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Iptacopan in Paroxysmal Nocturnal Hemoglobinuria: Mechanisms, Clinical Efficacy, Safety, and Quality of Life Outcomes. A Narrative Review

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Abstract

Background. Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal disorder caused by a somatic PIGA mutation with loss of CD55 and CD59. Anti-C5 agents control intravascular hemolysis but leave extravascular hemolysis unaddressed, causing persistent anemia.

Aim of the study. To synthesize current evidence on iptacopan — the first oral complement factor B inhibitor approved for PNH — covering mechanism, pharmacokinetics, efficacy, safety, and quality of life.

Material and methods. A structured PubMed/MEDLINE search was performed for English-language publications from January 2010 to March 2026, including Phase 2 and Phase 3 trials, pharmacokinetic studies, real-world cohorts, and case reports.

Results. Iptacopan inhibits factor B, controlling intravascular and extravascular hemolysis. In APPLY-PNH, 82.3% of patients switching from anti-C5 therapy achieved sustained hemoglobin rise ≥2 g/dL without transfusion versus 0% of controls (P<0.001). In APPOINT-PNH, 92.2% met the primary endpoint and 97.6% achieved transfusion independence at week 24; outcomes were maintained at 48 weeks. Fatigue improved in 51–56% of patients. Breakthrough hemolysis occurred in 5–7%, without discontinuations.

Conclusions. Iptacopan is the first approved oral monotherapy targeting both hemolysis pathways in PNH. Phase 3 and real-world evidence confirm efficacy, tolerability, and quality of life benefit, while reducing treatment burden versus intravenous inhibitors.

Keywords: paroxysmal nocturnal hemoglobinuria; iptacopan; complement factor B inhibitor; quality of life

1. Introduction

Few diseases illustrate the complexity of complement biology quite like paroxysmal nocturnal hemoglobinuria. It lies at an unusual intersection of hematology and immunology, and is an acquired clonal condition in which a somatic mutation of the X-linked PIGA gene disrupts the surface expression of glycosylphosphatidylinositol (GPI)-anchored proteins on hematopoietic cells. Two of those proteins — CD55 and CD59 — are the cell's primary defenses against complement attack. When these proteins are lost, red blood cells become vulnerable to destruction both inside the vessels and in the liver and spleen.[1,2]

Although the disease is rare, its clinical consequences are severe. Global prevalence is estimated at 10 to 20 cases per million, with roughly 1 to 1.5 new diagnoses per million each year.[1,3] Diagnosis typically comes in the third or fourth decade of life. Before complement inhibition existed as a treatment strategy, thrombotic complications were the leading cause of death in PNH.[1,3] Even now, with effective therapy available, the combination of persistent anemia and the demands of lifelong intravenous treatment substantially impairs quality of life.[4,5]

Eculizumab substantially altered the disease course upon its introduction in 2007. Blocking C5 brought intravascular hemolysis under control and essentially eliminated thrombotic risk. Ravulizumab improved on the convenience side by stretching the dosing interval from fortnightly to every eight weeks. What neither drug managed, however, was to reach the upstream mechanism that drives extravascular hemolysis — C3b accumulation on red cell surfaces proceeds regardless of C5 blockade, and a significant proportion of patients remain anemic despite treatment.[6] Iptacopan was approved by the FDA on 5 December 2023 as the first oral monotherapy for PNH; the EMA followed in May 2024.[7] This review covers what we currently know about the drug: how it works, its pharmacological profile, the Phase 2 and Phase 3 trial results, safety, quality of life data, and the early real-world evidence.

2. Aim of the Study

This narrative review is intended to provide clinicians, particularly hematologists and internists managing patients with PNH, with an integrated synthesis of the rapidly expanding evidence base on iptacopan since its 2023 approval. We aimed to consolidate data from pivotal Phase 2 and Phase 3 trials with their long-term extensions, real-world cohorts, and patient-reported outcomes, while also situating iptacopan within the wider therapeutic landscape of approved complement inhibitors. A narrative format was chosen over a systematic review to allow for mechanistic context, comparative discussion across treatment classes, and integration of qualitative patient experience — aspects difficult to address within strict systematic review methodology.

3. Material and Methods

A structured search of the PubMed/MEDLINE database was performed for English-language articles published between January 2010 and March 2026. The following keywords and their combinations were used: “iptacopan,” “paroxysmal nocturnal hemoglobinuria,” “complement factor B inhibitor,” and “alternative complement pathway.” The year 2010 was chosen as the lower boundary because it coincides with foundational work on targeted complement inhibition and factor B biology.

Eligible for inclusion were Phase 2 and Phase 3 clinical trials, pharmacokinetic and pharmacodynamic studies, real-world cohort studies, and selected case reports. Articles published in languages other than English, as well as those available exclusively as subscription-only material, were excluded. Consistent with the narrative design of this review,

no formal quality assessment tool (e.g., GRADE) or adherence to PRISMA guidelines was applied.

4. Pathophysiology and Disease Burden of PNH

Three activation routes feed into the complement cascade — the classical, lectin, and alternative pathways — and all three converge at the point where C3 is cleaved.[8] CD55 normally suppresses C3b deposition; CD59 prevents the membrane attack complex from assembling. In PNH cells, both are absent.[8,9] Without CD55, C3b accumulates on the red cell surface through spontaneous tick-over activation of the alternative pathway. Without CD59, the MAC forms and lyses the cell directly. This is intravascular hemolysis in its classical form — producing the dark morning urine, back pain, and acute breathlessness that define a hemolytic episode.[9] C3b-opsonized cells that escape direct lysis are removed by macrophages in the reticuloendothelial system, producing extravascular hemolysis that anti-C5 drugs cannot address. In PNH, the PIGA mutation means that every affected red cell faces this dual threat throughout its lifespan.[1,2]

The consequences of free hemoglobin release go well beyond the red cell itself. Hemoglobin scavenges nitric oxide from the circulation, triggering smooth muscle dysfunction throughout the body — dysphagia, abdominal cramping, erectile dysfunction, pulmonary hypertension. Platelet activation follows, and with it an elevated thrombotic risk that historically made stroke and Budd-Chiari syndrome leading causes of death in this population.[9] Fatigue is the symptom patients most consistently identify as most disabling. It is present in the majority regardless of clone size, driven by anemia, nitric oxide depletion, and chronic inflammation, and scores on the FACIT-Fatigue scale are consistently well below population norms.[4,5] Chronic fatigue — whether in PNH or in other conditions — remains a diagnostic and therapeutic challenge, largely because it arises from the interplay of immune, metabolic, and neurohormonal disturbances rather than any single cause.[10]

5. Complement Inhibition in PNH: Efficacy and Limitations

The arrival of eculizumab fundamentally altered the prognosis of PNH. For the first time there was a drug that targeted the disease mechanism rather than its symptoms, and the results were clear: hemolysis came under control, thrombotic events fell dramatically, and survival improved.[6] Ravulizumab delivered equivalent efficacy with the practical advantage of eight-weekly rather than biweekly infusions. For most newly diagnosed patients today, one of these two agents is the starting point.

However, significant limitations remained. The unresolved problem is extravascular hemolysis. Anti-C5 agents block MAC formation but leave the proximal cascade intact. C3b accumulates on affected erythrocytes regardless of whether C5 is blocked, and those opsonized cells are cleared by macrophages in the spleen and liver. This mechanism explains why a meaningful proportion of patients on anti-C5 therapy continue to have hemoglobin below 10 g/dL and require regular transfusions despite apparent therapeutic compliance.[5,6]

Pegcetacoplan reached this problem first, targeting C3 rather than C5. Clinical data showed superiority over eculizumab in correcting anemia, and the drug was approved in 2021.[6,7] Its drawback is the twice-weekly subcutaneous self-injection, which replaces one set of logistical demands with another. For patients already burdened by a chronic condition that affects every aspect of daily life, the prospect of yet another parenteral therapy — however effective — is not always welcome. An oral agent blocking the alternative pathway at its earliest amplification step was therefore not just a logical pharmacological progression but also an answer to a clearly expressed patient need. Table 1 summarizes the main features of the four complement inhibitors currently approved for PNH.

Table 1. Approved complement inhibitors for paroxysmal nocturnal hemoglobinuria.

Drug	Target	Route	Dosing interval	First approval	Mechanism addressed
Eculizumab	C5	Intravenous	Every 2 weeks	2007	IVH only
Ravulizumab	C5	Intravenous	Every 8 weeks	2018	IVH only
Pegcetacoplan	C3	Subcutaneous	Twice weekly	2021	IVH and EVH
Iptacopan	Factor B	Oral	Twice daily	2023 (FDA)	IVH and EVH

IVH — intravascular hemolysis; EVH — extravascular hemolysis.

6. Mechanism of Action of Iptacopan

To understand why iptacopan works, it helps to look at what factor B actually does. It is the serine protease that drives the alternative pathway amplification loop. It binds C3b to form the proconvertase C3bB; factor D cleaves this to generate the active C3 convertase C3bBb, which cleaves additional C3 molecules and exponentially amplifies complement activation. The resulting C5 convertase then initiates the terminal pathway and MAC assembly.[11] Iptacopan (formerly LNP023) binds factor B reversibly and with high selectivity, preventing C3bBb

assembly and thereby arresting the amplification loop before C3 cleavage begins. Reduced C3b deposition means less extravascular hemolysis; reduced MAC formation means less intravascular hemolysis; reduced anaphylatoxin generation means less systemic inflammation.[12]

Because iptacopan targets only the alternative pathway, the classical and lectin routes remain functional. Complement-dependent killing of Neisseria meningitidis in previously vaccinated individuals is preserved, which is directly relevant to the infection risk associated with complement inhibitor use.[13] Pharmacodynamic data confirm rapid target engagement. In Phase 1 and Phase 2 studies, plasma Bb fragment — a direct marker of alternative pathway activity — decreased rapidly within hours of the first dose, with sustained suppression observed at the 200 mg twice-daily regimen alongside parallel reductions in serum Wieslab activity.[14] This rapid onset supports the case for iptacopan as a monotherapy capable of replacing, rather than supplementing, prior complement inhibition.

7. Pharmacokinetics

From a practical standpoint, the pharmacokinetic profile of iptacopan is favorable. Oral bioavailability is good. Peak plasma concentrations are reached within approximately 1.5 hours of dosing, and the elimination half-life of around 12.5 hours is consistent with twice-daily administration. Inter-individual pharmacokinetic variability is low, meaning most patients achieve similar drug exposures without individualized adjustment.[15]

Metabolism proceeds predominantly through CYP2C8 (approximately 98%), with minor contributions from CYP2D6 and phase 2 glucuronidation. All identified metabolites are pharmacologically inactive. Approximately 71% of the administered dose is excreted via the feces; roughly 25% appears in urine. An important pharmacokinetic feature is target-mediated drug disposition: iptacopan's high affinity for plasma factor B means that binding to its target shapes the drug's own concentration-time profile, a phenomenon that was incorporated into exposure-response modeling during Phase 2 dose selection.[16]

From a clinical perspective, the twice-daily oral regimen and predictable pharmacokinetics make iptacopan straightforward to prescribe and monitor, a notable contrast to the weight-based dosing and infusion logistics associated with intravenous complement inhibitors. No dose adjustment is needed in mild or moderate hepatic impairment. Severe hepatic impairment substantially increases unbound exposure and is a contraindication in the current prescribing information. Formal pharmacokinetic data in severe renal impairment are not yet available,

though a published case report documents successful and well-tolerated use in a patient receiving peritoneal dialysis.[17]

8. Phase 2 Clinical Evidence

The first clear evidence that iptacopan monotherapy could normalize hemolysis in PNH came from an open-label Phase 2 study (NCT03896152) enrolling 13 patients with active hemolysis who had not received complement inhibitors in the three months before entry.[18] Patients were assigned to one of two escalating dose cohorts. At interim analysis, all 12 evaluable participants achieved the primary endpoint — a reduction in serum LDH of at least 60% from baseline by week 12. Mean LDH fell 77–85% by week 2 and remained durably suppressed. Hemoglobin improved meaningfully in most patients; all but one remained transfusion-free through week 12. No serious drug-related adverse events were observed.[18]

A second Phase 2 study (NCT03439839) tested iptacopan as add-on therapy in patients with persistent hemolysis despite established eculizumab treatment.[14] Adding factor B inhibition on top of C5 blockade produced further reductions in hemolysis markers beyond what eculizumab alone could achieve. This confirmed that the two mechanisms are additive and independent.[14] Taken together, both studies validated the 200 mg twice-daily dose and established the pharmacological rationale for iptacopan monotherapy in Phase 3. Importantly, the consistent and rapid suppression of hemolysis markers across both treatment-naïve and eculizumab-experienced populations suggested that the drug's mechanism of action translated reliably into clinical benefit regardless of prior complement inhibitor exposure — a finding that would prove central to the design of the subsequent pivotal trials.

9. Phase 3 Trials: APPLY-PNH and APPOINT-PNH

Two Phase 3 trials provided the regulatory basis for iptacopan's approval: APPLY-PNH (NCT04558918) and APPOINT-PNH (NCT04820530), reported jointly in the New England Journal of Medicine in 2024.[19] APPLY-PNH enrolled adults with PNH who had been on stable eculizumab or ravulizumab for at least six months but retained a hemoglobin below 10 g/dL. The trial ran at 39 centers across 12 countries. Patients were randomized 8:5 to switch to iptacopan 200 mg twice daily or continue their existing intravenous anti-C5 therapy for 24 weeks.

The two co-primary endpoints were a sustained hemoglobin increase of at least 2 g/dL without transfusion, and a sustained hemoglobin level of at least 12 g/dL without transfusion. Both endpoints were met — and the magnitude of the difference was striking. A sustained

hemoglobin rise of at least 2 g/dL was achieved by 82.3% of iptacopan-treated patients against 0% of those continuing anti-C5 therapy (P<0.001). Sustained hemoglobin of at least 12 g/dL was reached by 67.7% versus 0% (P<0.001). Transfusion avoidance through 24 weeks stood at 95.2% with iptacopan and 45.7% in the control arm. Mean hemoglobin change from baseline was +3.6 g/dL with iptacopan and −0.1 g/dL in those who stayed on anti-C5 therapy.[19]

APPOINT-PNH was a single-arm study enrolling complement inhibitor-naïve patients with hemoglobin below 10 g/dL and elevated LDH across 12 hospitals in 8 countries. All 40 participants received iptacopan 200 mg twice daily. Among the 33 evaluable patients, 92.2% (95% CI 82.5–100%) achieved the transfusion-free hemoglobin endpoint. A hemoglobin level of at least 12 g/dL was reached by nearly 63%, and 97.6% achieved complete transfusion independence through week 24. Mean LDH normalized in both studies.[19] Key efficacy outcomes from both Phase 3 trials are summarized in Table 2.

Table 2. Key efficacy outcomes of iptacopan from Phase 3 APPLY-PNH and APPOINT-PNH trials at week 24.

Outcome	APPLY-PNH iptacopan (n=62)	APPLY-PNH anti-C5 (n=35)	APPOINT-PNH (n=40)
Sustained Hb increase ≥2 g/dL without transfusion	82.3%	0% (P<0.001)	92.2%
Sustained Hb ≥12 g/dL without transfusion	67.7%	0% (P<0.001)	62.8%
Transfusion avoidance	95.2%	45.7%	97.6%
Mean Hb change from baseline	+3.6 g/dL	−0.1 g/dL	+4.3 g/dL
LDH normalization	Yes	Yes	Yes

10. Long-Term Outcomes: 48-Week Extension Data

A drug that demonstrates efficacy at 24 weeks but loses it by week 48 would be of limited value in a lifelong condition. Both trials included prespecified extension periods in which all patients received iptacopan, and the 48-week data were encouraging.[20] Durability was well maintained. In the APPLY-PNH iptacopan arm, 86% of patients retained hemoglobin increases of at least

2 g/dL at week 48, and 68% had hemoglobin of at least 12 g/dL. Patients who had continued on anti-C5 therapy and crossed over to iptacopan during the extension achieved comparable results within weeks of the switch, with 72% reaching the hemoglobin improvement threshold. In APPOINT-PNH, 97% maintained their hemoglobin gains and 79% had hemoglobin of at least 12 g/dL at 48 weeks.[20]

Markers of extravascular hemolysis — reticulocyte count and unconjugated bilirubin — remained suppressed throughout the extended follow-up. LDH stayed below 1.5 times the upper limit of normal. Breakthrough hemolysis occurred in 7% of APPLY-PNH and 5% of APPOINT-PNH patients at 48 weeks; all were mild or moderate, and not a single patient stopped iptacopan because of a hemolytic episode.[20] The consistency of these results over nearly a year of treatment is particularly meaningful in PNH, where patients and clinicians need assurance that switching from an established intravenous regimen to an oral agent will not come at the cost of disease control. The extension data provide that assurance — not just in terms of hemoglobin maintenance, but across the full range of hemolytic and inflammatory markers.

11. Patient-Reported Outcomes and Quality of Life

Laboratory parameters reflect only a portion of the total disease burden in a condition defined by chronic symptoms and lifelong treatment demands. Both Phase 3 trials included prespecified assessments of fatigue using the FACIT-Fatigue scale and health-related quality of life using the EORTC QLQ-C30 questionnaire.[21] In APPLY-PNH, 51% of patients receiving iptacopan achieved a meaningful within-patient change in FACIT-Fatigue by day 168, against only 11% of those continuing anti-C5 therapy. On the EORTC QLQ-C30 functional and symptom subscales, between 39% and 49% of iptacopan-treated patients reached the threshold for clinically meaningful improvement, compared with 9% to 20% in the comparator group.

In APPOINT-PNH, 56% achieved meaningful FACIT-Fatigue improvement, and 41 to 55% reached the meaningful change threshold across the EORTC QLQ-C30 subscales. Correlation analyses within both trials confirmed that fatigue improvements tracked hemoglobin increases, pointing to anemia correction as the primary driver of quality of life benefit in this setting.[21]

A qualitative dimension derives from structured in-trial interviews conducted across three Phase III iptacopan studies, involving 61 participants across eight countries.[22] What emerged was a consistent picture of transformation: patients described returning to work, scheduling travel previously constrained by infusion timetables, and re-engaging with family and social

life in ways that questionnaire items capture only partially. The recurring theme was not merely a reduction in fatigue, but rather the recovery of autonomy over time and daily decisions.

12. Safety Profile

As with all therapeutic agents, iptacopan is associated with adverse effects, and complement inhibition carries inherent immunological trade-offs. Nevertheless, the overall tolerability profile across both Phase 3 trials was favorable. The most frequently reported adverse events in APPLY-PNH included headache, nasopharyngitis, gastrointestinal symptoms, and low-grade infections (Table 3).[19] The vast majority of events were mild or moderate in severity. Crucially, no patient discontinued iptacopan permanently because of a drug-related adverse event in either Phase 3 study.

Like every complement inhibitor approved to date, iptacopan carries a boxed warning for serious infections with encapsulated bacteria — specifically Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae type B.[7] Vaccination against all three at least two weeks before starting therapy is mandatory. The mechanistic reassurance here is that complement-dependent killing of meningococci in vaccinated individuals is preserved because the classical pathway remains functional under factor B inhibition.[13]

Breakthrough hemolysis was infrequent. Over 48 weeks, it occurred in 7% of APPLY-PNH and 5% of APPOINT-PNH patients; triggers varied and included infection, missed doses, and in some cases no identifiable cause. All episodes were mild or moderate and none led to treatment discontinuation.[20] Hyperlipidemia was a notable laboratory finding: 43% of APPLY-PNH and 24% of APPOINT-PNH patients with normal baseline total cholesterol developed Grade 1 hypercholesterolemia during treatment, with mean total cholesterol increases of approximately 37 mg/dL and 17 mg/dL respectively at month 6, and corresponding LDL cholesterol increases of 32 mg/dL and 18 mg/dL. Mean values nonetheless remained within normal ranges, and periodic monitoring of serum lipid parameters is recommended in the prescribing information, with cholesterol-lowering therapy initiated if clinically indicated.[19,20]

Table 3. Most frequent adverse events reported in the Phase 3 APPLY-PNH trial of iptacopan.

Adverse event	Frequency
Headache	19%

Adverse event	Frequency
Nasopharyngitis	16%
Diarrhea	~15%
Abdominal pain	~15%
Bacterial infections	11%
Viral infections	10%

No patient discontinued iptacopan permanently because of a drug-related adverse event.

13. Real-World Evidence

Randomized trials, by design, enroll patients who meet predefined inclusion criteria. The generalizability of any drug is ultimately tested in the heterogeneous conditions of routine clinical practice. For iptacopan, the real-world evidence base remains limited, but early data are consistent with the trial findings. The first published real-world cohort, reported by Kelly et al. in the British Journal of Haematology in 2025, described 20 patients treated at centers in Leeds and London after exhausting other complement inhibitor options, including several who had failed or been intolerant of pegcetacoplan.[23] Mean hemoglobin rose from 109 g/L at baseline to 124 g/L at three months. LDH was well controlled in nearly all patients. Switching from other proximal complement inhibitors to iptacopan was completed without complications across the entire cohort. One breakthrough hemolysis event was observed over the follow-up period, and no thrombotic events were recorded.

A methodologically distinct contribution by Holt et al. used target trial emulation to construct an indirect comparison between iptacopan and C5 inhibitors in complement inhibitor-naïve patients.[24] Across all pre-specified endpoints — hemoglobin normalization, LDH control, transfusion independence — results favored iptacopan, lending external validity to the Phase 3 findings beyond the trial setting.

Case reports have extended the evidence to populations excluded from the pivotal trials. A patient with PNH and end-stage renal disease on peritoneal dialysis was treated successfully with iptacopan after switching from eculizumab; both hemolytic mechanisms were controlled, and the patient became transfusion-independent with only mild adverse effects and no infections.[17] A second case from Vienna documented rapid resolution of extravascular

hemolysis in a patient with treatment-experienced PNH in whom residual anemia had persisted for years on anti-C5 therapy.[25]

14. Future Perspectives

Factor B inhibition has demonstrated clinical efficacy in PNH, and the same mechanism is now being tested across a widening range of complement-mediated diseases. In IgA nephropathy, the Phase 3 APPLAUSE-IgAN trial reported a 38.3% reduction in 24-hour urinary protein-to-creatinine ratio at nine months versus placebo ($P<0.001$),[26] consolidating earlier Phase 2 evidence of significant dose-dependent proteinuria reduction.[27] FDA accelerated approval for this indication was granted in August 2024. In C3 glomerulopathy, the Phase 3 APPEAR-C3G study achieved a statistically significant 35.1% relative proteinuria reduction versus placebo ($P=0.0014$) alongside stabilization of kidney function, building on the Phase 2 data that established the trial design.[28,29,30] FDA approval was granted in March 2025. Atypical hemolytic uremic syndrome, immune complex membranoproliferative glomerulonephritis, and lupus nephritis are among the indications under active investigation. The broader family of thrombotic microangiopathies — including thrombotic thrombocytopenic purpura, for which diagnostic and therapeutic approaches have recently been reviewed[31] — shares pathophysiological overlap with PNH through complement-mediated endothelial and hematological damage, further reinforcing the rationale for targeted complement modulation across this spectrum of disorders.

Within PNH specifically, the Phase 3b APPULSE-PNH trial (NCT05630001) has expanded the evidence base to a population not enrolled in APPLY-PNH: patients with hemoglobin of 10 g/dL or higher on stable anti-C5 therapy who might conventionally be considered adequately controlled. In this single-arm open-label study of 52 patients who switched from eculizumab or ravulizumab to iptacopan 200 mg twice daily for 24 weeks, the primary endpoint was met: mean hemoglobin increased by 2.01 g/dL (95% CI 1.74–2.29), demonstrating both noninferiority and superiority over prior anti-C5 treatment. At week 24, mean hemoglobin reached 13.88 g/dL, and 92.7% of patients achieved hemoglobin of at least 12 g/dL. No patient experienced clinical breakthrough hemolysis or a major adverse vascular event. These data, presented at the European Hematology Association Congress 2025, suggest that iptacopan may benefit a broader population than initially defined — including patients who appear to be doing well on anti-C5 therapy but continue to have residual extravascular hemolysis limiting full hemoglobin normalization.[32]

In a parallel line of evidence, an anchored indirect treatment comparison found broadly comparable hematological outcomes between iptacopan and pegcetacoplan.[33] Head-to-head trial data remain unavailable. Several important questions remain unanswered. Among them: how best to manage patients with concurrent bone marrow failure, in whom reduced erythropoietic reserve may limit the hemoglobin response to any complement inhibitor; the long-term implications of sustained alternative pathway suppression for innate immune surveillance; and whether there is a case for offering iptacopan as first-line treatment to all newly diagnosed patients rather than only those who fail or incompletely respond to anti-C5 agents.

15. Limitations

Several limitations of this review should be acknowledged. As a narrative rather than systematic review, the present work does not include a formal quality assessment of the included studies (e.g., GRADE) nor adherence to PRISMA reporting guidelines, which may affect the reproducibility of the synthesis. Restricting the literature search to freely accessible publications may introduce selection bias, as relevant subscription-only articles were not reviewed. The primary efficacy evidence derives from two open-label Phase 3 trials, a design necessitated by the different routes of administration being compared but one that introduces potential for bias in subjective endpoints including fatigue scores.

Forty-eight weeks of follow-up, while reassuring, is not long for a lifelong condition. Real-world experience remains limited to two small cohorts and individual case reports. APPULSE-PNH data, while promising, are currently available only as a conference abstract and have not yet undergone full peer review as a journal article. The patient populations enrolled in both Phase 3 studies were also relatively homogeneous in terms of ethnicity and geographic distribution, which may limit the generalizability of the findings to broader populations. Additionally, the impact of iptacopan on long-term outcomes such as thrombotic risk reduction, organ damage progression, and overall survival has not yet been formally assessed in prospective studies. Finally, without a randomized head-to-head comparison against pegcetacoplan, definitive guidance on the choice between proximal complement inhibitors cannot be provided on current data.

16. Conclusion

The approval of iptacopan marks a genuine shift in what is possible for patients with PNH. For those who have been managed on anti-C5 therapy but remain transfusion-dependent because

extravascular hemolysis persists, the Phase 3 trial data demonstrate this clearly: switching to iptacopan improves hemoglobin, achieves transfusion independence in the vast majority of patients, and meaningfully reduces fatigue. These are not merely statistical improvements — patients describe them in terms of fundamental changes to how they live their lives.

The importance of the oral route extends well beyond convenience. Decades of scheduled intravenous infusions impose constraints on travel, employment, and daily autonomy that compound over a lifetime. Removing that constraint is itself a clinical benefit, one that numerical endpoints only partially capture. Furthermore, regaining daily autonomy and the capacity for a more active lifestyle are crucial, as such factors are widely recognized to significantly reduce anxiety symptoms and improve overall psychological well-being.[34]

What can be said with confidence, on the strength of the available evidence, is that oral factor B inhibition addresses a mechanism of disease that terminal complement blockade simply cannot reach, does so with a safety profile that is manageable and predictable, and gives patients with PNH something they have not had before: an effective treatment that accommodates their daily lives rather than dictating them.

Disclosure

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