Paroxysmal Nocturnal Hemoglobinuria, Pathophysiology, Diagnostics, and Treatment

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Abstract

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by intravascular hemolysis (IVH) due to diminished or absent inhibition of the complement system because of deficient expression of cell-anchored complement regulating surface proteins. IVH leads to heterogeneous symptoms such as anemia, abdominal pain, dyspnea, fatigue and increased rates of thrombophilia. Inhibitors of the terminal Complement cascade can reverse IVH leading to a significant reduction of disease burden such as thrombembolic events and also mortality. **Summary:** Therapeutic inhibitors of the terminal complement cascade such as eculizumab or ravulizumab significantly improve overall survival through IVH-inhibition. However, not all patients experience complete disease control with normalization of hemoglobin levels and absolute reticulocyte counts (ARC) under terminal complement inhibition as a significant part of patients develop extravascular hemolysis (EVH). EVH can be clinically relevant causing persistent anemia and fatigue. New proximal complement inhibitors (CI) mainly targeting complement component C3 or factors of the amplification pathway such as pegcetacoplan, danicopan, and iptacopan became available and are meanwhile approved for marketing. Additional complement-inhibiting strategies are under clinical development. A switch from terminal to proximal CI in patients with significant EVH can achieve hemoglobin and ARC normalization and significant improvement in quality of life (QoL). Additional approvals of proximal CI agents for the treatment of hemolytic PNH in the first line are available for pegcetacoplan and iptacopan. So far, no evidence-based algorithm is available for decision-making in first-line treatment of which type of drug should be used for individual patients. **Key Messages:** Terminal CIs in hemolytic PNH patients can block IVH and have led to a dramatically improved survival. Proximal CIs ameliorate anemia and improve QoL in patients with relevant EVH. However, more (real-world) data are needed to demonstrate long-term improvement in all patients with hemolytic PNH, especially those under first-line treatment with proximal CI.

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Pathophysiology and Clinical Presentation

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, clonal disorder affecting hematopoiesis. It is characterized by chronic intravascular hemolysis (IVH), pronounced thrombophilia and variable cytopenia. Most patients are diagnosed in young adulthood with a median of 35–40 years. The prevalence of PNH is estimated to be approximately 38 per million individuals, with an incidence of 0.08–0.57 per 100,000 person-years [1, 2].

The PNH phenotype is caused by different somatic mutations of the phosphatidylinositol-N-

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acetylglucosaminyltransferase gene A (PIGA) on the short arm of the X chromosome causing a deficiency of glycosylphosphatidylinositol (GPI)-anchored complement regulatory proteins. In rare cases, mutations of other parts of the PIG enzyme complex may impair the expression of GPI-linked proteins and induce complement-dependent hemolysis [3, 4].

Clinical PNH is not triggered by a single PIGA mutation. As very small polyclonal PIGA-mutated-, GPI-deficient cell populations were detected in healthy individuals and aplastic anemia (AA)-patients without any PNH signs [5], a second event for the progression of PIGA-mutated hematopoietic stem cells is postulated. In this context, additional myeloid or immune escape mutations have been detected opening a putative potential to drive clonal expansion [6]. The association between PNH and bone marrow failure syndromes, especially AA provides support for a putative immunological mechanism as a cofactor driving clonal expansion [7]. Large registry data show that about 53% of PNH patients had a history of aplastic or hypoplastic anemia [8].

The PIGA gene encodes an enzyme that synthesizes the first step of the formation of the GPI anchor on the cytosolic side of the endoplasmic reticulum. In case of functional relevant mutations, proteins without an alternative transmembrane form, such as complement regulatory proteins CD55 as a regulator of C3 convertase and CD59 preventing formation of the membrane attack complex (MAC), cannot be expressed on the cell surface due to the absence of the GPI anchor [7]. On red blood cells (RBCs) downregulation of complement is primarily restricted to these two molecules. Thus, the uncontrolled formation of MAC at the end of the terminal complement cascade leads to IVH. Furthermore, physiological complement activation conditions (CACs), such as infection, inflammation, surgery or pregnancy can lead to severe hemolytic crises.

Intravascular lysis of erythrocytes leads to a reduction of nitric oxide (NO), through reduced formation as well as increased consumption: after the haptoglobin reserve is exhausted free hemoglobin will be converted to methemoglobin by consuming NO. In addition, released arginase reduces L-arginine, the educt for the synthesis of NO. Finally, NO depletion leads to smooth muscle constriction, endothelial dysfunction and platelet aggregation causing the diverse clinical characteristics of PNH [9]. The interaction between complement activity and coagulation is of particular importance. In addition, due to the NO deficiency lacking inhibition of factor XIII and the formation of microvesicles play an important role in the pathophysiology of PNH-associated thrombophilia [10].

Clinical symptoms of PNH are well documented. A large registry analysis demonstrates that over 90% of PNH patients have at least one PNH-associated symptom

and a subset of patients have multiple symptoms [8]. In this analysis of 4439 PNH patients included in the International PNH patient registry, just 45% of patients had a history of hemoglobinuria, but 81% reported fatigue, 56% hemolysis, 45% dyspnea, 43% impaired renal function, 35% abdominal pain, 17% dysphagia, 13% thrombembolic events (TE), with 24% of the male patients reporting erectile dysfunction. In general, high disease activity defined by LDH >1.5x ULN and at least one PNH-related symptom correlates with a larger GPI-deficient granulocyte clone size [8].

Manifestation of thromboembolic events (TE) is the most serious complication and the leading cause of death in untreated PNH patients [11]. These events are often located at unusual sides such as splanchnic, liver (e.g., Budd-Chiari syndrome) or cerebral veins. Pulmonary embolism, deep vein, or arterial thrombosis is present in up to 40%, and central nervous system or myocardial events occur in up to 23% of cases [12]. The origin of TE in PNH is complex and multifactorial. It has been attributed to complement-mediated hemolysis, platelet and leukocyte activation, NO depletion, pro-inflammatory processes, and defective fibrinolysis [10]. Before the availability of complement inhibition, TE were accounting for 40%–67% of deaths with a 5-year mortality rate of approximately 30% [13]. Again, a larger clone size was directly proportional to an increased proportion of patients with high disease activity and TEs. Thus, the size of the GPI-deficient population in the context of decision-making for the treatment of PNH patients appears to be a relevant issue.

Diagnosis

Detection and quantification of GPI-deficient populations is crucial for optimal therapy selection. Therefore, flow cytometry of GPI-anchored proteins on peripheral blood cells is the gold standard for diagnostics in PNH. Different markers and staining strategies such as multiparameter cytometry for PNH testing are available [14].

It is generally recommended to use at least two different GPI markers on 2 cell lines (leukocytes and erythrocytes). This requirement is even more relevant for the detection of cases with polymorphic variants (e.g., CD157) or rare cases of isolated deficiency of GPI-anchored proteins such as isolated inherited CD59 deficiency. A suboptimal approach can lead to misinterpretation [15].

Flow cytometry for PNH will detect a mosaic of GPI-deficient PNH cells together with normally expressing cells having all GPI-anchored proteins present. Complete GPI-deficient populations are referred to as type III cells in diagnostic assays with flow cytometry associated with

monoclonal antibodies or GPI-binding toxins linked to fluorochromes. Populations with reduced expression of GPI-anchor molecules or GPI-linked proteins are referred to as type II cells [16]. Missense mutations are in some cases the background of suboptimal but not completely disrupted presence or function of the PIGA gene product. Type I cells show a normal phenotype.

Highly sensitive flow cytometric GPI-deficiency analysis enables the detection of even very small GPI-deficient populations. In addition, it allows a quantitative assessment of the PNH populations during follow-up of PNH patients. In addition, this technique is suitable for patients suffering from bone marrow failure syndromes such as AA.

Diagnosis of PNH should be considered in the presence of the following:
1. Signs of IVH without specific characteristics within microscopic blood counts (e.g., exclusion of helmet cells, sickle cells, etc.)
2. Thrombosis, especially at atypical sites (e.g., sinus vein thrombosis, Budd-Chiari syndrome, mesenteric, portal or splenic vein thrombosis, dermal thrombosis); in combination with hemolysis
3. Unclear cytopenia, diagnosis of AA or hypoplastic myelodysplasia
4. Abdominal pain crises of unknown origin or dysphagia, especially with concomitant signs of hemolysis
Follow-up of the flow cytometric analysis should be scheduled depending on the current clinical situation. If a significant GPI-deficient population is detected the analysis should be repeated at intervals of 6 months regularly. In case of a change in clinical symptoms, examination intervals should be adjusted individually. In addition, physical examination, and detailed medical history including PNH-associated symptoms should be carried out with special regard to thromboembolic events, renal function, and bone marrow failure [1].

Treatment with Terminal Complement Inhibitors

Before 2000, patients with hemolytic PNH could only be treated symptomatically, e.g., by transfusions and by primary or secondary anticoagulation [17]. Data for primary anticoagulation for patients with intense hemolysis were collected retrospectively [18]. Nevertheless, it has been general practice before the introduction of complement inhibitors (CI) because of frequent TE relapses even under running secondary anticoagulation. Patients with such complications often received allogeneic bone marrow transplantation before the introduction of CIs. However, this procedure was associated with high morbidity and mortality. Meanwhile, bone marrow transplantation is mainly restricted to patients with secondary bone marrow failure.

The development of inhibitors of the Complement cascade mainly changed the treatment strategy of hemolytic PNH [19]. However, before starting such CI therapy clone size and patient's symptoms are needed to be determined. If clone size is low (below 50–60%), especially in the absence of hemolytic symptoms there might be no significant benefit for the patient [14]. Bone marrow failure is not ameliorated by Cis [14] and should therefore be treated according to AA guidelines. The first CI effectively blocking IVH was eculizumab [19]. It binds to C5 and inactivates the formation of MAC resulting in inhibition of intravascular destruction of PNH RBCs. Reduction of thromboembolic events by 92% under eculizumab compared to the pre-eculizumab era led to a highly improved survival in these patients compared to age- and sex-matched controls [20].

Meanwhile, eculizumab biosimilars have been developed and are available for alternative clinical use [21]. In this context, the phase 3 non-inferiority trials studying the Amgen biosimilar (ABP959) and the Samsung Biosimilar (SB12) have demonstrated equivalent clinical activity in terms of hemolysis control, transfusion requirements and prevention of hemolysis-induced symptoms and complications such as fatigue or major adverse vascular events [22, 23].

Almost one-third of the patients not reaching normal hemoglobin levels suffer from associated bone marrow failure. Thus, surveillance of bone marrow function needs to be performed during the follow-up of treatment. Another issue to be considered in patients with persistent anemia is breakthrough hemolysis (BTH) presenting with signs of IVH even in the presence of C5i. BTH has not yet been clearly defined by limiting values. Considering parameters such as increased LDH and symptomatic drop in hemoglobin BTH should be separated into pharmacokinetic or pharmacodynamic events. In 10–15% of the cases, a pharmacokinetic BTH event occurs at the end of the 14-day treatment interval of eculizumab treatment. Treatment recommendations should either include shortened dose intervals or increasing each single dose. Shortening of dose intervals from 14 to 12 days can be applied to the label of the drug. As a pharmacodynamic event, CACs will take place such as infections, pregnancy etc. In these conditions, it will be possible to reduce the intensified dosage after the termination of CAC.

Further development using a newly discovered antibody recycling mechanism by ph-dependent neonatal Fc receptor binding resulted in a significantly prolonged dosing interval from 2 to 8 weeks as shown for ravulizumab. In two randomized phase III studies for treatment-naive and experienced patients, respectively, ravulizumab demonstrated non-inferiority compared to eculizumab [21, 24]. In contrast to eculizumab, ravulizumab-treated patients exhibited continuously

suppressed free C5 serum levels [24]. Ravulizumab was licensed in 2018 by the FDA and in 2019 by the EMA. Meanwhile, ravulizumab has replaced eculizumab in many countries because of patients' decisions and better control of pharmacokinetic BTH.

The antibody recycling technology has been further developed by smart Ig technology. Crovalimab is a C5 blocking agent using PH-depending binding to neonatal FcR- and antigen-binding. In addition, further modification has led to an increased level of isoelectric point of the antigen/antibody complex to allow an enhanced uptake of the positively loaded complex by pinocytosis through negative cellular membrane potential [25]. Thus, crovalimab maintenance can be applied by small volume doses. Crovalimab is targeting a different C5 epitope, thereby allowing treatment of rare cases with the C5 polymorphism p.Arg885His. As a result, the serum levels of free C5 could be demonstrated to be continuously suppressed. As a consequence, terminal Complement blockade by Crovalimab provides more independency for patients by easy self-application of the drug. In addition, there is no pharmacokinetic loss of C5 suppression and sustained clinical efficacy [26]. Licencing of crovalimab by the EMA is expected to take place in September 2024.

Cemdisiran, a recently developed liver-targeted RNA interference therapeutic is focusing on the suppression of liver production of C5 protein. It is currently under clinical development for complement-mediated diseases such as hemolytic PNH. Since C5 is produced in small amounts by endothelial cells the addition of antibody against C5 (pozelimab) is needed for optimal suppression of IVH in PNH patients. Since large amounts of C5 will not be produced in cemdisiran treated patients 1 could speculate that the application of this new approach would be helpful to prevent BTH either pharmacokinetically driven or related to CAC. This will be evaluated within the current trials [27].

Pregnancy in PNH

One special issue to deal with PNH is the management of pregnancy. The mortality rate in untreated pregnant PNH patients has been unacceptably high by 8–20% even though such risk patients have been supervised more closely in several centers. The major complication in these patients has been TEs either during pregnancy or within the postpartum period. In addition, fetal mortality has been reported to occur in 4 and 9% of cases. The observations in single case reports suggested that eculizumab might improve the outcome of pregnant PNH patients. Young female PNH patients with improved clinical symptoms under CI therapy might be more likely to consider pregnancy. A retrospective analysis of 61 PNH patients suggests that eculizumab appears to be safe and

efficacious during pregnancy as there were fewer premature births and miscarriages plus greater fetal survival when eculizumab was given compared to pregnancies without eculizumab. There was a need in >50% of patients for modification of the eculizumab dose either by increasing each single dose or by shortening the dosing intervals. Thrombembolic events did not occur during pregnancy. However, 2 events happened during the postpartum period. One of the two occurred after plasma infusions because of postpartum hemorrhage. No pregnant PNH patient under eculizumab died during the observation period. In conclusion, the authors find that eculizumab during pregnancy is safe and does affect the clinical outcome of mother and child during and after pregnancy [28]. Engineered antibodies to modify their decay by neonatal Fc receptors have been applied reluctantly in pregnancy [29]. For pregnant PNH patients, the application of ravulizumab has not yet been published. So far, there is only some experience available for patients with atypical hemolytic uremic syndrome [30].

The pharmacokinetic cause for BTH as seen under treatment with eculizumab mainly at the end of each dosing interval could be almost abolished by antibody modification technique as demonstrated for ravulizumab or crovalimab leading to constant C5 suppression below 0.5 µg/mL. BTH due to CAC such as infections as a pharmacodynamic effect might additionally be driven by a bypass effect within the complement cascade leading to C5 activation even in the effective presence of C5 inhibitor [31]. Thus, early treatment of any infection for patients under CIs is highly recommended.

Extravascular Hemolysis as a Unmet Need under Terminal CI

There is still an unmet need in terms of normalization of hemoglobin levels in some patients. A recently published study of 501 patients under C5i in the UK revealed that only about 20% of patients reached hemoglobin normalization [20]. A sequel from C5 inhibition is the switch from IVH to extravascular hemolysis (EVH) leading to PNH in turn to a Coombs test positive state [32]. The first published description on clinically significant hemolysis was a description of a patient in which the initiation of eculizumab leads to a stop in IVH resulting in a reduction of transfusion requirement. However, this requirement could not be completely abolished, and the patient remained in a fatigued state. It could be demonstrated that RBCs have been sequestered in the spleen and partially in the liver. Splenectomy for this case led to increased hemoglobin levels accompanied by an increase of PNH RBCs. Increased bilirubin due to Gilbert's syndrome and LDH levels were unaffected by the procedure. In addition, it has been discovered that the extravascular RBC destruction is mainly

Table 1. Anti-complement compounds targeting the proximal complement cascade (alphabetical order)

Compound	Type of compound/target	Administration	Study in switch patients, EVH definition/inclusion criteria	Randomization, treatment period, number of patients, BTH in experimental arm	Study in naive patients
Danicopan [37, 38]	Small molecule inhibitor, FD	Oral TID 150–200 mg	Hb ≤9.5 g/dL, ARC ≥120/nL, on C5i ≥6 months	2:1; $N = 86^*$ 12 weeks $N = 42$, danicopan; $N = 21$, placebo 4.1% (2/49) with BTH	$N = 10$ 100–150 mg TID 2 patients with BTH
Iptacopan [39]	Small molecule inhibitor, FB	Oral BID 200 mg	Hb <10 g/dL; ARC ≥100/nL, on C5i ≥6 months	8:5; $N = 97$ 48 weeks $N = 63$, iptacopan; $N = 35$, Ecu/Ravu 8.3% (8/96) with BTH	$N = 40$ Oral BID 200 mg No patients with BTH
Pegcetacoplan [40, 41]	Pegylated cyclic peptide inhibitor (compstatin), C3	s.c. 1,080 mg twice weekly	Hb ≤10.5 g/dL, ARC >1.0 × ULN; eculizumab for ≥3 months	1:1; $N = 80$ $N = 41$, pegcetacoplan; $N = 39$, eculizumab, 48 weeks BTH 23% (19/80)	$N = 53$; $N = 35$, pegcetacoplan $N = 18$, BST 1,080 mg twice weekly 2 patients with BTH
OMS906 [42]	Monoclonal antibody, MASP-3	s.c. 5 mg/kg BW every 4 weeks	NA	NA	$N = 11$ 5 mg/kg BW every 4 weeks 1 BTH reported

due to a deposition of C3 fragments on the PNH RBC surface despite full inhibition of the terminal part due to the stimulated proximal part of the complement cascade because of missing membrane regulatory molecule decay accelerating factor (DAF, CD55). This deposition on PNH RBC can be detected either by C3-specific Coombs test or directly by flow cytometry using monoclonal antibodies against C3d or C3c [32]. Such C3 fragment deposition on PNH RBCs almost occurs in every patient with hemolytic PNH under C5 inhibitor therapy. In addition, every RBC can be principally affected as shown by in vitro analysis. Differences between single PNH patients are therefore rather a quantitative but not a qualitative difference. Depending on the definition of clinically relevant EVH, between 10 and 30% of hemolytic PNH treated with ravulizumab or eculizumab ultimately experience EVH [33, 34] with symptomatic anemia (hemoglobin ≤10.5 g/dL) reticulocytosis (absolute reticulocyte count [ARC] >100 G/L). The latter argues against anemia due to bone marrow failure. Simultaneous targeting of terminal complement and the alternative pathway (AP) may therefore address both IVH and EVH in patients with PNH.

Further investigation revealed that there is a correlation in comparison of different PNH patients under C5 inhibition between ARC and the number of C3 fragment-positive PNH cells leading to the conclusion that the more C3 fragment deposition the higher the chance for clinically symptomatic EVH. In addition, stronger deposition of C3 fragments is related to genetic variants of Complement Receptor 1 and also of C3 [35]. So far standardized tests for detection of these genetic variants are not yet available for clinical diagnostics.

In order to decide which patients would fit to be switched from C5i to a proximal inhibitor, a clinical definition of significant EVH is warranted. The SAA working party of the European Bone Marrow Transplantation Group has proposed laboratory criteria for the definition of EVH. These criteria consist of the detection of C3 fragment deposition on GPI-deficient RBC, LDH ≤1.5 ULN, and ARC ≥100 G/L [33]. Using these criteria, in a multicenter analysis about 48% of patients could be attributed to the EVH subgroup in the whole cohort. A significant part of patients with EVH according to the definition criteria has been found in all subgroups of patients (from complete response to minor response) under C5i. Depending on the definition of clinically relevant EVH, between 10 and 30% of hemolytic PNH treated with ravulizumab or eculizumab ultimately experience EVH [33, 34] with symptomatic anemia (hemoglobin ≤10.5 g/dL) reticulocytosis, which rules out anemia due to bone marrow failure.

An evidence-based definition of clinically significant EVH is still missing. Randomized clinical studies for switching patients from terminal to proximal CI providing new substances have used non-uniform criteria for

such definition in terms of hemoglobin and reticulocyte counts (Table 1). In addition, a recent analysis revealed that even in the case of measurable significant EVH caring physicians described in those identified patients a well-controlled PNH in ≥75%. Affected patients reported a good to excellent quality of life (QoL) in ≥60% of cases [36].

Newly Developed Proximal Complement Inhibitors

The first successful trial in patients responding suboptimally to terminal CI was initiated using pegcetacoplan with C3 as the primary target. The so-called PEGASUS phase 3, randomized open-label, active-comparator study was the proof of principle needed to demonstrate that proximal CI can be successfully and effectively applied to patients with hemolytic PNH and clinically relevant EVH by using a compound, which can effectively block IVH while attenuating EVH simultaneously [40]. In this first completed trial 80 patients with suboptimal response to (in 24/80 patients even up-dosed) eculizumab with a Hb ≤10.5 g/dL despite a median of ≥3.4 ears of eculizumab treatment, were randomized to receive either pegcetacoplan (1,080 mg, self-administered as a 20 mL subcutaneous infusion twice weekly) or eculizumab after initial combination treatment with both drugs for 4 weeks. This trial for the first time demonstrated, that proximal complement inhibition enables rescue of patients with clinically relevant EVH in order to achieve almost normal hemoglobin levels and freedom from transfusions in a significant fraction of patients [41]. In addition, ARC will be almost normalized and FACIT-Fatigue scores in a clinically relevant size. However, the trial also showed that the effective shielding of GPI-deficient RBCs from complement attacks leads to an increase in the fraction of these susceptible cells, which in turn can cause unprecedented forms of severe BTH with a marked increase in LDH [43, 44]. Approximately 19.5% of participants reported TEAEs of hemolysis across 48 weeks.

Pegcetacoplan has also been tested in a therapy naive population [45] validating the efficacy of anti-C3-therapy. The same fact – the availability of CIs per se – effectuates such studies with the need for swift recruitment to be performed in countries with no standard CI available (allowing randomization against best supportive care) and precludes head-to-head trials of new compounds in therapy naive PNH patients. Both pegcetacoplan trials led to FDA approval in May 2021 in patients with PNH, while EMA approved it for adults with PNH remaining anemic despite at least 3 months of anti-C5-treatment. This label has recently been modified so that pegcetacoplan is now licensed and available for all patients with PNH also in Europe.

There is an ongoing refinement of therapeutic anti-complement strategies leading to the development of several proximal CIs mainly targeting modules of the AP [46] (Table 1; Fig. 1). In addition to these drugs, there is a plethora of new complement targeting strategies against an abundance of diseases and pathologies including recombinant proteins, antibodies, nanobodies, specific peptides and small molecules as well as genetic therapies, e.g., interfering RNA therapeutics [47, 48].

Danicopan is an oral factor D (FD) inhibitor [37]. FD is considered to be the key rate-limiting serine protease cleaving factor B with as little as 1–2% of active FD required to activate FB, which is why an effective antagonist needs to be available in sufficient concentrations.

Danicopan has been evaluated in phase 3, randomized, placebo-controlled ALPHA trial as an add-on therapy in patients with clinically relevant EVH under ravulizumab or eculizumab. Hence, in contrast to studies with iptacopan and pegcetacoplan, patients within the ALPHA trial received a combination of terminal and proximal CI. Study participants received danicopan (150 mg TID) or placebo during a 12-week treatment period. Thereafter, placebo-treated patients have been switched to danicopan for an additional 12-week open-label period followed by a long-term extension period. The primary study endpoint of change from baseline to week 12 in Hb was met [44]; long-term follow-up data have been recently presented [38] and confirm the pre-specified interim results: Increases in Hb levels were maintained up to week 104 (≥2.8 g/dL), and a relevant proportion of participants experienced increases in Hgb levels (≥2 g/dL; 42% and 54%, respectively) in the absence of transfusion (78–90%), while no new safety signals were observed in the second-treatment period or during the LTE with some hepatic abnormalities (ALT, AST, bilirubin levels) in the danicopan arm. In accordance with other switch trials patients under dual CI showed a decrease in ARC and an increase in FACIT-Fatigue scores. Interestingly, despite the dual complement inhibition, 7.1% experienced a BTH. However, these events have been mild and were self-limiting. Danicopan has been licensed on April 2024 by the FDA and on May 2024 by the EMA as an add-on therapy to terminal CI using eculizumab or ravulizumab.

Iptacopan is an oral proximal CI targeting factor B in the AP (Fig. 1) [49, 50]. A phase 2 trial showed that iptacopan as an add-on to eculizumab generated relevant hemoglobin increases in anemic C5-pre-treated patients, even when eculizumab was discontinued [51]. Iptacopan monotherapy also demonstrated efficacy in treatment-naive PNH patients within the phase 2 APPOINT-PNH trial [39].

Endpoints in the switch APPLY trial were a ≥2 g per deciliter hemoglobin increase from baseline and hemoglobin ≥12 g per deciliter (both assessed between days 126 and 168 and sustained for at least 3 out of 4 assessments), each in the absence of RBC transfusions. After 24 weeks, in which patients were randomized between
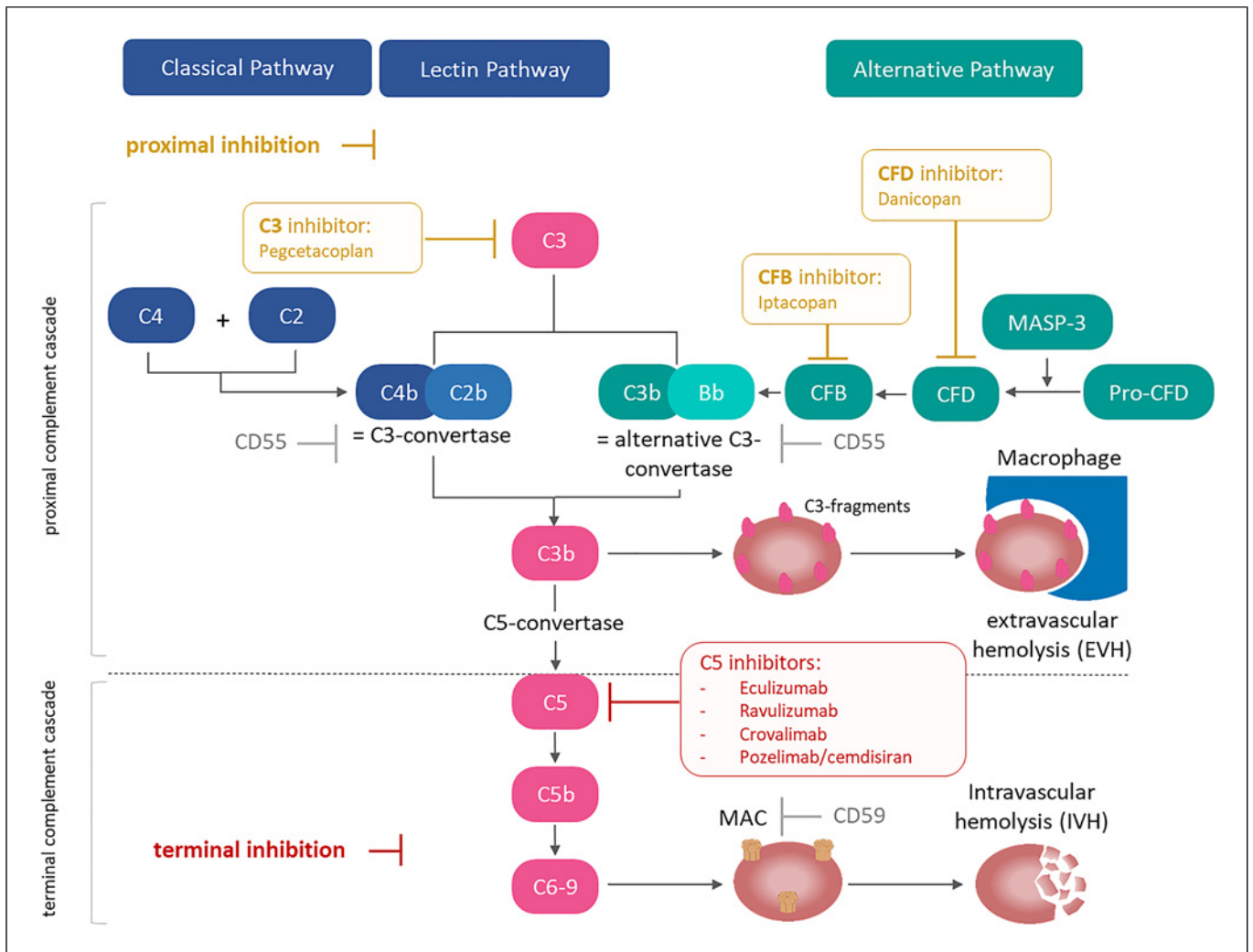
Fig. 1. The complement is divided into a proximal and a terminal cascade. Intravascular (IVH) and extravascular (EVH) hemolysis are depicted as well as targets of current and new complement inhibitors (CI). MAC, membrane attack complex; MASP-3, mannan-binding lectin associated serine protease 3; CFB, complement component factor b; CFD, complement component factor d; C3, complement component 3.

iptacopan 200 mg BI and placebo, all patients received iptacopan in the extension treatment period. Iptacopan led to a mean hemoglobin increase from baseline of 3.59 g/dL with only 57/62 patients remaining transfusion free, mean hemoglobin levels a 48 weeks were 12.1/12.2 g/dL in both treatment groups [52]. Mean FACIT-Fatigue scores increased to 43.6 and 44.6, respectively, and ARC normalized under iptacopan [39].

Both, the APPOINT and the APPLY study did not report cases of meningococcal infections. Non-severe infections like nasopharyngitis, bacterial infection viral infection were the most commonly reported adverse reactions (≥10). In AP-PLY, serious ARs were reported in 2 (3%) patients with PNH receiving iptacopan, which included pyelonephritis, urinary tract infection and COVID-19, while from APPOINT serious ARs were reported in 2 (5%) patients which included COVID-19 and bacterial pneumonia. However, a risk mitigation strategy with additional vaccinations against

Streptococcus pneumoniae which is mandatory or *Haemophilus influenzae* which is highly recommended in addition to meningococcal vaccinations was established. Real-world data about infectious complications once this orally taken medication will be available outside study guidelines should be closely monitored. This holds true for all proximal CIs as, e.g., recently presented 3-year follow-up data from the PEGASUS and PRINCE studies revealed serious infections as a complication in about a fifth of all patients (27/132) with 6/132 experiencing a septic complication [53]. Iptacopan has been approved in December 2023 by the FDA and in June 2024 by the EMA for the treatment of adults with hemolytic PNH.

Licensing has been given for both proximal CIs pegcetacoplan and iptacopan by the FDA and EMA even in first-line PNH treatment for patients with significant hemolytic disease, acknowledging the results of the PRINCE and the APPOINT trials. The general concept of

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proximal, AP-specific CIs is to demonstrate their aptitude to specifically block the respective proximal serine protease patients only partially responding to C5 inhibitors when given in addition to a C5I. This is generally followed by a phase III trial in which patients are randomized between the new proximal treatment concept and the already established C5 inhibitor. This strategy, and the fact that CIs are only available in a fraction of countries means that several compounds are tested against the so-called therapeutic standard, while this standard depends on the availability of drugs as well as on reimbursement issues [29, 54]. Switch studies are conceptualized in order to demonstrate repression of IVH and EVH in a population, in which EVH has emerged as a clinically relevant problem. With the ongoing reassurance that refined risk mitigation strategies such as extended vaccination strategies allow us at this point in time to assume that proximal CI in adults does not lead to a significant increase in infection rates or other hitherto unforeseen consequences (although we still have to learn in detail, what sequelae proximal CI will in the eventually lead to) the question is if also therapy-naive PNH patients need to be tackled the same way. Reliable inhibition of IVH in addition to the prevention of the development of EVH due to the mode of action of these AP-specific compounds might allow a more effective strategy from the beginning, especially as improvements in hemoglobin levels, transfusion avoidance, ARC normalization and amelioration of fatigue were unforeseen before with terminal CIs. In other words, the question was (is) should we control IVH first and then see, which patient will develop clinically relevant EVH or should we go all-in from the get-go as we are not dealing with a malignant disease in which we need first- and second-line therapies but a classical hematologic chronic disease for which the best available therapy should be given to all patients once therapy is indicated. This notion of course meets – at this point in time – some arguments, which have to be addressed, e.g., best compound, mode of administration, side effects, and retention of potentially beneficial proximal complement functions [55]. Thus, missing an evidence-based algorithm for decision-making on which type of drug should be used for each individual patient, it is highly recommended to include all treated patients, especially those under proximal Cis in the International PNH Registry, in order to provide more surveillance and information during the course of treatment on these promising new agents. The Registry is now going to be headed by the International PNH Interest Group (IPIG) and thus independent from commercial interests.

Another proximal CI which gained recent interest has already recruited therapy naive and switch patients for phase 1 and 2 studies and is for which a phase 3 study is soon planned to also recruit patients in European countries is OMS906 [42, 56] a highly selective humanized IgG4 mAb that binds to and inhibits mannan-binding lectin-associated serine protease-3 (MASP-3) a serine protease which continuously converts the zymogen (pro-FD), to FD [57]. A phase 1 study in healthy subjects showed that OMS906 given at 5 mg/kg SC providing substantial MASP-3 inhibition through Day 42, while a phase 1b trial in treatment-naive PNH patients showed hemoglobin normalization in 9/11 patients with monthly s.c. dosing without clinical breakthrough hemolysis, LDH (8/11) and ARC normalization (10/11), and transfusion independence in all 11 patients. The drug has been well tolerated with no safety signals of concern. A C5-switchover PNH trial is fully enrolled in sites in the UK, Germany, and Switzerland and OMS906 dose escalation guided by is underway with the ultimate goal to achieve quarterly s.c. In addition to the mentioned substances, innovative strategies using factor H fusion protein and a bifunctional C5 antibody are on the way.

Terminal complement inhibition has led to a normalized survival of PNH patients whereas proximal inhibition will improve the quality of life, especially in a subgroup of these patients. Taking into account that clinical studies addressing the switch from terminal to proximal or dual complement inhibition have established different inclusion criteria in terms of ARC or hemoglobin levels, a definition of clinically significant EVH is so far hard to define and apart from any evidence. In order to find a suitable therapy for each individual patient, the symptoms experienced by the individual patient such as symptomatic anemia or fatigue will become the main important decision point in addition to the laboratory findings such as ARC or Hb and LDH levels. It has often been postulated that fatigue and loss of QoL might be in part independent of reached hemoglobin levels in PNH patients under complement inhibition.

Fatigue is usually assessed using the patient-reported FACIT-Fatigue instrument [58], and a clinically important change on the FACIT-Fatigue scale for patients with PNH was defined as five points [59]. The recent switch trials all reported an increase in FACIT-Fatigue beyond these clinically relevant 5 points, which demonstrates the clinically relevant improvement in this group of PNH patients. As we are all aware, QoL consists of more dimensions than fatigue [60], but unfortunately, QoL tools used within PNH trials so far only consist of cancer-related QoL tools besides the FACIT-Fatigue score. We think that it is really important to apply disease-related QoL tools when assessing this group of patients [61, 62].

Future studies will also have to consider genetic factors as mentioned above potentially affecting the efficacy of CI therapies. With the approval of now seven anti-complement therapies (eculizumab, two biosimilars, ravulizumab, pegcetacoplan, iptacopan, and danicopan) (Fig. 1) and many more around the corner, transparent pharmacokinetic and pharmacodynamic data must

accompany upcoming study data [63]. In addition to new needed biomarkers reflecting disease activity and drug efficacy, we will hopefully enter a new era of personalized anti-complement therapy with improved individual treatment success for PNH patients, and the hope for more reasonable pricing.

Conflict of Interest Statement

Jens Panse received honoraria from Alexion, Apellis, Blueprint Medicines, BMS, Boehringer Ingelheim, Chugai, MSD, Novartis, Pfizer, Roche, Samsung Bioepics, and SOBI. Britta Höchsmann received honoraria from Alexion, Apellis, Novartis, Pfizer, Roche, and SOBI. Jörg Schubert received honoraria from Alexion, Amgen, Novartis, Pfizer, Roche, Samsung Bioepics, and SOBI.

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