.0% of RAV and 33.1% of ECU pts. SAEs in 11 RAV and 9 ECU pts. No deaths or cases of meningitis were reported in either treatment group. SAEs in 2.1% RAV and 1.0% ECU pts		
302 (NCT03056040)	Active-controlled, multicenter, randomized, open-label study (complement inhibitor-experienced pts stable for ≥ 6 months on ECU)	26 weeks	191 ($n = 96$ RAV and $n = 95$ ECU); mean age 35.5 years	Efficacy: percentage change in hemolysis assessed by LDH from baseline to Day 183	Efficacy: percentage change in LDH: difference, 9.2% (95% CI, 20.4 to 18.8; $p = 0.058$ for superiority), showing RAV was non-inferior to ECU	NR	Kulasekararaj et al. 2019 [33]
				Safety: AEs	Safety: headache occurred in 26.8% of RAV and 17.3% of ECU pts. SAEs in 4 RAV and 8 ECU pts. No cases of meningitis were reported in either treatment group. SAE—pyrexia in 1 RAV and 2 ECU pts		

Table 1 continued

Study (ClinicaTrials.gov identifier)	Study design (population characteristics)	Trial duration	Patients, *n*; median age	Primary efficacy and safety endpoints	Key outcomes		Ref
					Efficacy and safety outcomes	Transfusion independence achieved	
Pegcetacoplan (C3 inhibition)							
PEGASUS (NCT03500549)	Active-controlled, multicenter, randomized, open-label study (complement inhibitor-experienced pts stable for ≥ 3 months on ECU with Hb < 10.5 g/dL at screening)	16 weeks	80 ($n = 41$ PGC and $n = 39$ ECU); mean age 48.8 years	Efficacy: percentage change in Hb level from baseline to Week 16 during the randomized, controlled period Safety: AEs, TEs, laboratory and ECG variables	Efficacy: improvement in adjusted means of 3.8 g/dL of Hb at week 16 ($p < 0.001$), showing superiority of PGC to ECU Safety: AEs occurred in 88.0% PGC and 87.0% ECU patients. Most common AEs: injection-site reactions (37.0% vs. 3.0%), diarrhea (22.0% vs. 3.0%), BTH (10.0% vs. 23.0%), headache (7.0% vs. 23.0%), and fatigue (5.0% vs. 15.0%). SAEs occurred in 17.0% of PGC and 15.0% of ECU patients. Infections were reported in 29.0% PGC and 26.0% ECU pts; meningitis was not reported in either treatment group. No TEs in either group. BTH in 10.0% PGC and 23.0% ECU pts	85.0% vs. 15.0% ($p < 0.001$) for PGC and ECU-treated pts, respectively	Hillmen et al. 2021 [37]
		48 weeks	77 ($n = 38$ PGC-to-PGC and $n = 39$ ECU to PGC)	Efficacy and safety endpoints were as per the 16-week study (see above)	Efficacy: Patients in the PGC-to-PGC group maintained a high mean [Hb] between 16 weeks (11·5 g/dL) and 48 weeks (11·3 g/dL; $p = 0{\cdot}140$). Patients in the ECU-to-PGC group had significantly greater mean [Hb] at 48 weeks (11·6 g/dL) versus 16 weeks (8·6 g/dL; $p < 0{\cdot}0001$). Clinically meaningful improvements in FACIT-Fatigue scores: mean change from baseline for all patients receiving PGC of 9·9 points (SD 9·6), for patients in the PGC-to-PGC group mean 10.1 points (9.1), and for patients in the ECU-to-PGC group mean 9.6 points (10·3) Safety: 16.0% of patients discontinued treatment (7.0% through to week 16 due to BTH, and 13.0% due to severe treatment-emergent adverse events) and 18 patients ($n = 8$ PGC-to-PGC, $n = 10$ ECU-to-PGC) had at least one serious TEAE during the OL period, four of which were considered to be related to PGC treatment. The most common TEAEs (in ≥ 10.0% patients) among both PGC-treated groups during the OL period were injection site reactions (26.0%), hemolysis (19.0%), nasopharyngitis (16.0%), and diarrhoea (13.0%). No treatment-related deaths occurred throughout the study	73.0% vs. 72.0% in the PGC-to-PGC and ECU-to-PGC groups, respectively	De Latour et al. 2022 [38]

Table 1 continued

Study (ClinicaTrials.gov identifier)	Study design (population characteristics)	Trial duration	Patients, *n*; median age	Primary efficacy and safety endpoints	Key outcomes		Ref
					Efficacy and safety outcomes	Transfusion independence achieved	
PRINCE (NCT04085601)	Multicenter, randomized, open-label trial of PGC vs. SOC (excluding complement-inhibitors) in complement-inhibitor-naïve PNH pts	26 weeks	53 ($n = 35$ PGC and $n = 18$ SOC); mean age 48.8 years	Coprimary efficacy endpoints: Hb stabilization (avoidance of $a > 1.0$ g/dL decrease in Hb levels in the absence of transfusions) and change from baseline (CFB) in LDH level from baseline to Week 26	Efficacy: PGC was superior to SOC in both co-primary endpoints. Hb stabilization was achieved by 85.7% ($n = 30$) of PGC-treated patients and 0.0% of SOC patients through Week 26 ($p < 0.0001$). PGC-treated patients demonstrated superior reductions in mean LDH levels from baseline to Week 26 compared to SOC patients (least-squares mean CFB: PGC, −1870.5 U/L; SOC, −400.1 U/L; $p < 0.0001$), and mean LDH levels in PGC-treated patients at Week 26 (mean level: 204.6 U/L) were below the ULN for LDH (226.0 U/L)	NR	Wong et al. 2021 [39]
				Safety (secondary endpoint): incidence of AEs	Safety: serious AEs were reported by 8.7% ($n = 4$) of PGC-treated patients and 16.7% ($n = 3$) of SOC patients through Week 26. Two deaths (PGC, 2.9%, $n = 1$, septic shock related to medullary aplasia; SOC, 5.6%, $n = 1$, respiratory failure), both deemed unrelated to treatment, occurred. No events of meningitis or thrombosis were reported in either group. The most common AEs reported during the study were injection site reaction (PGC, 30.4%, $n = 14$; SOC, 0.0%), hypokalemia (PGC, 13.0%, $n = 6$; SOC, 11.1%, $n = 2$), and fever (PGC, 8.7%, $n = 4$; SOC, 0.0%). There were no AEs leading to discontinuation of PGC		

AE adverse event, *AUC* area under curve, *BTH* breakthrough hemolysis, *CI* confidence interval, *ECG* electrocardiogram, *ECU* eculizumab, *Hb* hemoglobin, *EU* European Union, *ITT* intent to treat, *LDH* lactate dehydrogenase, *NR* not reported, *OL* open-label, *PBO* placebo, *PGC* pegcetacoplan, P_{inf} *p* value for noninferiority, *PNH* paroxysmal nocturnal hemoglobinuria, *PRBC* packed red blood cells, *pts* patients, *RAV* ravulizumab, *SAE* serious adverse event, *SOC* standard of care, *TE* thromboembolic event, *TEAE* treatment-emergent adverse event, *TCP* thrombocytopenia, *U/L* units per liter

Table 2 Advantages and disadvantages of C5 and C3 inhibition

	C5 inhibition	C3 inhibition
Advantage(s)	• Several years of real-world data/experience • Clinically effective in a large proportion of patients • Very well tolerated, few side effects	• [a]Superior efficacy compared to C5 eculizumab in improving Hb and improvements in clinical and hematologic outcomes in patients with PNH (PEGASUS trial) • Current C3 inhibitor available as SQ treatment; option for self-administration • Well tolerated, few side effects
Disadvantage(s)	• Not effective in all patients • Accentuates C3-related extravascular hemolysis • Current C5 inhibitors available as IV treatments • *Neisseria meningitidis* vaccination required • High direct cost • High indirect cost (e.g., breakthrough hemolysis and loss of work/school productivity due to treatment regimen)	• Only one approved treatment is available in the EU • Twice weekly applications • Limited clinical and real-world data/experience • *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Hemophilus influenzae* vaccination required • High direct cost • Indirect cost unknown

[a]Superior efficacy was only for patients who remained anemic on a stable dose of eculizumab
C3 complement component 3, *C5* complement component 5, *EU* European Union, *Hb* hemoglobin, *PNH* paroxysmal nocturnal hemoglobinuria, *IV* intravenous, *SQ* subcutaneous

eculizumab or ravulizumab monotherapy or after eculizumab to ravulizumab switch [34–36]. The advantages and disadvantages of C5 inhibition are shown in Table 2.

C3 Inhibition

Pegcetacoplan is the first and only licensed C3 inhibitor in Europe [12]. It was recently approved for subcutaneous use in adult patients with PNH who are anemic after treatment with a C5 inhibitor for at least 3 months [12]. Before starting pegcetacoplan treatment, patients must be vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Hemophilus influenzae* [12]. Pegcetacoplan functions proximally in the complement cascade, regulating C3b-mediated extravascular hemolysis and, by blocking the cascade proximally, it prevents terminal intravascular hemolysis [12]. The approval of pegcetacoplan was based on the results of a 16-week, multi-center, randomized, open-label, active comparator-controlled Phase 3 clinical trial, PEGASUS [37]. The primary aim of the PEGASUS trial was to compare the efficacy and safety of pegcetacoplan with that of eculizumab in adults with PNH and hemoglobin levels lower than 10.5 g/dL despite eculizumab therapy (Table 1) [37]. Results from this trial demonstrated the superiority of C3 inhibition with pegcetacoplan compared to eculizumab in improving hemoglobin and noninferiority in other clinical and hematologic outcomes in patients with PNH by providing broad hemolysis control, including control of intravascular and extravascular hemolysis [37]. In the open-label period of the PEGASUS study, the long-term efficacy and safety of pegcetacoplan over 48 weeks of treatment were assessed compared to the C5 inhibitor eculizumab [38]. Pegcetacoplan demonstrated superiority to eculizumab with a statistically significant improvement in adjusted means of 3.8 g/dL of hemoglobin at week 16 ($p < 0.001$) [38]. Additionally, 85% of pegcetacoplan-treated patients were transfusion free over 16 weeks versus

15.0% of eculizumab-treated patients [38]. Furthermore, meaningful improvements were also observed across key markers of disease (e.g., absolute reticulocyte count, lactate dehydrogenase, and fatigue) [38]. The Phase 3 PRINCE study of pegcetacoplan vs. standard-of-care (SOC, excluding complement inhibitors) in treatment-naïve patients with PNH further supports the efficacy and safety profile of pegcetocoplan in PNH [39]. Pegcetacoplan demonstrated statistical superiority on the co-primary endpoints of hemoglobin stabilization and reduction in lactate dehydrogenase (LDH) compared to SOC at week 26 (Table 1). In addition, the safety profile of pegcetacoplan was consistent with previous studies [39]. QoL data from the PRINCE study have recently been reported, showing that patients with PNH who were naïve to complement inhibition exhibited meaningful QoL improvements through 26 weeks of pegcetacoplan treatment [40]. Fatigue symptom score, measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale (EORTC QLQ-C30) increased, and the Functional Assessment of Chronic Illness Therapy-Fatigue FACIT-Fatigue (FACIT-F) score improved with pegcetacoplan to 45.3 at week 26, i.e., similar to the population norm of 44.0 [40, 41]. The mean total linear analog self-assessment score also improved from 186.5 points at baseline to 241.0 points at week 26 in the pegcetacoplan group but decreased in the SoC group., indicating a better QoL was achieved in the pegcetacoplan treatment group [40]. In a subgroup analysis of patients with PNH and baseline hemoglobin levels $\geq$ 10.0 g/dL from the PEGASUS (NCT03500549), PADDOCK (NCT02588833), and PRINCE (NCT04085601), the results suggest that pegcetacoplan can be efficacious in patients with less severe anemia regardless of prior complement inhibitor treatment, further improving clinical markers of hemolysis and fatigue [42]. A recently reported matching-adjusted indirect comparison study showed that pegcetacoplan is more efficacious than ravulizumab or eculizumab among complement inhibitor–naïve patients with PNH [43]. The advantages and disadvantages of C3 inhibition are shown in Table 2.

Novel Therapies in Late-Stage Clinical Development

Various novel agents are under evaluation in ongoing Phase 3 clinical trials and hold promise for patients suffering from PNH (https://clinicaltrials.gov/). These include three fully human anti-C5 monoclonal antibodies: crovalimab [NCT03157635, COMMODORE-1 (NCT04432584), COMMODORE-2 (NCT04434092), COMMODORE-3 (NCT04654468)], LFG316 [NCT02534909; APPLY-PNH (NCT04558918)] and pozelimab/REN3918 (NCT05131204, NCT04811716, NCT05133531, NCT03946748), in addition to several eculizumab biosimilars. A small protein complement C5 inhibitor, rVA576 (Coversin), which prevents the cleavage of C5 by C5 convertase into C5a and C5b, is being investigated in Phase 2/3 trials [CONSERVE (NCT03829449, NCT02591862)], including in patients with PNH resistance to eculizumab due to complement C5 polymorphisms [CONSENTII (NCT03427060)]. Cemdisiran (ALN-CC5) is a subcutaneously administered N-acetylgalactosamine (GalNAc) conjugated RNA interference (RNAi) therapeutic targeting the C5 component of the complement pathway in development for the treatment of PNH (NCT02352493). Danicopan, a first-in-class oral small molecule Factor D inhibitor, has been designed to control intravascular hemolysis and prevent C3-mediated extravascular hemolysis, and is currently being investigated in patients with PNH with inadequate response to eculizumab (NCT03472885) and as add-on therapy to a C5 inhibitor in patients with PNH (NCT05389449); and in patients with PNH and clinically evident extravascular hemolysis (NCT04469465). Two other oral, selective small molecule inhibitors of Factor D are also currently being evaluated in Phase 2/3 PNH trials: BCX9930 [NCT04702568, NCT04330534, REDEEM-1 (NCT05116774), REDEEM-2 (NCT05116787)] and vemircopan, formerly ALXN 2050 and ACH 0145228, (NCT04170023). A first-in-class, oral, targeted

factor B inhibitor, iptacopan (LNP023), has also shown promise in clinical trials to reduce both intravascular and extravascular hemolysis [APPLY-PNH (NCT04558918 [44], NCT038961 52, NCT03439839, APPOINT-PNH (NCT048 20530)].

METHODS

Procedures

A modified Delphi method was used to collect experts' opinions. The Delphi method is a validated consensus process, frequently used when clinical evidence is missing. A virtual advisory board meeting was held on October 4, 2021, allowing the experts to identify specific recommendations for switching from C5 to C3 anti-complement agents in five special patient populations: (1) patients with breakthrough intravascular hemolysis during regular C5 inhibitor treatment, administered for at least 3 months; (2) patients with clinically relevant C3-mediated extravascular hemolysis on C5 inhibitor treatment for at least 3 months; (3) patients with an unprovoked thromboembolic episode (TE) while on C5 inhibitor for at least 3 months; (4) patients with severe fatigue and impaired QoL despite more than 3 months of C5 inhibitor treatment; and (5) patients with rare C5 polymorphisms (mostly of Japanese ethnicity). In addition, further discussions via email communications and file exchanges took place to assess the extent of agreement on the different recommendation statements and to achieve consensus. Two independent reviewers collected and analyzed anonymized statement responses, and then emailed them to all expert panel members for second-round review. This allowed the experts to rerate the recommendations for or against a consensus. This process was repeated to help the experts reach a final consensus. Consensus was reached if at least 9 of the 11 experts (> 80%) agreed to the recommendations. As no patient was involved in the study, no formal ethics approval was necessary.

Expert Panel

The expert consensus panel comprised 11 PNH senior hematologists from 9 countries across Central Europe (Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, and Slovenia). Panel qualification included hematology as the primary medical specialty, practicing as a hematology specialist between 5 and 30 years and spending more than half of their time in direct patient care. Collectively, the experts have amalgamated many years of real-world clinical experience in treating patients with PNH in Central Europe. All 11 members of the Delphi panel are included as authors.

Literature Review and Expert Recommendations

To support each expert consensus statement with up-to-date evidence, and in addition to the early pivotal clinical trial data for eculizumab [8, 30], EMA product information [12], and existing PNH-specific treatment guidelines [13–21], an Embase and PubMed/Medline systematic literature search was conducted (access date November 16, 2022) following the PRISMA method to identify clinical and real-world data relevant to PNH and EU-licensed anti-complement therapies. Clinical trials and real-world studies in patients with PNH treated with eculizumab, ravulizumab, and/or pegcetacoplan were searched separately in a parallel one-stage selection procedure, and using the following search terms: Search A: {[Paroxysmal Nocturnal Hemoglobinuria(Title/Abstract) AND [y_6(Filter)]} AND {[eculizumab(Title/Abstract)] OR [ravulizumab(Title/Abstract)] OR [pegcetacoplan(Title/Abstract)] AND [y_6[Filter)]} filters: in the last 6 years; and Search B: {[Paroxysmal Nocturnal Hemoglobinuria(Title/Abstract)] AND [y_6(Filter)]} AND {[real world(Title/Abstract)] OR [real-life(Title/Abstract)] OR [Observational(Title/Abstract)] AND [y_6(Filter)]}. Only full-text articles within the last six years were included in the analysis. After removing duplicates, the search resulted in a total of 318 unique records that underwent

manual title/abstract review by an independent reviewer. Of these, 77 articles were reviewed in full for eligibility, with 50 final articles identified with relevant data (Supplementary Fig. S1).

RESULTS

Use of Complement Inhibitors in Classic PNH (Hemolytic Anemia)

For patients who present with classic PNH symptoms indicative of high disease activity, regardless of transfusion history, and with an LDH level $\geq$ 1.5 ULN, treatment with a C5 inhibitor [standard-of-care (SOC) eculizumab or ravulizumab] is recommended [8, 16, 20, 30, 32, 33, 45]. In cases of inadequate response, dose and frequency can be increased according to product information guidance [12]. Patients with a significant PNH clone (> 50% PNH granulocytes), intravascular hemolysis (marked elevation of LDH level $\geq$ 1.5 ULN), and adequate bone marrow reserves (robust reticulocyte count) are most likely to benefit from treatment with C5 inhibitors [8, 16, 20, 30, 32, 33]. C5 inhibitor treatment should be considered even in the absence of transfusion-dependent anemia [8, 12, 16, 20, 30, 32, 33]. Allo-HCT is the only potentially curative treatment but is not recommended as initial therapy, except in the case of PNH associated with bone marrow failure [46–51]. It is not recommended for patients with PNH and thrombotic complications [52]. Due to the risk of transplant-related morbidity and mortality, allo-HCT should only be considered in selected patient groups, such as patients resistant to thromboprophylaxis and C5 inhibitor therapy, and patients with PNH/AA and PNH/MDS with prominent bone marrow deficiency [46–51].

No randomized clinical trials have evaluated the use of eculizumab or ravulizumab in pregnancy [8, 30, 32, 33, 53]. However, contradicting outcomes with eculizumab have been reported in several retrospective/prospective case series and individual patient cases [54–60]. It is recommended that pregnant patients with PNH who have not previously been treated with a C5 inhibitor should be assessed individually and strongly considered for treatment with eculizumab to prevent thromboembolic complications [53–61]. C5 inhibitors should be continued after birth to avoid an increased risk of thrombotic complications [62].

Use of Complement Inhibitors in PNH in the Setting of Bone Marrow Failure

For patients with bone marrow failure who present with a significant PNH clone size and active hemolysis, treatment with a C5 inhibitor is recommended (SOC) [63–68]. Rarely, in patients with AA and a large PNH clonal expansion treated with immunosuppressive therapy, PNH manifestations of hemolysis or thrombosis may worsen, similar to what is observed in patients with classic PNH [20, 69]. In such cases, patients should be treated as classic PNH cases [20, 69]. For patients with bone marrow failure and active hemolysis with an indication for an allo-HCT, anti-C5 treatment prior to HCT should be recommended to decrease transplant-related mortality [50, 70].

Use of Complement Inhibitors in Subclinical PNH

For subclinical patients who are asymptomatic, anti-complement treatment is not required [71, 72]. However, close monitoring (6- to 12-month intervals) should be ensured to detect possible expansion of the PNH clone and symptoms of hemolysis [20, 73].

Switching from Eculizumab to Ravulizumab

Patients with PNH may be safely and effectively switched from the labeled dose of eculizumab administered every 2 weeks to ravulizumab administered every 8 weeks at the discretion of the treating physician on an individual patient basis [12, 32, 33, 45, 74]; physicians should verify that meningococcal vaccination is current according to national guidelines for vaccination [12]. Recent clinical trials have demonstrated that ravulizumab is as effective as eculizumab for treating patients with PNH

[9, 32, 33, 74, 75]. In eculizumab-responding patients, switching to ravulizumab maintained disease control as evidenced by stable hematologic and renal parameters, with no apparent impact on safety [9, 32, 33, 74, 75]. Some patients develop regular pharmacokinetic breakthrough hemolysis during eculizumab treatment, and switching such patients to ravulizumab might have a profound effect on controlling symptoms [32, 33, 75]. Ravulizumab is administered intravenously every 8 weeks, which reduces treatment burden on patients and their families compared with eculizumab [12, 76, 77].

Other Considerations

Thromboprophylaxis in the context of C5 inhibition should be considered in patients with PNH and severe COVID-19 symptoms requiring hospitalization [78–81]. Note that patients with PNH and a history of thrombosis or other thrombophilic markers should receive secondary thromboprophylaxis while on C5 inhibition therapy, regardless of whether or not they have COVID-19. Preclinical data have demonstrated a role for complement activation in severe acute respiratory syndrome coronavirus mediated disease [82]. Eculizumab is currently used off-label to treat COVID-19, but its efficacy in this setting has yet to be proven [79]. However, recently published data indicate that patients with PNH may only present with mild symptoms of COVID-19 despite or even because of eculizumab treatment [78–81]. Further studies are needed to validate these observations [78–81].

Expert Panel Recommendations for Switching from C5 to C3 Inhibition in Special Patient Populations with PNH Relevant to Real-World Practice

The Central European expert group recognized a number of real-world settings representing clinical conundrums with regard to the management of patients with PNH falling outside the inclusion criteria of clinical trials. These settings, relevant for Central European countries and most countries worldwide, require special treatment considerations and guidance. Indeed, with the recent approval of the proximal complement inhibitor, pegcetacoplan, many questions about treating patients in the real world are emerging. Thus, the experts selected five distinct patient populations most relevant for switching from a C5 to a C3 inhibitor. The recommendations for the five special patient groups and the consensus percentage are summarized in Table 3.

DISCUSSION

The recent EMA approval of the C5 inhibitor ravulizumab in 2019 and the C3 inhibitor pegcetacoplan in 2021 has led to significant knowledge gaps regarding best treatment practices for patients with PNH in Central Europe and worldwide. There is increasing evidence supporting the use of terminal and proximal complement inhibition in PNH, but when and in which particular patient groups to use anti-C5 or -C3 agents remains unclear. To address this need, we present the results of an international Delphi effort involving 11 PNH experts from 9 Central European countries. Consensus recommendations regarding when to switch from a C5 inhibitor to a C3 inhibitor were developed for special patient populations, i.e., difficult-to-treat patients typically seen in real-world clinical practice but who did not meet the inclusion criteria for enrollment in the pivotal trials. As expected for an ultra-rare disease, this is an area with limited results on treatment response and QoL.

A recent real-life U.S. cross-sectional study surveyed patients with PNH (34% AA, 4% MDS, and 2% other bone marrow disorders) treated with C5 inhibitors, eculizumab ($n = 35$) or ravulizumab ($n = 83$) for at least 3 months, concluding that there remains a need for improved PNH therapies [83]. After 3 months of C5-inhibitor treatment, approximately 85% of patients remained anemic with hemoglobin levels 12 g/dL or less [83]. TEs were still reported for about 10–20% of patients with PNH receiving C5-inhibitor for at least 12 months, of whom between 20 and 50% had required

Table 3 Consensus recommendations for switching from C5 to C3 anti-complement agents in special patient populations

Special patient populations with PNH	Proportion of patients with PNH (%)	Expert recommendation(s)	Consensus ($n = 11$) n (%)
1. Patients with BT IVH during regular C5 inhibitor treatment for ≥ 3 months	Occurs in 11.0–27.0% patients with PNH on C5 inhibitor [9]	• Consider a clinical trial if available • For recurrent PK BTH[a] (typically 10.0–15.0% of patients) [87], consider a clinical trial; alternatively, increase the dose of ECU to 1200 mg or decrease dosing interval to 10 days[c] [88] • Alternatively switch to RAV[c] • Alternatively switch to PGC[c, d] [12, 37, 83, 87, 89] • For sporadic PD BTH[b], do not switch therapy [87]. Treat the triggering condition	11 (100)
2. Patients with clinically relevant C3-mediated EVH on C5 inhibitor treatment for ≥ 3 months	100.0% of patients treated with ECU show some degree of EVH [11]	• Consider a clinical trial if available • Alternatively, switch to PGC[d] [12, 87, 90]	11 (100)
3. Patients with unprovoked TE while on C5 inhibitor for ≥ 3 months (a rare event)	The rate of both venous and arterial TE during ECU treatment is 1.1 events per 100 PY [31]	• Consider a clinical trial if available • Consider secondary thrombo-PPX with anticoagulants unless contraindicated [91] • Alternatively, switch to PGC[d] and treat with anticoagulants; strongly consider switching if the TE event occurs on thrombo-PPX. Note: all patients should be examined for additional thrombophilic markers	11 (100)
4. Patients with severe fatigue and impaired QoL despite ≥ 3 months of C5 inhibitor treatment[e]	Mean change in FACIT-F score from BSL to Week 16 was 10.3 vs. −1.2 in the PGC and ECU treatment groups, respectively [84]	• Consider a clinical trial if available • Review markers of hemolysis and switch to PGC[d] [84, 89, 92–94]. Note: all patients should be evaluated in relation to Hb level	9 (72)

Table 3 continued

Special patient populations with PNH	Proportion of patients with PNH (%)	Expert recommendation(s)	Consensus ($n = 11$) n (%)
5. Patients with PNH and rare C5 polymorphisms (mostly of Japanese ethnicity) non-responsive to C5 inhibition	A rare C5 polymorphism (R885H) is found in 3.0% of the Japanese population which prevents C5 inhibitors from binding to C5 [95–97]	• Consider a clinical trial if available • Switch to PGC[d] [84, 89, 92, 98, 99]	11 (100)

Considering > 10 years of experience with ECU and at least 2 years with RAV, it is difficult to make a recommendation about switching from PGC where there is less clinical experience, to a C5 inhibitor; however, intolerance and inefficiency are important considerations for switching

AA aplastic anemia, *AML* acute myeloid leukemia, *ANLL* acute non-lymphoblastic leukemia, *BMD* bone marrow disorder, *BMF* bone marrow failure, *BSL* baseline, *BT* breakthrough, *BTH* breakthrough hemolysis, *C3* complement component 3, *C5* complement component C5, *ECU* eculizumab, *EVH* extravascular hemolysis, *FACIT-F* functional assessment of chronic illness therapy—fatigue, *IVH* intravascular hemolysis, *MDS* myelodysplastic syndrome, *PD* pharmacodynamic, *PGC* pegcetacoplan, *PK* pharmacokinetic, *PNH* paroxysmal nocturnal hemoglobinuria, *PPX* prophylaxis, *PY* patient-years, *QoL* quality of life, *RAV* ravulizumab, *SQ* subcutaneous, *TE* thromboembolic episode

[a]PK BTH: regularly occurring > 7 to 10 days from previous dose due to insufficient drug dosing

[b]PD BTH: sporadically occurring anytime due to complement amplifying conditions, e.g., pregnancy, infection and major surgery

[c]It is difficult to provide general recommendations about the order and duration of these treatment options because different countries have different regulations that favor one agent over another. In general, we consider all three choices equally acceptable. The duration of treatment will also depend on the patient's response. For a new dosing schedule, we consider five doses of ECU, three doses of RAV, and 3 weeks of PGC to be a fair trial duration; if the patient has an inadequate response, we recommend switching to another option

[d]For patients switching to PGC from a C5 inhibitor, for the first 4 weeks, PGC is administered as twice-weekly SQ doses of 1080 mg in addition to the patient's current dose of C5 inhibitor treatment to minimize the risk of hemolysis with abrupt treatment discontinuation [12]. After 4 weeks, the patient should discontinue the C5 inhibitor before continuing on monotherapy with PGC [12]

[e]Note that this is a difficult criterion since fatigue is subjective. While using formalized tools to assess fatigue is encouraged, these are not always practical in a busy clinic

transfusions within the past year [83]. The high number of transfusions, anemia, and TEs suggests persisting disease activity, which the authors suggest may be due to underlying extravascular hemolysis in patients with PNH treated with C5 inhibitors [83]. Moreover, most patients (approximately 80%) reported fatigue symptoms [83]. Patients reported scores below the average population norms on the FACIT-F and EORTC QLQ-C30 scales [83]. Notably, the reported TEs on C5 inhibitors were patient-reported symptoms and, unlike fatigue, which is subjective, should be proven by imaging [83]. A post hoc analysis of the Phase 3 PEGASUS trial showed that patients on pegcetacoplan, and those who switched to pegcetacoplan after 16 weeks on eculizumab, experienced clinically meaningful improvements in FACIT-Fatigue, including improved hemoglobin levels and reduced fatigue levels [84]. Similarly, QoL analysis of complement-naïve patients in the PRINCE study exhibited meaningful QoL improvements through 26 weeks of pegcetacoplan treatment [40]. Our recommendation to consider switching to pegcetacoplan in patients with PNH and severe fatigue and impaired QoL despite at least 3 months of C5 inhibitor treatment was the only recommendation that did not achieve 100% consensus from the experts. Possible reasons for a difference in opinion

among experts may be due to limited clinical data in this specific population, lack of objective criteria for fatigue assessment, lack of availability of C3 inhibition in certain countries and lack of personal experience switching between agents. Notably, objective evaluation of patient status and the indication of C3 inhibitors cannot be made on a QoL scoring system only; however, persisting anemia, related to hemolysis or due to developing bone marrow failure, may be used as an objective criterion.

The experts acknowledge that healthcare infrastructure is a key factor in supporting the implementation of their recommendations to improve standards of care and well-being for patients with PNH. The organization of healthcare systems can vary between countries, and reconfiguration of services may be needed to improve healthcare efficiency, e.g., flexible models of care to accommodate home infusions. As highlighted in a recent report by the European Commission, the COVID-19 pandemic has also identified the pressing need to manage public health issues and health systems better in Europe and elsewhere [85]. Moreover, due to the high cost of therapy, adequate organization of healthcare infrastructure is critical to optimize the utilization of available resources.

Electronic communications were used to anonymously collect and disseminate information to the experts using a Delphi-like process [86]. The Delphi method is a broadly accepted strategy for developing consensus recommendations based on objective expert opinion. This method is intended to provide guidance in areas where limited evidence-based literature is available [86]. A key strength of the Delphi method is its use of a systematic, anonymous process that promotes the free sharing of opinions and ideas, weighs all experts' opinions equally, and helps prevent bias by leveling the opinions of influential individuals [86]. Another strength of our study is differing levels of individual experts' experience with anti-complement inhibitors may help reflect practice in the real world, allowing a full range of practice opinions to be captured. However, there are several important limitations to our treatment recommendations. First, some recommendations were reached by consensus and are not supported by prospective, randomized data. Because of the rarity of the disease, there are few clinical studies available to support switching from C5 inhibition to C3 inhibition in specific patient populations with PNH. Although we conducted an in-depth literature search, it should be noted that case reports, retrospective/prospective case series, and real-world observational studies with short follow-up durations, which are subject to publication bias, make up a large portion of the evidence base. No formal assessment of bias or quality control of the studies included in this review was conducted. Furthermore, only one or two experts were invited to participate from each of the nine countries, and their opinions may not reflect the broader view of PNH treaters within each country.

CONCLUSIONS

Informed by the best available evidence and real-world experience, 11 experts from 9 Central European countries developed consensus recommendations on the use of anti-complement agents in specific patient populations with PNH. These recommendations will help towards improving outcomes for patients with the disease across Central Europe and hopefully/likely worldwide. In addition, by better understanding the unmet needs in Central European healthcare systems, necessary changes can be implemented so that patients with PNH can be offered appropriate anti-complement treatment independent of clinical trial settings. Such changes to the healthcare systems would benefit not only patients with PNH but also a potentially very large number of patients with chronic disorders.

ACKNOWLEDGEMENTS

This work was partially supported by the Hungarian National Research Development and Innovation Office (NFKI) grant OTKA-K19_131945 (I.B.).

Funding. Funding for the Rapid Service Fee and the Open Access Fee was provided by Sobi™, the Czech Republic.

Medical Writing and/or Editorial Assistance. Medical writing and editorial assistance in preparing this manuscript were provided by Klara J. Belzar, Ph.D., and XLR8-Health, Hertfordshire, UK. Funding was provided by Sobi™, the Czech Republic.

Author Contributions. All authors made substantial contributions to the conception and design of the study, acquisition of data, or interpretation of data; took part in revising the article critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosures. Ana Boban has received honoraria for participating on advisory boards and consultant fees from Sobi and Alexion; Alexander Kulagin has received honoraria and research grants (to Pavlov University) from Alexion, AstraZeneca Rare Disease, Novartis, Biocad and JSC Generium; Agnieszka Piekarska has received honoraria for lectures from Alexion, Swixx Biopharma, Celgene, Santen, Astellas, Teva, and travel grants for participating on advisory boards from Sobi and Alexion; Elena Lukina has received honoraria and travel grants for participating on advisory boards from Sanofi Genzyme, Takeda, Novartis, Bristol Myers Squibb and Generium; Jaroslav Cermak has received honoraria and travel grants for participating on an advisory board from Sobi; Horia Bumbea has received honoraria for participating on advisory boards and consultant fees from Sobi, Janssen, Roche, Abbvie, Novartis, Accord, Novo Nordisk, Sandoz, Alvogen, Amgen, Genesis, Angellini, Takeda, Bristol Myers Squibb and Sanofi; Ismail Amine has received a travel grant for participation on an advisory board and consultancy fees from Sobi; Imre Bodó has received travel grants for international meetings, including a Sobi advisory board meeting; Irena Preloznik Zupan received honoraria and travel grants from Sobi and Alexion; Jerzy Windyga has received honoraria for lectures from Alfasigma, Bayer AG, Novo Nordisk, Octapharma, Roche, Sanofi-Aventis, Shire, Sobi, Swixx BioPharma, Takeda and Werfen, and research grants from Novo Nordisk, Rigel Pharmaceuticals, Roche, Shire and Takeda; Juraj Sokol reported no conflicts of interest.

Compliance with Ethics Guidelines. No formal Ethics approval was necessary for this study.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

REFERENCES

1. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014;124(18):2804–11.

2. Shah N, Bhatt H. Paroxysmal nocturnal hemoglobinuria. StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2021.

3. Gulbis B, Eleftheriou A, Angastiniotis M, et al. Epidemiology of rare anaemias in Europe. Rare Dis Epidemiol. 2010;686:375–96.

4. Kulagin AD, Klimova OU, Dobronravov AV, et al. Paroxysmal nocturnal hemoglobinuria in children and adults: comparative clinical profile and long-term prognosis. Ped Hematol/Oncol Immunopathol. 2018;17(3):11–21.

5. Urbano-Ispizua A, Muus P, Schrezenmeier H, et al. Different clinical characteristics of paroxysmal nocturnal hemoglobinuria in pediatric and adult patients. Haematologica. 2016;102(3):e76–9.

6. Babushok DV. When does a PNH clone have clinical significance? Hematology. 2021;2021(1):143–52.

7. Fu R, Li L, Li L, et al. Analysis of clinical characteristics of 92 patients with paroxysmal nocturnal hemoglobinuria: a single institution experience in China. J Clin Lab Anal. 2020;34(1): e23008.

8. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006;355(12):1233–43.

9. Brodsky RA, Peffault de Latour R, Rottinghaus ST, et al. Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. Haematologica. 2021;106(1):230–7.

10. Al-Ani F, Chin-Yee I, Lazo-Langner A. Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selection and special considerations. Ther Clin Risk Manag. 2016;12(1): 1161–70.

11. McKinley CE, Richards SJ, Munir T, et al. Extravascular hemolysis due to C3-loading in patients with PNH treated with eculizumab: defining the clinical syndrome. Blood. 2017;130(1):3471.

12. European Medicines Agency (EMA). 2021. https://www.ema.europa.eu/en. Accessed 17 Jan 2022.

13. Risitano AM, Marotta S, Ricci P, et al. Anti-complement treatment for paroxysmal nocturnal hemoglobinuria: time for proximal complement inhibition? A position paper from the SAAWP of the EBMT. Front Immunol. 2019;10(1157):1–24.

14. Schubert J, Bettelheim P, Brümmendorf TH, et al. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie—PNH (2018). https://www.onkopedia-guidelines.info/de/hinweise/erstellung-von-leitlinien-1. Accessed 25 Jan 2022.

15. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005;106(12):3699–709.

16. Sahin F, Akay OM, Ayer M, et al. Pesg PNH diagnosis, follow-up and treatment guidelines. Am J Blood Res. 2016;6(2):19–27.

17. Villegas A, Arrizabalaga B, Bonanad S, et al. Spanish consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. Med Clin (Barc). 2016;146(6):278.e1-7.

18. Griffin M, Munir T. Management of thrombosis in paroxysmal nocturnal hemoglobinuria: a clinician's guide. Ther Adv Hematol. 2017;8(3):119–26.

19. Morado M, Freire Sandes A, Colado E, et al. Diagnostic screening of paroxysmal nocturnal hemoglobinuria: prospective multicentric evaluation of the current medical indications. Cytometry B Clin Cytom. 2017;92(5):361–70.

20. Devos T, Meers S, Boeckx N, et al. Diagnosis and management of PNH: review and recommendations from a Belgian expert panel. Eur J Haematol. 2018;101(6):737–49.

21. Weitz IC. Nocturnal paroxysmal hemoglobinuria. 2018. https://bestpractice.bmj.com/topics/pt-br/894. Accessed 25 Jan 2021.

22. Cannizzo E, Raia M, De Propris MS, et al. Features, reason for testing, and changes with time of 583 paroxysmal nocturnal hemoglobinuria clones from 529 patients: a multicenter Italian study. Ann Hematol. 2019;98(5):1083–93.

23. Brodsky RA. How I treat paroxysmal nocturnal hemoglobinuria. Blood. 2009;113(26):6522–7.

24. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013;121(25):4985–96.

25. Huang Y, Liu X, Chen F, et al. Prediction of thrombosis risk in patients with paroxysmal nocturnal hemoglobinuria. Ann Hematol. 2019;98(10): 2283–91.

26. Schrezenmeier H, Röth A, Araten DJ, et al. Baseline clinical characteristics and disease burden in patients with paroxysmal nocturnal hemoglobinuria (PNH): updated analysis from the International PNH Registry. Ann Hematol. 2020;99(7):1505–14.

27. Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. Nat Rev Dis Primers. 2017;3(17028):1–29.

28. Sun L, Babushok D. Secondary myelodysplastic syndrome and leukemia in acquired aplastic anemia and paroxysmal nocturnal hemoglobinuria. Blood. 2020;136:1.

29. Kinoshita T, Murakami Y, Morita YS. 4.21—Diseases associated with GPI anchors. In: Kamerling H, editor. Comprehensive glycoscience. Oxford: Elsevier; 2007. p. 393–419.

30. Brodsky RA, Young NS, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008;111(4):1840–7.

31. Hillmen P, Muus P, Dührsen U, et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. Blood. 2007;110(12):4123–8.

32. Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs. eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019;133(6):530–9.

33. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs. eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019;133(6):540–9.

34. Tomazos I, Hill A, Royston M. Ravulizumab and eculizumab reduce transfusions in adult patients with paroxysmal nocturnal hemoglobinuris: evidence from three real-world databases: TRINETX US EMR, TRINETX US CLAIMS and KOMODO HEALTH. E-poster EP1337. In: Presented at the virtual EHA 2021; 9–17 June.

35. Kulagin A, Klimova O, Rudakova T, et al. Benefits and limitations of long-term eculizumab treatment for paroxysmal nocturnal hemoglobinuria (PNH): real-world data from large cohort study in Russia. Blood. 2018;132(1):2589.

36. Burke JP, Sahli B, Broderick K, Gleason PP. Paroxymsal nocturnal hemoglobinuria real-world effectiveness of C5 inhibitors and cost assessment 2021. https://www.primetherapeutics.com/wp-content/uploads/2021/10/4085-B_PNH-C5-Assessment-1.pdf. Accessed 17 Jan 2022.

37. Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2021;384(11):1028–37.

38. de Latour RP, Szer J, Weitz IC, et al. Pegcetacoplan versus eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PEGASUS): 48-week follow-up of a randomised, open-label, phase 3, active-comparator, controlled trial. Lancet Haematol. 2022;9(9):e648–59.

39. Wong RS, Navarro JR, Comia NS, et al. Efficacy and safety of pegcetacoplan treatment in complement-inhibitor naïve patients with paroxysmal nocturnal hemoglobinuria: results from the phase 3 Prince study. Blood. 2021;138:606.

40. Gomez-Almaguer D, Wong R, Dumagay T, et al. S303: Effect ofpegcetacoplan on quality of life in complement-inhibitor naive patients with paroxysmal nocturnal hemoglobinuria: results from the phase 3 Prince study. HemaSphere. 2022;6:606.

41. Montan I, Löwe B, Cella D, et al. General population norms for the functional assessment of chronic illness therapy (FACIT)-fatigue scale. Value Health. 2018;21(11):1313–21.

42. Desai D, Panse J, Daguindau N, et al. MDS-112 Normalization of hematologic and health-related quality of life markers in patients with paroxysmal nocturnal hemoglobinuria treated with pegcetacoplan and baseline hemoglobin at or above 10 g/dL. Clin Lymphoma Myeloma Leuk. 2022;22:S305.

43. Desai D, Wong R, Fishman J, et al. MDS-254 A matching-adjusted indirect comparison of the efficacy of pegcetacoplan using PRINCE trial data versus ravulizumab and eculizumab in complement inhibitor naive-patients with paroxysmal nocturnal hemoglobinuria. Clin Lymphoma Myeloma Leuk. 2022;22:S306–7.

44. Peffault de Latour R, Roeth A, Kulasekararaj A, et al. Oral monotherapy with iptacopan, a proximal complement inhibitor of factor B, has superior efficacy to intravenous terminal complement inhibition with standard of care eculizumab or ravulizumab and favorable safety in patients with paroxysmal nocturnal hemoglobinuria and residual anemia: results from the randomized, active-comparator-controlled, open-label, multicenter, Phase III Apply-PNH Study. Blood. 2022; 140(Supplement 2):LBA-2-LBA.

45. Kulasekararaj AG, Griffin M, Langemeijer S, et al. Long-term safety and efficacy of ravulizumab in patients with paroxysmal nocturnal hemoglobinuria: 2-year results from two pivotal phase 3 studies. Eur J Haematol. 2022;109(3):205–14.

46. Cooper JP, Farah RJ, Stevenson PA, et al. Hematopoietic cell transplantation for paroxysmal nocturnal hemoglobinuria in the age of eculizumab. Biol Blood Marrow Transplant. 2019;25(7):1331–9.

47. KamranzadehFumani H, Zokaasadi M, Kasaeian A, et al. Allogeneic hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria: a retrospective single-center study. Hematol Oncol. 2017;35(4):935–8.

48. Mei M, Gupta R, O'Donnell M, et al. Post-allogeneic hematopoietic stem cell transplantation

eculizumab as prophylaxis against hemolysis and thrombosis for patients with hematologic disorders associated with paroxysmal nocturnal hemoglobinuria clones. Biol Blood Marrow Transplant. 2019;25(5):e183–5.

49. Shasheleva DA, Maschan AA, Shelikhova LN, et al. Hematopoietic stem cell transplantation with alpha/beta T-lymphocyte depletion and short course of eculizumab in adolescents and young adults with paroxysmal nocturnal hemoglobinuria. Ter Arkh. 2018;90(7):57–64.

50. Vallet N, de Fontbrune FS, Loschi M, et al. Hematopoietic stem cell transplantation for patients with paroxysmal nocturnal hemoglobinuria previously treated with eculizumab: a retrospective study of 21 patients from SFGM-TC centers. Haematologica. 2018;103(3):e103–5.

51. Markiewicz M, Drozd-Sokolowska J, Biecek P, et al. Allogeneic hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria: multicenter analysis by the Polish Adult Leukemia Group. Biol Blood Marrow Transplant. 2020;26(10): 1833–9.

52. Peffault de Latour R, Schrezenmeier H, Bacigalupo A, et al. Allogeneic stem cell transplantation in paroxysmal nocturnal hemoglobinuria. Haematologica. 2012;97(11):1666–73.

53. Vinogradova MA, Kulagin AD, Shmakov RG. Pregnancy in paroxysmal nocturnal hemoglobinuria: from survival to life. TA. 2022;94(7):859–64.

54. Alashkar F, Saner FH, Vance C, et al. Pregnancy in classical paroxysmal nocturnal hemoglobinuria and aplastic anemia–paroxysmal nocturnal hemoglobinuria: a high-risk constellation. Front Med. 2020;7(543372):1–7.

55. Al-Dosari Y, Al-Zahrani H, Al-Mohareb F, Hashmi S. Pregnancy with paroxysmal nocturnal hemoglobinuria: a case series with review of the literature. Saudi J Med Med Sci. 2021;9(2):178–89.

56. Fassett MJ, Hernandez Lopez AL. Treatment of paroxysmal nocturnal hemoglobinuria in pregnancy with eculizumab: a case report. Case Rep Women's Health. 2021;30(1): e00294.

57. Horányi D, Várkonyi A, Nagy GR, et al. Rare case of a pregnancy in a woman with paroxysmal nocturnal hemoglobinuria. Case Rep Orv Hetil. 2016;157(23):916–8.

58. Lauritsch-Hernandez LS, Kraehenmann F, Balabanov S, Kimmich N. Eculizumab application during pregnancy in a patient with paroxysmal nocturnal hemoglobinuria: a case report with review of the literature. Clin Case Rep. 2018;6(8): 1582–7.

59. Miyasaka N, Miura O, Kawaguchi T, et al. Pregnancy outcomes of patients with paroxysmal nocturnal hemoglobinuria treated with eculizumab: a Japanese experience and updated review. Int J Hematol. 2016;103(6):703–12.

60. Rodríguez-Ferreras A, Velasco-Roces L. Eculizumab-related abortion in a woman with paroxysmal nocturnal hemoglobinuria: a case report. J Reprod Infertil. 2019;20(4):252–5.

61. Czyż J, Szukalski Ł, Szukalska A, et al. Eculizumab treatment in pregnant women with paroxysmal nocturnal hemoglobinuria: a Polish experience. Adv Clin Exp Med. 2022;31(6):707–10.

62. Kelly RJ, Höchsmann B, Szer J, et al. Eculizumab in pregnant patients withparoxysmal nocturnal hemoglobinuria. New Engl J Med. 2015;373(11): 1032–9.

63. Choi CW, Jang JH, Kim JS, et al. Efficacy of eculizumab in paroxysmal nocturnal hemoglobinuria patients with or without aplastic anemia: prospective study of a Korean PNH cohort. Blood Res. 2017;52(3):207–11.

64. Dudina G. A mini-review on paroxysmal nocturnal hemoglobinuria and a case of eculizumab treatment of PNH in elderly MDS patient. Cell Ther Transplant. 2017;6(1):48–54.

65. Giannotta JA, Fattizzo B, Barcellini W. Paroxysmal nocturnal hemoglobinuria in the context of a myeloproliferative neoplasm: a case report and review of the literature. Front Oncol. 2021;11(1): 1–8.

66. Lee JW, Peffault de Latour R, Brodsky RA, et al. Effectiveness of eculizumab in patients with paroxysmal nocturnal hemoglobinuria (PNH) with or without aplastic anemia in the International PNH Registry. Am J Hematol. 2019;94(1):e37–41.

67. Shakir A, Narula S, LaGrow A, Nusrat S. Two roads diverge: treatment choice in coexisting severe aplastic anemia and paroxysmal nocturnal hemoglobinuria. J Med Cases. 2020;11(6):182–4.

68. Griffin M, Kulasekararaj A, Gandhi S, et al. Concurrent treatment of aplastic anemia/paroxysmal nocturnal hemoglobinuria syndrome with immunosuppressive therapy and eculizumab: a UK experience. Haematologica. 2018;103(8):e345–7.

69. Raghupathy R, Derman O. Response of paroxysmal nocturnal hemoglobinuria clone with aplastic anemia to rituximab. Case Rep Hematol. 2012;2012: 106182.

70. DeZern AE, Jones RJ, Brodsky RA. Eculizumab bridging before bone marrow transplant for marrow failure disorders is safe and does not limit engraftment. Biol Blood Marrow Transplant. 2018;24(12): e26–30.

71. Parker CJ. Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy. Hematology Am Soc Hematol Educ Program. 2011;2011(1):21–9.

72. DeZern AE, Dorr D, Brodsky RA. Predictors of hemoglobin response to eculizumab therapy in paroxysmal nocturnal hemoglobinuria. Eur J Haematol. 2013;90(1):16–24.

73. Ekinci O, Dogan A, Demircioglu S, et al. Clinical features and responses to eculizumab of paroxysmal nocturnal hemoglobinuria patients: a single-center experience. Med Sci. 2019;8(3):624–7.

74. Kulasekararaj AG, Hill A, Langemeijer S, et al. One-year outcomes from a phase 3 randomized trial of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria who received prior eculizumab. Eur J Haematol. 2021;106(3):389–97.

75. Füreder W, Valent P. Switching from high-dose eculizumab to ravulizumab in paroxysmal nocturnal hemoglobinuria: a case report. Hemasphere. 2020;4(4): e455.

76. Peipert JD, Kulasekararaj AG, Gaya A, et al. Patient preferences and quality of life implications of ravulizumab (every 8 weeks) and eculizumab (every 2 weeks) for the treatment of paroxysmal nocturnal hemoglobinuria. PLoS ONE. 2020;15(9): e0237497.

77. Yenerel MN, Sicre de Fontbrune F, Piatek C, et al. Phase 3 study of subcutaneous versus intravenous ravulizumab in eculizumab-experienced adult patients with PNH: primary analysis and 1-year follow-up. Adv Ther. 2022;40:18.

78. Araten DJ, Belmont HM, Schaefer-Cutillo J, et al. Mild clinical course of COVID-19 in 3 patients receiving therapeutic monoclonal antibodies targeting C5 complement for hematologic disorders. Am J Case Rep. 2020;21(1): e927418.

79. Genthon A, Chiarabini T, Baylac P, et al. Severe COVID-19 infection in a patient with paroxysmal nocturnal hemoglobinuria on eculizumab therapy. Leuk Lymphoma. 2021;62(6):1502–5.

80. Schüller H, Klein F, Lübbert M, Prager EP. Hemolytic crisis in a patient treated with eculizumab for paroxysmal nocturnal hemoglobinuria possibly triggered by SARS-CoV-2 (COVID-19): a case report. Ann Hematol. 2021;100(3):841–2.

81. Shikdar S, Borogovac A, Mohamad E, Khawandanah M. COVID19 infection in a patient undergoing treatment for paroxysmal nocturnal hemoglobinuria (PNH) with ravulizumab. Thromb J. 2021;19(1):75.

82. Gralinski LE, Sheahan TP, Morrison TE, et al. Complement activation contributes to severe acute respiratory syndrome coronavirus pathogenesis. MBio. 2018;9(5):e0175318.

83. Dingli D, Matos JE, Lehrhaupt K, et al. The burden of illness in patients with paroxysmal nocturnal hemoglobinuria receiving treatment with the C5-inhibitors eculizumab or ravulizumab: results from a US patient survey. Ann Hematol. 2022;101(2): 251–63.

84. Cella D, Sarda SP, Hsieh R, et al. Clinically meaningful and long-term improvements in fatigue with the C3 inhibitor pegcetacoplan in paroxysmal nocturnal hemoglobinuria: post-hoc analyses from the PEGASUS study week 48. In: Abstract LPB0118. Presented at the ISTH congress, July 17–21, 2021; Philadelphia.

85. European Commission. Health at a glance: Europe 2020: state of health in the EU cycle. https://ec.europa.eu/health/system/files/2020-12/2020_healthatglance_rep_en_0.pdf. Accessed 25 Jan 2022.

86. de Villiers MR, de Villiers PJ, Kent AP. The Delphi technique in health sciences education research. Med Teach. 2005;27(7):639–43.

87. Risitano AM, Peffault de Latour R. How we('ll) treat paroxysmal nocturnal haemoglobinuria: diving into the future. Br J Haematol. 2022;196(2): 288–303.

88. Nakayama H, Usuki K, Echizen H, et al. Eculizumab dosing intervals longer than 17 days may be associated with greater risk of breakthrough hemolysis in patients with paroxysmal nocturnal hemoglobinuria. Biol Pharm Bull. 2016;39(2): 285–8.

89. de Castro C, Grossi F, Weitz IC, et al. C3 inhibition with pegcetacoplan in subjects with paroxysmal nocturnal hemoglobinuria treated with eculizumab. Am J Hematol. 2020;95(11):1334–43.

90. Shammo J, Gajra A, Patel Y, et al. Low rate of clinically evident extravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria treated with a complement C5 inhibitor: results from a large, multicenter, US real-world study. J Blood Med. 2022;13:425–37.

91. Patriquin CJ, Kiss T, Caplan S, et al. How we treat paroxysmal nocturnal hemoglobinuria: a consensus

statement of the Canadian PNH Network and review of the national registry. Eur J Haematol. 2019;102(1):36–52.

92. de Castro C, Hillmen P, Szer J, et al. CT-286: Results of the PEGASUS phase 3 randomized trial demonstrating superiority of the C3 inhibitor, pegcetacoplan, compared to eculizumab in patients withparoxysmal nocturnal hemoglobinuria. Clin Lymphoma Myeloma Leuk. 2020;20(1):S216–7.

93. Sakai K. Even mild hemolysis in paroxysmal nocturnal hemoglobinuria could severely compromise the quality of life due to long-term sustained intolerant fatigue. Leuk Res Rep. 2020;14(1): 100224.

94. Cella D, Sarda SP, Hsieh R, et al. Changes in hemoglobin and clinical outcomes drive improvements in fatigue, quality of life, and physical function in patients with paroxysmal nocturnal hemoglobinuria: post hoc analyses from the phase III PEGASUS study. Ann Hematol. 2022;101(9): 1905–14.

95. Nishimura J, Yamamoto M, Hayashi S, et al. Genetic variants in C5 and poor response to eculizumab. N Engl J Med. 2014;370(7):632–9.

96. Nishimura J, Kanakura Y. The C5 gene polymorphism in patients with PNH. Rinsho Ketsueki. 2015;56(2):103–10.

97. Nishimura J-I, Yamamoto M, Hayashi S, et al. A rare genetic polymorphism in C5 confers poor response to the anti-C5 monoclonal antibody eculizumab by nine Japanese patients with PNH. Blood. 2012;120(21):3197.

98. Ishiyama K, Nakao S, Usuki K, et al. Results from multinational phase 3 studies of ravulizumab (ALXN1210) versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria: subgroup analysis of Japanese patients. Int J Hematol. 2020;112(4):466–76.

99. Tamura S, Hori Y, Hiroi T, et al. Pegcetacoplan for refractory paroxysmal nocturnal haemoglobinuria associated with the C5 genetic variant. Br J Haematol. 2021;1(1):1–3.