REVIEW

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The Advancing Landscape of Paroxysmal Nocturnal Hemoglobinuria Treatment

Paroksismal Noktürnal Hemoglobinüri Tedavisinde Gelişen Manzara

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Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare chronic bone marrow failure condition characterized by complement-mediated hemolytic anemia and thrombosis. While its initial clinical description occurred in 1882, somatic mutations in *PIGA* were discovered in the 1990s. With an improved understanding of PNH biology, a focused effort on complement inhibitors led to the discovery of eculizumab, a C5 inhibitor initially approved by the US Food and Drug Administration in 2007. Terminal complement pathway inhibition reduced intravascular hemolysis, anemia, and thrombosis. Further advancements in drug development for PNH have included improved pharmacokinetics with ravulizumab in 2018 and the introduction of proximal complement inhibitors such as pegcetacoplan (2021), iptacopan (2023), danicopan (2024), and crovalimab (2024) to enhance patient outcomes. With these new proximal and distal complement inhibitors in the treatment landscape, it is timely for clinicians to review the evolving landscape of PNH treatments and patient selection.

Keywords: Paroxysmal nocturnal hemoglobinuria, Aplastic anemia, Novel complement inhibitors

Öz

Paroksismal nokturnal hemoglobinüri (PNH), kompleman aracılı hemolitik anemi ve tromboz ile karakterize nadir görülen kronik bir kemik iliği yetmezliği durumudur. İlk klinik tanımlaması 1882 yılında yapılmış olsa da, *PIG*'deki somatik mutasyonlar 1990'larda keşfedilmiştir. PNH biyolojisinin daha iyi anlaşılmasıyla, kompleman inhibitörlerine odaklanan çalışmalar, ilk olarak 2007 yılında ABD Gıda ve İlaç Dairesi tarafından onaylanan bir C5 inhibitörü olan ekulizumabın keşfedilmesine yol açmıştır. Terminal kompleman yolu inhibisyonu intravasküler hemolizi, anemiyi ve trombozu azaltmıştır. PNH için ilaç geliştirmedeki diğer ilerlemeler 2018 yılında ravulizumab ile farmakokinetiğin iyileştirilmesi ve hasta sonuçlarını iyileştirmek için pegcetacoplan (2021), iptacopan (2023), danicopan (2024) ve crovalimab (2024) gibi proksimal kompleman inhibitörlerinin piyasaya sürülmesi yer almaktadır. Tedavi sahnesindeki bu yeni proksimal ve distal kompleman inhibitörleri ile klinisyenlerin PNH tedavilerinin ve hasta seçiminin gelişen ortamını gözden geçirmelerinin zamanıdır.

Anahtar Sözcükler: Paroksismal noktürnal hemoglobinüri, Aplastik anemi, Yeni kompleman inhibitörleri

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH), initially described in 1882 by Strübing [1], is a rare clonal hematopoietic stem cell (HSC) disorder. It is characterized by chronic hemolytic anemia due to complement-mediated red cell lysis, thrombosis, smooth muscle dystonia, and bone marrow failure [2,3]. Until 2007, treatment for PNH was largely supportive, with stem cell transplantation being the only definitive therapy. The complement inhibitor eculizumab improved the prognosis for individuals with PNH by inhibiting C5-mediated intravascular hemolysis [4]. Eculizumab therapy greatly reduces mortality, improves quality of life, decreases fatigue and thrombotic risk, and reduces transfusion dependence and other anemia-associated symptoms [4,5,6]. However, a significant proportion of patients with PNH continue to experience breakthrough hemolysis (BTH) and transfusion dependence due to C3-mediated extravascular hemolysis (EVH) despite eculizumab therapy [7,8,9]. The development of novel complement inhibitors has changed the treatment paradigm for patients with PNH suffering from anemia owing to extravascular as well as BTH. These novel agents and the evolving PNH treatment landscape are discussed in this review.

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Pathophysiology

PNH arises from an acquired mutation in the *PIGA* gene, which plays a critical role in the biosynthesis of glycosylphosphatidylinositol (GPI) anchors [10,11,12]. These anchors are essential for attaching various surface proteins, including CD55 (a decay-accelerating factor) and CD59 (the membrane inhibitor of reactive lysis), which regulate complement activation [13,14]. *PIGA*-mutated HSCs produce erythrocytes deficient in CD55 and CD59, leaving them vulnerable to complement-mediated lysis [12]. This loss of complement regulation underlies hemolysis in PNH [11].

PIGA-mutated cells may be present in low and clinically insignificant amounts. Evolution to PNH requires clonal expansion of the *PIGA*-mutated population and frequently occurs in the setting of aplastic anemia (AA). The mechanism of clonal expansion is believed to be due to a survival advantage of *PIGA*-mutated cells compared to the normal HSC population in the setting of AA [15,16]. AA and PNH are closely related disorders due to their shared immune-mediated pathogeneses. While 40% of AA patients have detectable PNH clones, 10%-30% of all AA patients will eventually develop hemolytic PNH [17]. Because PNH is a bone marrow failure disorder linked to T-cell-mediated autoimmunity, it is also associated with an increased risk of secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Approximately 2% to 6% of PNH patients develop secondary MDS/AML within 10 years, while the prevalence is 9% in PNH patients with AA [17]. Factors associated with progression from PNH to secondary MDS/AML include longer duration of disease, increased telomere attrition, presence of adverse prognostic mutations, and multiple mutations [17,18].

Thrombosis is the most common cause of morbidity and mortality in patients with PNH and is responsible for approximately 40% to 67% of deaths [19]. The mechanism of thrombosis in PNH has not been entirely elucidated but it is attributed to a combination of factors [20,21]. Notably, thrombosis in PNH is more common in patients with large PNH clones (>50% PNH granulocytes) [22]. PNH is associated with both venous and arterial thrombosis, but venous sites are most common [19]. Thrombosis may occur in typical sites such as the limbs and lungs as well as in more unusual sites such as the sagittal and cavernous sinuses, mesenteric veins, and the hepatic vein (Budd-Chiari syndrome). Budd-Chiari syndrome is the most common thrombotic event in patients with PNH [19,20,23].

Management of Paroxysmal Nocturnal Hemoglobinuria

In general, therapy should be initiated for patients exhibiting symptoms of significant hemolysis, such as severe anemia, thrombosis, pain paroxysms, debilitating fatigue, and worsening renal insufficiency [15,16]. The size of the PNH clonal population is another factor to consider in initiating treatment. Patients with small clonal populations (usually <30%) often lack clinical hemolysis and PNH-associated symptoms; therefore, they do not benefit from complement inhibitors. In contrast, those with large PNH clonal populations (usually >50%) do benefit from complement inhibitors. For symptomatic patients with moderate PNH clonal populations (30%-50%), treatment should be based on symptom severity. Providers should assess each case individually, as some patients may still benefit from complement inhibitor therapy [24].

The goals of PNH treatment are to limit complement-mediated hemolysis and subsequent complications and ultimately improve survival patient survival. The efficacy of PNH treatment can be measured by several key endpoints. The degree of hemolysis is estimated using lactate dehydrogenase (LDH) levels, reticulocyte counts, and hemoglobin levels. Other disease- and treatment-related endpoints include thrombotic events, BTH, fatigue as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale, and transfusion dependency. To understand the need for novel therapeutics and their clinical application, we discuss the BTH and EVH seen in PNH in the following subsections, along with the differences from intravascular hemolysis.

Breakthrough Hemolysis

Two humanized monoclonal antibodies (mAbs), eculizumab and ravulizumab, targeting C5 have been approved by the US Food and Drug Administration (FDA) for use in patients with PNH. BTH usually occurs while a patient is on complement inhibitor therapy. BTH can be attributed to suboptimal C5 inhibition and may be pharmacokinetic (i.e., suboptimal C5 inhibition/dosing or missed treatments). Serum drug trough levels may become too low, particularly with eculizumab in the last few days of each biweekly cycle. Pharmacodynamic BTH is likely to be due to conditions that lead to complement activation, such as infections. When the C3b density on the erythrocyte surface is too high, high-affinity C5 convertases can cleave C5 even when bound to a C5 inhibitor or can cause conformational changes to C5, triggering hemolysis [7,8,9].

Extravascular Hemolysis

While C5 inhibitor therapy can effectively halt complement-mediated intravascular hemolysis in patients with PNH, anemia tends to persist in a subset of patients due to EVH [15,25]. The PNH erythrocytes of patients on therapy accumulate C3 fragments, particularly C3d, on their surfaces, which then serve as opsonins. Opsonized erythrocytes are subsequently recognized and phagocytosed by macrophages. Consequently, EVH occurring in the liver and spleen leads to anemia [15,25]. This can be identified based on a persistently high reticulocyte count with concomitant anemia. Notably, C3 fragments are detected

only on PNH erythrocytes after C5 inhibitor treatment. This can be identified using flow cytometry and/or a Coombs test. Normal erythrocytes are not coated by C3 fragments, even after C5 inhibitor treatment. This is likely due to the deficiency of CD55 in PNH cells, as CD55 is a regulator of the C3 convertase. As C5 inhibitors block the complement pathway at the level of C5, the earlier steps in the pathway continue to occur. The activation, deposition, and proteolytic cleavage of C3 to C3b result in the accumulation of C3 fragments on the surfaces of PNH erythrocytes, creating the conditions necessary for significant EVH [25]. Recognition of this limitation in PNH therapy prompted the development of C3 inhibition therapies aimed at preventing both EVH and intravascular hemolysis. The blockade of C3 abolishes intravascular hemolysis by directly inhibiting C3 and prevents EVH by stopping the accumulation of C3d on the surface of PNH erythrocytes [7].

Current Approved Paroxysmal Nocturnal Hemoglobinuria Therapeutics

Eculizumab

The first-line treatment for PNH has historically been eculizumab, an anti-C5 mAb first approved by the FDA in 2007 [26]. Eculizumab compensates for the lack for CD59 by binding C5 and preventing its cleavage by the C5 convertase (Figure 1). Inhibiting C5 cleavage prevents the formation of the membrane attack complex and limits intravascular hemolysis. However, eculizumab does not compensate for the lack of CD55. As a result, the deposition of C3b opsonin will continue and mild to moderate EVH in the liver and spleen may still occur [22].

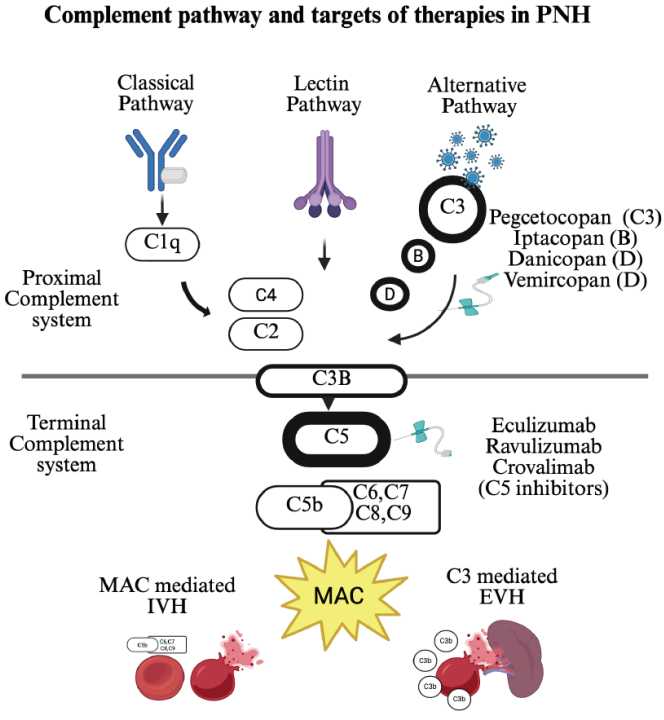

Figure 1. Classical pathway activated by antibodies, lectin pathway activated by ficolins or lectins, and alternative pathway activated by viral or bacterial surfaces.

PNH: Paroxysmal nocturnal hemoglobinuria; MAC: membrane attack complex; IVH: intravascular hemolysis; EVH: extravascular hemolysis.

Eculizumab significantly reduces hemolysis, as demonstrated by marked declines in LDH in all patients to near normal levels after 1 week [5]. Administration of the FACIT-Fatigue scale showed a mean improvement of 12.2 points during the course of a multicenter phase 3 study (scale scores range from 0 to 52, with higher scores indicating improvement) [5]. Additionally, 51% of participants remained transfusion-independent during the course of the study. The average number of red blood cell units required by participants dropped from 12.3 units per patient in the preceding year to 5.9 during the eculizumab trial [5].

During the aforementioned trial, two patients experienced a thrombotic event, including one case of deep vein thrombosis and one of pulmonary embolism. The most common side effect reported was headache (96.4%). Headache is likely associated with the acute increase in nitric oxide levels shortly after beginning eculizumab. Headache is rarely reported after the first few doses [5]. The reduction of thrombotic events results in dramatically improved survival in patients receiving eculizumab therapy. A follow-up retrospective study examined a PNH cohort taking eculizumab between 2002 and 2010. The 5-year survival rate on eculizumab was 95.5%, with no treatment-related deaths, compared to 66.8% in the pre-eculizumab control group. Before initiating eculizumab, there were 34 thrombotic events in 21 of the patients. After eculizumab, there were only 2 thrombotic events. The rate of thrombosis thus decreased from 5.6 to 0.8 thrombotic events per 100 patient years on eculizumab [27]. Furthermore, 21 patients who were previously on prophylactic anticoagulation were able to discontinue therapy without experiencing any thrombotic events after cessation [27].

Ravulizumab

The next advancement in C5 inhibition occurred in 2018 with the approval of ravulizumab, a mAb C5 inhibitor with higher binding affinity for C5 than eculizumab (Figure 1) [28]. Ravulizumab requires dosing every 8 weeks, whereas eculizumab requires biweekly administration (Table 1) [28]. This extended dosing interval is achieved through enhanced endosomal recycling of the mAb. The ravulizumab 301 phase 3 trial compared ravulizumab and eculizumab in complement inhibitor-naïve patients with PNH. Ravulizumab demonstrated non-inferiority for both primary endpoints of the study: transfusion avoidance and hemolysis as measured by LDH. Among patients receiving ravulizumab, 73.6% avoided transfusion compared to 66.1% in the eculizumab group [29]. LDH normalization was observed in 53.6% of patients on ravulizumab compared to 49.4% on eculizumab. BTH occurred at lower rates in the ravulizumab group (4.0%) compared to the eculizumab group (10.7%) [29].

Table 1. FDA-approved treatments for PNH: approval year, mechanism of action, and dosing.

Drug (brand name)	Approval year	Mechanism of action	Loading dose	Maintenance dose	Route	Dosing frequency
Eculizumab (Soliris)	2007	C5 inhibitor	600 mg IV weekly for 4 weeks	900 mg	IV	Q2W
Ravulizumab (Ultomiris)	2018	C5 inhibitor	Weight-based IV dose (2400-3000 mg)	3000-3600 mg	IV	Q8W
Pegcetacoplan (Empaveli)	2021	C3 inhibitor	None	1080 mg	SUBQ	BIW
Iptacopan (Fabhalta)	2023	Factor B inhibitor	None	200 mg	Oral	BID
Danicopan (Voydeya)	2024	Factor D inhibitor	None	150 mg	Oral	TID
Crovalimab (Piasky)	2024	C5 inhibitor	1000 mg IV on day 1, then 4 weekly SUBQ doses of 340 mg	680 mg	SUBQ	Q4W

FDA: US Food and Drug Administration; PNH: paroxysmal nocturnal hemoglobinuria; IV: intravenous; SUBQ: subcutaneous; Q2W: once every 2 weeks; Q8W: once every 8 weeks; BIW: twice every week; BID: twice every day; TID: three times every day; Q4W: once every 4 weeks.

The ravulizumab 302 phase 3 trial evaluated the efficacy of ravulizumab versus eculizumab in patients previously treated with eculizumab. Ravulizumab demonstrated non-inferiority for the study's primary endpoint: change in LDH from baseline. The ravulizumab group experienced a 0.82% reduction in LDH from baseline while the eculizumab group showed an 8.39% increase from baseline [30]. No patients in the ravulizumab group experienced BTH, whereas 5 patients (5.1%) in the eculizumab group did. The mean number of red blood cell units transfused was comparable between the groups, with ravulizumab patients receiving an average of 4.3 units [30]. FACIT-Fatigue scores were also comparable between the groups, with ravulizumab achieving a 2.01-point improvement from baseline and eculizumab showing a 0.54-point improvement [30]. No patients in either group experienced a major adverse vascular event. Headache was the most frequently reported adverse event, occurring in 26.8% of the ravulizumab group and 17.3% of the eculizumab group [29,30].

Pegcetacoplan

Pegcetacoplan, a peptide-based inhibitor of C3 designed to control both EVH and intravascular hemolysis, received FDA approval in 2021 for treatment of PNH (Figure 1) [31]. A phase 3 trial evaluated the efficacy and safety of pegcetacoplan monotherapy versus eculizumab in patients with PNH with hemolysis poorly controlled by eculizumab (hemoglobin of 10.5 g/dL). Pegcetacoplan demonstrated superiority to eculizumab in limiting hemolysis. The mean hemoglobin change from baseline in the pegcetacoplan group was an increase of 2.37 g/dL, whereas the eculizumab group experienced a mean decrease of 1.47 g/dL (Table 2). The mean hemoglobin difference between treatments was thus 2.69 g/dL in favor of pegcetacoplan [32]. A total of 85% of patients in the pegcetacoplan group avoided transfusion, compared to only 15% in the eculizumab group [32]. FACIT-Fatigue scores increased by an average of 9.2 points in the pegcetacoplan group and decreased by 2.7 points in the eculizumab group [32]. BTH occurred in 10% of patients receiving pegcetacoplan and 23% of those receiving eculizumab [32]. The most common adverse event in both groups was infusion site reaction. Headache was reported in 7% of those taking pegcetacoplan compared to 23% in the eculizumab group [32].

Iptacopan

Iptacopan was approved in 2023 as the first oral monotherapy for the treatment of PNH in adults (Table 1) [33]. Iptacopan is a selective inhibitor of factor B. Inhibiting factor B prevents the formation of the C3 convertase, thereby limiting complement pathway amplification and significantly reducing hemolysis (Figure 1). Adding iptacopan to treatment led to significant reduction in LDH levels, from 539 IU/L at baseline to 235 IU/L at week 13 [34]. Significant improvements were also observed in other hematological markers and no serious adverse events were reported [34]. A follow-up 12-week phase 2 trial evaluated iptacopan monotherapy in patients with PNH who had not received complement inhibition therapy in the previous 3 months and had a baseline hemoglobin level of 8.58 g/dL [35]. At week 12, LDH levels had decreased by ≥60% from baseline. Hemoglobin levels improved from 8.85 to 11.52 g/dL in cohort 1 and from 7.69 to 10.9 g/dL in cohort 2 (Table 2) [35]. Five patients achieved hemoglobin levels of >12.0 g/dL and an overall upward trend persisted beyond the 12-week study period [35]. All but one patient remained transfusion-independent during the trial. The patient requiring transfusion had preexisting MDS and was enrolled in the trial despite significant reticulocytopenia. No serious adverse events were reported. The most commonly reported adverse event was headache, affecting 4 out of 13 participants [35].

Danicopan

Danicopan is an oral small-molecule inhibitor of factor D approved for PNH treatment in 2024 [36]. Factor D is a serine protease that catalyzes the cleavage of factor B into its active components. Inhibiting factor D prevents the formation of active C3 convertase, thereby blocking amplification of the complement pathway (Figure 1). Factor D is an attractive drug target because it catalyzes a rate-limiting step in complement

Table 2. Summary of clinical trials on PNH treatment.

Drug	Trial name	Cohort	Therapy approach	BTH rate	Thrombotic events	FACIT-Fatigue improvement	Hgb increase (g/dL)
Eculizumab	TRIUMPH	PNH with transfusion dependency	Monotherapy	10.8%	0	6.4	1.4
Ravulizumab	CHAMPION-301	Treatment-naïve	Monotherapy	4.0%	2/125*	7.07	Not reported§
	CHAMPION-302	Eculizumab with persistent anemia	Monotherapy	0.0%	0	2.1	Not reported§
Pegcetacoplan	PEGASUS	C5 inhibitor with persistent anemia	Monotherapy	10.0%	0	9.2	2.37
	PRINCE	Treatment-naïve	Monotherapy	0.0%	0	7.8	2.9
Iptacopan	APPLY	C5 inhibitor with persistent anemia	Monotherapy	3.2%	1/62†	8.0	3.59
	APPOINT	Treatment-naïve	Monotherapy	0.0%	0	Not reported	3.87
Danicopan	ALPHA	C5 inhibitor with persistent anemia	Add-on	8.3%	0	7.9	2.94
Crovalimab	COMMODORE 2	Treatment-naïve	Monotherapy	10.4%	0	7.8	2.2

*: One patient who was using an oral contraceptive developed deep vein thrombosis and one patient discontinued anticoagulation at the initiation of the trial.
†: Transient ischemic attack considered unrelated to iptacopan; iptacopan treatment was ongoing.
§: The ravulizumab trials reported a hemoglobin stabilization rate (avoidance of a ≥2 g/dL decrease in hemoglobin from baseline) and the ravulizumab rate was non-inferior to eculizumab in both trials.
PNH: Paroxysmal nocturnal hemoglobinuria; BTH: breakthrough hemolysis; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue scale.

amplification and is present at the lowest concentration of any complement protein [37]. In the phase 3 ALPHA clinical trial, danicopan was evaluated as an add-on treatment in patients with clinically significant EVH despite treatment with a C5 inhibitor. A total of 42 participants received danicopan at 150 mg three times daily, while the placebo group continued to receive eculizumab or ravulizumab monotherapy. Danicopan treatment resulted in a clinically significant mean increase in hemoglobin concentration of 2.94 g/dL after 12 weeks (Table 2) [38]. Danicopan in combination with ravulizumab or eculizumab achieved an increase of >2 g/dL in hemoglobin in 60% of patients and transfusion avoidance in 83% of patients [38]. The placebo group experienced a mean increase of 0.5 g/dL in hemoglobin and no members of the placebo group had a hemoglobin increase of >2.0 g/dL [38]. FACIT-Fatigue scores had improved by a mean of 8 points in the danicopan group at 12 weeks compared to 2.6 points in the placebo group [38]. No thromboembolic or other significant adverse events were reported. These findings suggest that danicopan is a promising therapeutic option for patients who continue to have clinically significant EVH despite C5 inhibitor therapy.

Crovalimab

Crovalimab, a humanized anti-complement component C5 (anti-C5) mAb, is the latest development in PNH treatment, having been approved in June 2024 for adult and pediatric patients aged 13 years and older with body weight of at least 40 kg. This approval was based on data from the COMMODORE 2 study (Table 1) [39]. There were 2 primary endpoints of that study: hemolysis control from week 5 to week 25 and transfusion avoidance from baseline to week 25. Key secondary endpoints included BTH from baseline to week 25, stabilized hemoglobin from baseline to week 25, and mean change in fatigue in adult patients from baseline to week 25. Data showed that crovalimab was non-inferior to eculizumab with respect to BTH rates (10.4% vs. 14.5%) and hemoglobin stabilization (63.4% vs. 60.9%) (Table 2) [40]. The advantage of crovalimab is its once-monthly subcutaneous administration [41]. The rates of any-grade treatment-related adverse effects were 33.3% for crovalimab versus 34.8% for eculizumab, while the rates of grade 3-5 adverse effects were 17.8% and 24.6%, respectively [40].

The Role of Allogeneic Hematopoietic Stem Cell Transplantation

While complement inhibitors remain the standard of care for patients with PNH experiencing hemolysis, allogeneic hematopoietic stem cell transplantation (HSCT) may be considered as an alternative for those with refractory disease or severe adverse effects from non-transplant therapies. According to the International Bone Marrow Transplant Registry, the 2-year overall survival (OS) rate was 56% among 48 recipients of human leukocyte antigen (HLA)-identical sibling transplants performed between 1978 and 1995 [42]. A more recent retrospective study evaluated 240 PNH patients who underwent HSCT between 2011 and 2020 across 125 European Society for Blood and Marrow Transplantation transplant centers in the Netherlands and reported a 3-year OS rate of 79%, with infections and graft-versus-host disease (GVHD) identified as

the primary causes of mortality [43]. Survival was associated with both donor type and patient age, and the 3-year OS rates were 86% for HLA-matched sibling donors, 78% for matched unrelated donors, and 62% for mismatched unrelated donors (p=0.003) [43]. Age-stratified OS rates were 83% for patients aged <20 years, 82% for those aged 20-40 years, and 67% for those aged >40 years [43]. Although outcomes following HSCT have improved over the past decade due to advances in donor selection, conditioning regimens, GVHD management, and post-transplant care, HSCT should be reserved for cases where other treatment options are contraindicated or have failed considering the persistent risks of infection and graft failure.

Gene Therapy and Other Biologics

Gene therapy to restore *PIGA* function or block the complement pathway has long been explored as a potential treatment for PNH. In vivo studies have demonstrated that lentiviral vectors can effectively deliver a functional copy of the *PIGA* gene to HSCs, thereby re-establishing the expression of GPI-anchored proteins [44]. HMI-104, an adeno-associated virus-based gene therapy, has shown success in utilizing the hepatic expression of a C5 mAb, resulting in complete inhibition of ex vivo hemolysis [45]. Human studies have yet to be performed, but the one-time application of the therapy and the potential of lifetime cure make such an approach attractive for PNH patients.

Another agent of interest, KP104, is a bifunctional fusion protein that combines an anti-C5 mAB with the regulatory domains of complement factor H, allowing the simultaneous inhibition of the terminal and proximal complement pathways. Results from a phase 2 trial (n=18) demonstrated that KP104 therapy induced rapid and sustained increases in hemoglobin levels, significant reductions in LDH, and complete elimination of transfusion requirements in all treated patients [46].

Patient Selection and Choice of Therapy

Shared decision-making plays a vital role in selecting the most appropriate treatment for PNH. PNH management has advanced significantly as PNH clinicians have widely adopted eculizumab and largely transitioned to ravulizumab due to its more convenient dosing schedule. Now, with subcutaneous injections and oral agents available, PNH management has become increasingly nuanced. While many clinicians await long-term safety data on proximal complement inhibitors, a well-validated quality-of-life tool is needed to determine whether additional proximal inhibition is necessary for patients on C5 inhibitors who do not have severe anemia. At the same time, key considerations when selecting a treatment include the patient's preference for the route of administration, the clinician's assessment of adherence to oral or subcutaneous therapy, and the management strategy for complement activation episodes.

Remaining Challenges in Paroxysmal Nocturnal Hemoglobinuria

With ongoing advances in treatment options, PNH is significantly more manageable today compared to the pre-eculizumab era. However, several challenges remain:

1. Underdiagnosis of PNH remains prevalent due to its rarity.

2. HSCT remains the only curative therapy, and 2% to 6% of patients with PNH develop clonal evolution to MSD or AML [17].

3. Reliable predictive tools to identify clonal evolution do not exist.

4. Assessing residual anemia in patients with PNH is a challenge. The relative contributions of bone marrow failure, clonal evolution, and EVH must be carefully evaluated.

5. BTH remains a concern with novel agents despite its low incidence in trials.

6. Managing hospitalized patients with PNH on oral therapy may be challenging, as most of these medications are non-formulary in hospitals in the United States.

7. The high cost of novel oral agents remains a significant barrier to widespread adoption in the community. Due the expense of proximal complement inhibitors, C5 inhibitors continue to be the first-line therapy in most institutions, with a gradual paradigm shift toward oral agents. Most physicians select a therapy based on extensive discussion with individual patients about their preferences. Long-term safety and real-world evidence will facilitate a shift in the standard of care toward more convenient oral agents.

Conclusion

PNH is a rare clonal HSC disorder characterized by chronic hemolytic anemia, thrombosis, smooth muscle dystonia, and bone marrow failure. HSCT remains the only curative therapy. Over the years, novel complement inhibitors have been developed to improve survival and quality of life, making PNH a more manageable disease. The emergence of multiple novel therapies has made shared decision-making essential, requiring a thorough evaluation of all available treatment options in collaboration with the patient.

Footnotes

Authorship Contributions

Concept: S.T.; Literature Search: C.P., X.V.B.; Writing: C.P., X.V.B., S.T.

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