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REVIEW

Pegcetacoplan: A New Opportunity for Complement Inhibition in PNH

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Abstract: Pegcetacoplan is the newest inhibitor of the complement system to be approved by the FDA and EMA for the treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH). The cyclic peptide inhibitor of C3 was evaluated in several clinical trials in PHN leading to its approval. The focus of this paper will review the efficacy and safety of Pegcetacoplan (PEG), and considerations for use in patients with PNH.

Keywords: PNH, complement inhibition, extravascular hemolysis

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria is a rare hematologic disorder. It is due to an acquired mutation on the X chromosome (PIG-A) which prevents the formation of the glycosylphosphatidylinositol (GPI) anchors on cell membranes. Among the multiple proteins bound to the cell membrane by these GPI anchors, are the complement regulators, CD55, (decay accelerating factor), and CD59, which blocks the insertion of Complement protein 9, the final protein of the membrane attack (MAC). The loss of these anchored complement regulators leads to uncontrolled complement activation on the cell membrane resulting in cellular destruction. This leads to intravascular hemolysis, granulocyte, monocyte and platelet activation leading to thrombosis and cytokine mediated inflammation. PNH is a very morbid disease, limiting the lifespan of the affected patients many of whom are in their 20–30s.[1–3]

PNH is the best studied of all the complement mediated disorders. The introduction of complement inhibition dramatically altered the morbidity and mortality of PNH and has given us new insights into the role of complement in health and disease. Red cell destruction with intravascular hemolysis is the most obvious manifestation of the effect of complement dysregulation. Hemolysis is continuous but may be exacerbated by increase complement activation, in the setting of infection (both bacterial and viral), vaccination, pregnancy, trauma, and surgery.[1–3] While more complement activity occurs at night due to exposure of blood to bacterial antigens in the gastrointestinal tract, intravascular hemolysis and hemoglobinuria occurs all time to varying degrees. Paroxysms represent episodes of increased complement activation, red cell destruction and cellular activation.[2]

Thrombosis, the most dreaded complication of PNH, occurs in up to 60% of patients. Complement activation of platelets, granulocytes, and monocytes contributes to and is the underlying mechanism of the thrombogenicity of the disorder.[4,5]

PNH is seen in all ages groups but most often presents in patient in their late twenties and early thirties[2] Untreated, thirty percent of patients the patients will die within 5 years of diagnosis, half will die by 10 years even with best supportive (BSC).[2] If the patient has a thromboembolic complication, it is likely they will die within 4 years. Historic treatments such as steroids, and prednisone are anecdotal and ineffective.[2]

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Complement Inhibition

The role of the Complement system in health and disease has become an active area of research and drug development. The development of C5 inhibitors for PNH/atypical hemolytic uremic syndrome (ahus), myasthenia gravis, and neuromyelitis optica spectrum disorder (NMSOD) has revolutionized the treatment of these diseases, improving the quality of life and survivals in these disorders. The most recent additions to this list of approved complement inhibitors are Pegcetacoplan (Empaveli), approved in 2019 for the treatment of PNH and a C1S inhibitor, Sutimlimab, approved in 2021, for the treatment of Cold Agglutinin disease (CAD).

The use of complement inhibition has dramatically changed the outlook for patients with PNH. Eculizumab and ravulizumab (inhibitors of complement protein 5) have altered the morbidity and mortality of the disease by blocking terminal complement activation. The pilot trial, Triumph, Shepherd and AEGIS trials all demonstrated rapid reproducible reduction of hemolysis as measured by lactic dehydrogenase (LDH) and a marked reduction in thrombotic risk, as measured by D-Dimer.[6–10] As a result, overall mortality has normalized to that of age matched controls. Ravulizumab, the long acting C5 inhibitor, has been shown to be non-inferior to the parent drug, eculizumab, with similar benefits.[6–10]

However, not all PNH patients respond equally to C5 inhibition There are rare patients who have a polymorphism in C5, which renders the C5 resistant to eculizumab and ravulizumab.[11] About 20–30% of patients achieve hemoglobin normalization, which leaves 70% of patients with some component of anemia.[12–16,] Fifteen to 20% will remain transfusion dependent. Unless there is a significant component of bone marrow failure, most patients have high retic counts with normal LDH consistent with extravascular hemolysis. LDH levels are usually normal or modestly increased (<1.5 times the upper limit of normal) in extravascular hemolysis. Risitano et al noted increased Complement 3b (C3b) loading of RBC due to C5 blockade resulting in extravascular clearance in the spleen and liver due to C3 fragments[12,13] Extravascular hemolysis is observed in most patients with PNH who are being treated with C5 inhibitors, and can manifest as persistent anemia, reticulocytosis, hyperbilirubinemia and the need for transfusion[14–16] (Table 1).[14] Complement 3 (C3) inhibition with Pegcetacoplan (APL-2) is designed to block extravascular clearance.

Pegcetacoplan

Pegcetacoplan (PEG) is a cyclic peptide related to compstatin, which blocks C3 preventing the generation of C3b and subsequent C3b loading of the red blood cells (Figure 1). [2,17,18,20]

Table 1 Proposed Classification of Response to Complement Inhibition in PNH

Response to C5 Inhibition	Need for Transfusion	Hemoglobin (g/dl)	LDH	ARC
Complete	None	>12	< 1.5X UNL	< 150,000
Major	None	>12	>1.5X UNL	>150,000
Good	None	>10 <12	A < 1.5X UNL B >1.5X UNL	r/o bone marrow failure
Partial	None or <2/ 6 mos	>8 <10	A <1.5XUNL B >1.5X UNL	r/o bone marrow failure
Minor	Occasional 50% reduction Regular >3/6 mos	>8 <10 < 10 < 10	A <1.5X UNL B>1.5X UNL	r/o bone marrow failure
No response	Regular >6/6 mos	< 10	A <1.5X UNL B >1.5X UNL	r/o bone marrow failure

Notes: Adapted from Risitano AM, Marotta S, Ricci P et.al. Anti-complement Treatment for Paroxysmal Nocturnal Hemoglobinuria: Time for Proximal Complement Inhibition? A Position Paper From the SAAWP of the EBMT. *Front Immunol.* 2019; 10: 1157.[14]
Abbreviations: LDH, lactic dehydrogenase; ARC, absolute reticulocyte response.

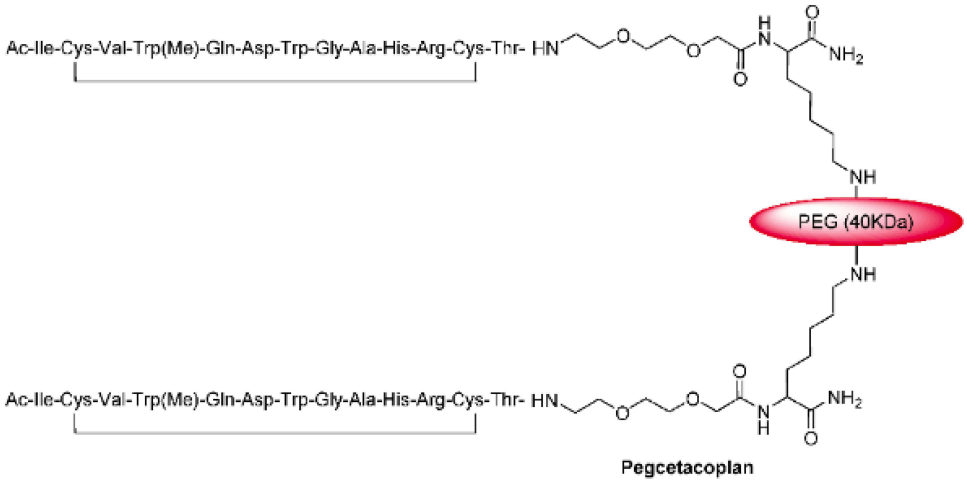

Figure 1 Structure of Pegcetacoplan. Reproduced from Al Shaer D, Al Musaimi O, Albericio F, de la Torre BG. 2021 FDA TIDES (Peptides and Oligonucleotides) Harvest. Pharmaceuticals. 2022; 15(2):222. Creative Commons.[28]

Pharmacology of Pegcetacoplan

Following a single subcutaneous infusion in healthy subjects, pegcetacoplan was gradually absorbed into the systemic circulation and reached maximum concentrations with a median time of 108–144 h (4.5–6.0 days)[17,18] In PNH patients treated with pegcetacoplan for sixteen weeks, steady-state serum concentrations were reached in 4–6 weeks after the first dose, with mean steady-state trough serum concentrations ranging from 655 to 706 µg/mL. Exposure to pegcetacoplan increased proportionally over a dose range of 45–1440 mg (0.015 L/h) and 8.0 days, respectively[17,18] Pegcetacoplan is metabolized by catabolic pathways into small peptides. The drug is broken down into peptides and amino acids and using radiolabeled peptides, the drug was primarily eliminated via urinary excretion.[17,18]

The estimated bioavailability in patients with PNH is 77%, mean volume of distribution has been measured at ≈ 3.9 L, the mean clearance and median effective elimination half-life of subcutaneous pegcetacoplan, 0.015 L/h, and 8.0 days, respectively.[17,18]

There may be interference between silica reagents in coagulation panels and pegcetacoplan that results in artificially prolonged activated partial thromboplastin time (aPTT). Therefore, avoid the use of silica reagents in coagulation panels. A chromogenic assay is preferred. Significant prolongation of the QT interval was not observed.

Clinical Studies

The PADDOCK study investigated PEG (APL-2) as monotherapy in untreated PNH demonstrated meaningful reduction in intravascular hemolysis, defined as LDH greater the 1.5 times the upper limit of normal. PEG (APL-2) was given SC as daily infusions, in different dosing cohorts 180 mg (cohort 1) or 270 mg (cohort 2). Reduction of LDH was observed in all patients, with 95% of patients achieving LDH normalization by day 29 of treatment. LDH remained in the normal range at all subsequent time points investigated. Similarly, hemoglobin increased from median 8.0 g/dL at baseline to median 10.8 g/dL at day 29, and 12.2 g/dL when APL-2 treatment was continued to day 85.[19]

The PHAROAH trial, a prospective, nonrandomized single and multiple ascending dose phase Ib trial demonstrated efficacy and safety of PEG (APL-2). Patients received 270mg/day. Of the 6 patients in cohort 4 (the highest dose cohort), 4 were able to discontinue their eculizumab with sustained improvement in hemoglobin and LDH on PEG alone.[20] Hemoglobin levels were below the LLN in all subjects at baseline (range 7.0–10.5 g/dL). By day 29, all patients had an increase in hemoglobin which remained stable throughout the rest of the study. Two subjects the increase in hemoglobin were high enough to allow for regular phlebotomies as treatment of severe transfusion-related iron overload.[20]

One patient developed transaminitis necessitating a pause of the APL2 (PEG). After resumption, the transaminases again increased. The patient then underwent a choledochojejunostomy with resolution of the transaminitis. After the operation, there was no recurrence of the transaminitis once the PEG was resumed.[20]

Pegasus

The PEGASUS trial randomized patients with PNH treated with eculizumab but who remained anemic, Hemoglobin < 10, or transfusion dependent were entered into 2 groups. Both groups received PEG + eculizumab for 4 weeks, then randomized to receive PEG alone vs eculizumab (ECU) alone for 16 weeks[21,22] The trial demonstrated superiority PEG to eculizumab in the reduction of hemolysis and transfusion avoidance. PEG was superior to the control for the coprimary endpoints of hemoglobin stabilization as well the change from baseline in LDH levels through Week 26 (Figure 2). Hemoglobin stabilization occurred in 85% of PEG patients compared to 0% (n=30) (n=0/18) in ECU arm at the treatment assessments point, week 26 (difference, 73·1%; 95% CI, 57·2%, 89·0%; P<0·0001). PEG treated patients demonstrated greater improvements from baseline in LDH levels compared to the ECU at Week 26; the least-square (LS) mean (SE) change from baseline in LDH levels at Week 26 in the PEG arm was –1870·5 U/L (101·0) versus –400·1 U/L (313·0) in the control arm (difference, –1470·4 U/L; 95% CI, –2113·4, –827·3; P<0·0001).[21,22] The side effect profile was similar to that seen in PADDOCK and PHAROAH. The PEGASUS 48-week data demonstrate a durable effect of PEG on hemolysis as measured by hemoglobin, reduction of LDH, reticulocytes and bilirubin. The favorable safety prolife, as well as quality of life outcomes, such as FACIT-fatigue score and transfusion avoidance, were sustained through 48 weeks. Patients in the Eculizumab-to-Pegcetacoplan group demonstrated significantly improved hemoglobin levels at 48 weeks (11·45 g/dL [SD, 2·14]) as compared to 16 weeks of treatment (ecu alone) (8·58 g/dL [SD, 0·96]; nominal p-value<0·0001). There was no significant change in Pegcetacoplan's safety profile at 48 weeks as compared with reported data at 16 weeks.[22] In a recent sub-analysis of PEGASUS trial, patients with AA-PNH on PEG had durable treatment benefits in all efficacy parameters at week 48, demonstrating outcomes comparable to patients with no history of AA. PEG safety profile was consistent with previous data at 16 weeks.[23]

Prince

Can patients start Pegcetacoplan without initial C5 inhibitor treatment? The PRINCE study looked at PNH patients without access to Eculizumab or Ravulizumab.[24] The Phase 3, randomized, multicenter (22 sites), open-label, controlled PRINCE study enrolled 53 adult complement-inhibitor naïve patients with PNH. Patients were randomized and stratified based on number of transfusions (<4 or ≥4) within 12 months before screening. Patients were assigned at a 2:1 ratio to receive pegcetacoplan (1080 mg subcutaneously twice-weekly [N=35]) or continue best supportive care (BSC) without

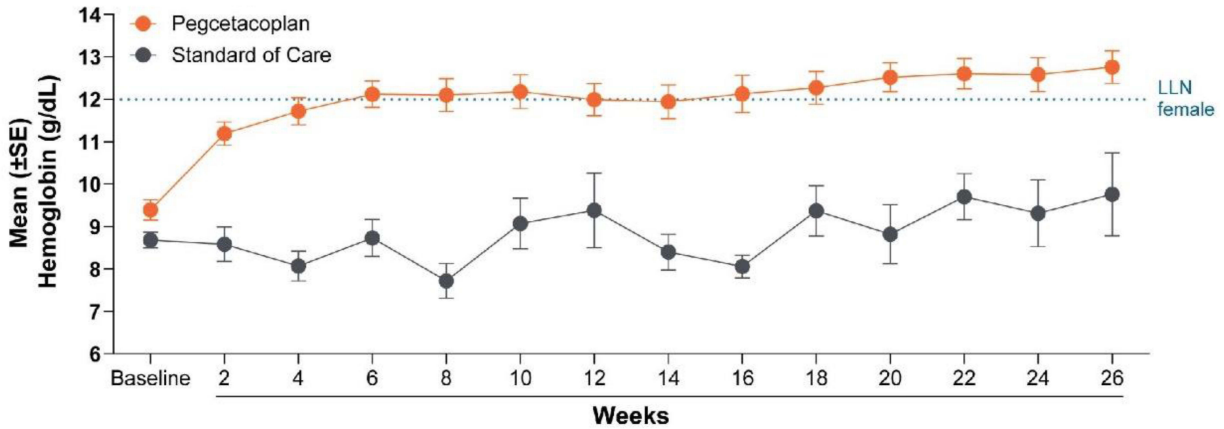

Figure 2 Prince: Observed hemoglobin over time. Reprinted from *Blood*, 138(supp1), Wong RS, Navarro JR, Comia NS, et al. Efficacy and safety of pegcetacoplan treatment in complement-inhibitor naïve patients with paroxysmal nocturnahemoglobinuria: results from the phase 3 prince study. 606, Copyright 2021, with permission from Elsevier.[24]

complement-inhibitors (control [N=18]) through the 26-week. Coprimary endpoints were hemoglobin stabilization (avoidance of >1 g/dL decrease in hemoglobin levels without transfusions) from baseline through Week 26 and change from baseline in lactate dehydrogenase (LDH) levels at Week 26. Secondary endpoints evaluated additional hematologic parameters, transfusion requirements, fatigue, and quality of life. Safety was analyzed in all patients. Data presented, as an abstract, revealed PEG was superior to SOC in both co-primary endpoints. Hemoglobin stabilization was achieved by 85.7% (n=30) of PEG-treated patients and 0.0% of SOC patients through Week 26 (p<0.0001). PEG-treated patients demonstrated superior reductions in mean LDH levels from baseline to Week 26 compared to SOC patients (least-squares mean change from baseline (CFB): PEG, −1870.5 U/L; SOC, −400.1 U/L; p<0.0001), and mean LDH levels in PEG-treated patients at Week 26 (mean level: 204.6 U/L) were below the ULN for LDH (226.0 U/L). PEG was also superior to SOC in the secondary endpoints: mean CFB in Hb levels (least-squares mean CFB: PEG, 2.9 g/dL; SOC, 0.3 g/dL; p=0.0019; Week 26 mean Hb: PEG, 12.8 g/dL; SOC, 9.8 g/dL) (Figure 1) and transfusion avoidance (PEG, 91.4%, n=32; SOC, 5.6%, n=1; p<0.0001). Serious AEs were reported by 8.7% (n=4) of PEG-treated patients and 16.7% (n=3) of SOC patients through Week 26. Two deaths occurred, one in each arm, and were both deemed unrelated to treatment (PEG, 2.9%, n=1, septic shock related to medullary aplasia; SOC, 5.6%, n=1, respiratory failure). No events of meningitis or thrombosis were reported in either group. The most common AEs reported during the study were injection site reaction (PEG, 30.4%, n=14; SOC, 0.0%), hypokalemia (PEG, 13.0%, n=6; SOC, 11.1%, n=2), and fever (PEG, 8.7%, n=4; SOC, 0.0%). None of the AEs led to discontinuation of PEG. It appears that patients with PNH, naïve to complement-inhibitor treatment demonstrated meaningful hematological and clinical improvements following 26 weeks of PEG treatment. The treatment was well tolerated and showed a safety profile similar to those seen in other Pegcetacoplan trials.[24,25] However, results of this trial remain unpublished at this time.

No thromboembolic events were noted. In the PRINCE study, concomitant use of antithrombotic treatment decreased from 21% (n=11/53) before study entry, to 7% (n=3/46) in pegcetacoplan patients. No change in the number of patients on antithrombotic therapy was observed in the control patients during the study. Two events occurred in the open-label extension, but were deemed unrelated to study drug, a case of Hodgkin's lymphoma, and one case of sepsis. D-dimer normalization rates in PEGASUS PEG arm were similar to those in who stayed on Eculizumab. In the PRINCE study, dimer normalization increased from 51% to 67% by week 8 and further increased to 68% by week 26.[26] Only 18% of patients in the control arm of patients (n=2/11) who escaped to PEG had normalized D-dimer levels at baseline, which increased to 27% (n=3/11) at their last lab reading before switching to PEG. After switching to PEG, 82% (n=9/11) had D-dimer normalization at Week 26. PEG treatment improved D-dimer normalization and reduced the incidence of thrombotic events in patients who were complement-inhibitor naïve or remained anemic after stable eculizumab treatment (≥3-months). This suggests that PEG treatment may inhibit complement mediated hemostatic activation, similar to the effect seen with C5 inhibition.[5,24]

Side Effects

Injection site reactions were the most common side effect in all of trials. However, they were mild and decreased over time, most likely due to increasing patient skill. In the PEGASUS trial, infections occurred in 29% of patients on the PEG arm and 26% in the Eculizumab arm. Diarrhea did occur more frequently in the PEG arm vs the ECU arm (22% vs 3%) but was mild. No grade 3 or 4 events were reported. Hemolysis, as a side effect, was more common in the ECU arm vs PEG (23% vs 10%).[22,23]

Because of the effectiveness of PEG, PNH clone size on treatment approaches 98%. A concern expressed by Luzzato et al, is that breakthrough hemolysis with PEG is more profound because of the increased clone size. Several cases of severe, life-threatening breakthrough hemolysis have been reported with LDH values of 10–15 times patient baseline. In the clinical trials, fifteen percent of patients discontinued treatment due to breakthrough hemolysis. This may have been due to constraints of the clinical trial which limited the amount of rescue medications. PEG half-life is short so compliance and adherence to the dosing regimen is crucial.[27] A maximally effective regimen for breakthrough should be established.

Patient Selection

PEG was broadly approved for the treatment of PNH. Based on the clinical trial data, patients with an inadequate response to C5 inhibition should be considered as candidates for PEG. This includes the rare C5 polymorphism described by Nishimura.[11] More often, patients accumulate C3b on the RBC membrane due to inhibition of C5.[12–16] This leads to opsonization by the red cells by splenic and liver macrophages. It is important to document the presence of C3b on the RBC via a Coombs test. It is also important to have an adequate reticulocyte count. A poor reticulocyte count may be evidence of coincident bone marrow failure (Aplastic Anemia) which is common in PNH. Since the complement cascade is not involved in immune-mediated bone marrow failure, changing the anti-complement treatment is not likely to improve underlying bone marrow failure.

For patients who prefer to do their own treatment, PEG affords an opportunity for self-administration and convenience.

Based on the preliminary PRINCE data, it appears that naïve PNH patients can be treated upfront with PEG with improvement in hemolysis, anemia and a decrease in thromboembolic events. However, at this time, the trial manuscript is pending peer evaluation.

There are no formal guidelines concerning monitoring the effect of Pegcetacoplan. Hemoglobin response, bilirubin, reticulocyte count, and LDH are used. Total hemolytic complement (CH50) does not accurately monitor the alternative complement pathway inhibition. AH50 can be used but may not be readily available.

Trials with Pegcetacoplan that are underway in thrombotic microangiopathy associated with following hematopoietic stem cell transplant (HSCT), C3Glomerulonephritis (C3GN)-Immune complex GN (ICGN), post-transplant C3GN and ICGN and cold agglutinin disease as well as intravitreal treatment for macular degeneration (geographic atrophy).

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