CME

PNH Highlights from ASH 2021

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Agenda

- Brief overview of PNH
- Brief overview of ASH 2021
- Summary of PNH clinical data presented at ASH 2021
- Clinical pearls

What is PNH?

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired blood disease characterized by hemolytic anemia, bone marrow failure, thrombosis, and fatigue
- Caused by:
  - a sporadic mutation of the *PIGA* gene, which affects one or more hematopoietic stem cells defective “PNH” blood cells, and
  - a process that leads to the multiplication and expansion of these defective stem cells
- FDA approved treatments include pegcetacoplan, eculizumab, and ravulizumab
- Additional treatments (e.g., iptacopan and pozelimab) are currently in development
- Since it is a rare condition, data presented at large medical conferences, like ASH 2021, can get overlooked

Brief Overview of ASH 2021

American Society of Hematology Annual Meeting and Exposition

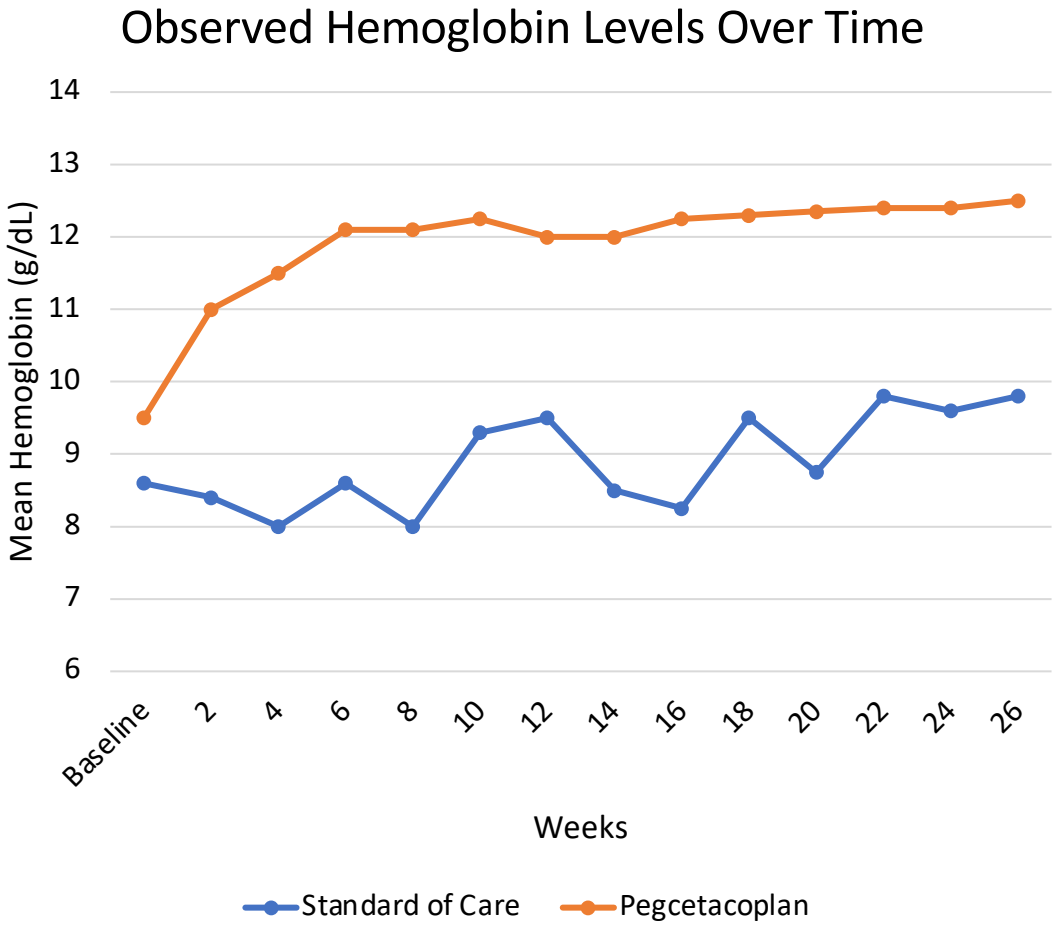
Held December 11-14, 2021 in Atlanta, Georgia with option to attend the event virtually via livestream

The largest gathering of clinical research focused on hematologic disorders and hematologic cancers

Abstracts published in *Blood*

Pegcetacoplan vs. Standard of Care

- Pegcetacoplan (PEG) is a C3 inhibitor
- Phase 3 PRINCE study – evaluated the efficacy and safety of PEG compared to SOC (excl. complement-inhibitors) in compliment-inhibitor naïve PNH patients (N = 53)
- Patients randomized 2:1 to receive PEG or SOC. Co-primary endpoints: Hb stabilization and change from baseline in LDH levels
- PEG was superior to SOC in both co-primary endpoints:
  - Hb stabilization was achieved by 85.7% (n=30) of PEG-treated patients and 0.0% of SOC patients through Week 26
  - PEG-treated patients demonstrated superior reductions in mean LDH levels from baseline to Week 26 compared to SOC patients
- Patients with PNH who were naïve to complement-inhibitor treatment demonstrated meaningful hematological and clinical improvements following 26 weeks of PEG treatment
- ***Clinical pearl: These results suggest PEG is effective and safe in patients with PNH who have not received compliment-inhibitor treatment.***



Wong R et al. Efficacy and Safety of Pegcetacoplan Treatment in Complement-Inhibitor Naïve Patients with Paroxysmal Nocturnal Hemoglobinuria: Results from the Phase 3 Prince Study. *Blood.* 2021; 138 (supply 1): 606.

Summary of Post-Hoc Analyses of PADDOCK, PALOMINO, and PEGASUS Trials

- The use of PEG is not restricted to naïve and complement-inhibitor experienced PNH patients with low baseline Hb but can be efficacious in those with near-normal baseline Hb, resulting in further clinical improvements in relevant PNH parameters
- A substantial proportion of patients achieved and maintained good, major, or complete hematologic responses to PEG, suggesting that PEG can lead to sustained improvements in hematologic parameters.
- PEGASUS data also demonstrated correlation of improved hematologic response category with clinically-meaningful improvements in quality of life, as measured by FACIT-Fatigue.
- ***Clinical pearl: These post-hoc analyses further establish the safety and efficacy of PEG as a treatment for PNH.***

Panse J et al. Post Hoc Analysis of the Effect of Pegcetacoplan Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria and Baseline Hemoglobin Levels Greater Than 10 Grams per Deciliter. *Blood.* 2021; 138 (supply 1): 2194.

Risitano A et al. Categorized Hematologic Response to Pegcetacoplan and Correlations with Quality of Life in Patients with Paroxysmal Nocturnal Hemoglobinuria: Post Hoc Analysis of Data from Phase 1b, Phase 2a, and Phase 3 Trials. *Blood.* 2021; 138 (supply 1): 1104.

PEG Extension Study

- Will include 160 adult PNH patients who have completed previous PEG trials (i.e., the phase 1b PADDOCK and PHAROAH trials, the phase 2a PALOMINO trial, and the phase 3 PEGASUS and PRINCE trials)
- Aim is to determine the long-term safety and efficacy of PEG for PNH treatment, as well as evaluate a treatment regimen to address acute hemolytic (AH) events in these patients
- The study will monitor safety outcomes such as occurrence and severity of adverse events within a 2-year timeframe from baseline.
- Trial results are anticipated in 2022.

Hoffman K et al. Evaluation of the Long-Term Safety and Efficacy of Pegcetacoplan Treatment for Paroxysmal Nocturnal Hemoglobinuria Patients: An Extension Study. *Blood.* 2021; 138 (supply 1): 2175.

Long-Term Survival Benefit of Eculizumab

- Eculizumab is a monoclonal antibody that targets C5. It was the first FDA approved drug for PNH (2007).
- Objective was to describe the baseline characteristics and overall survival of a large international cohort of eculizumab-treated patients compared with a contemporaneous untreated cohort using data from the prospective, observational International PNH Registry.
- Compared with never-treated patients, more ever-treated patients had LDH ≥1.5 × ULN, and fewer had <10% PNH granulocytes or history of BMF. The univariate Cox proportional hazard ratio (HR) for mortality in ever-treated vs never-treated patients was 0.48 indicating a 52% increase in survival in the treated group.

Terriou L et al. Long-Term Survival Benefit of Eculizumab Treatment in Patients with Paroxysmal Nocturnal Hemoglobinuria: Data from the International PNH Registry. *Blood.* 2021; 138 (supply 1): 2188

Long-Term Survival Benefit of Eculizumab

Adjusted Cox Proportional Hazard Ratios for Mortality (Ever-Treated vs Never-Treated Patients)

HDA Status at Baseline	Hazard Ratio for Mortality (95% CI)	Relative Survival Benefit
Positive	0.46 (0.33 – 0.64)	54%
Negative	0.65 (0.39 – 1.10)	35%
Unknown	0.50 (0.32 – 0.76)	50%

- Among ever-treated patients, those with high disease activity (HDA) at baseline experienced the largest reduction in mortality risk; however, decreased mortality was also evident in ever-treated patients without HDA or with unknown HDA status at baseline.
- ***Clinical pearl: Although long-term survival probability was shown to be highest in eculizumab-treated PNH patients with HDA at baseline, increased survival among all patients treated with eculizumab was evident regardless of HDA status at baseline.***

Terriou L et al. Long-Term Survival Benefit of Eculizumab Treatment in Patients with Paroxysmal Nocturnal Hemoglobinuria: Data from the International PNH Registry. *Blood.* 2021; 138 (supply 1): 2188. *Table recreated by author from published abstract.*

LDH Reductions Strongly Associated with Improvements in Fatigue and QoL

- Objective was to assess the relationship between clinical outcomes with fatigue and QoL, as measured by Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 Global Health (EORTC QLQ-C30 GH), in patients with PNH receiving C5 inhibitor therapy.
- Trial data showed that reduced LDH levels at day 183 were associated with improvements in FACIT-F in both treatment groups; however, no equivalent association was observed with Hb levels.
- Hb as a main effect, whether as an improvement in Hb levels from baseline to day 183, or Hb values at baseline, were not statistically-significant predictors of improvement in either PROM at day 183.
- When multiple clinical variables were considered, reductions in LDH were one of the strongest predictors of improvements in fatigue and QoL.
- Increases in Hb levels from baseline were only a significant predictor of improvement in FACIT-F for patients who had attained LDH level ≤ 1.5 × ULN at day 183, highlighting the importance of controlling IVH in patients with PNH.
- These results suggest that Hb alone is not a strong predictor of improvements of fatigue and QoL in this disease setting.

Schrezenmeier H et al. Predictors for Improvement in Patient-Reported Outcomes: Post-Hoc Analysis of a Phase 3 Randomized, Open-Label Study of Eculizumab and Ravulizumab in Complement Inhibitor-Naïve Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH). *Blood.* 2021; 138 (supply 1): 2196.

Treatments in Development: Iptacopan

- 12-Month interim data of Phase 2 trial of iptacopan, a factor B inhibitor
- Patients were randomized to receive BID iptacopan in one of two dose-sequences, either 25 mg for 4 weeks followed by 100 mg for up to 2 years (Cohort 1) or 50 mg followed by 200 mg (Cohort 2). The key objectives are to assess the effect of iptacopan on markers of IVH/EVH. Enrollment has been completed.
- Amongst the 12 evaluable patients, all of whom were anti-C5 naive, all reached the primary endpoint of lowering LDH by at least 60% within the first 12 weeks. The LDH response was rapid and durable, with all patients treated with ≥50 mg BID reaching this threshold after only one week of treatment and all ongoing patients except one maintaining the threshold for at least 52 weeks. Equivalent improvements were also observed for other markers of IVH and EVH.
- Similarly, Hb levels improved significantly and durably in most patients, and all except one of the ongoing patients have remained transfusion-free since the start of iptacopan treatment. Moreover, no thromboembolic events occurred during the study, and the FACIT fatigue score improved significantly in most patients.
- ***Clinical pearl: Iptacopan appears to be new, well-tolerated oral complement AP inhibitor that blocks both IVH and EVH in adult PNH patients with hemolytic PNH.***

Jang JH et al. 12-Month Analysis of a Phase 2 Study of Iptacopan (LNP023) Monotherapy for Paroxysmal Nocturnal Hemoglobinuria. *Blood.* 2021; 138 (supply 1): 2173.

Treatments in Development: Pozelimab

- Data from Phase 2, open-label, single-arm study of pozelimab, a monoclonal antibody targeting C5
- Treatment regimen consists of pozelimab as a single IV loading dose of 30 mg/kg followed thereafter by weekly subcutaneous 800 mg administrations
- Treatment with pozelimab led to a rapid and sustained reduction in LDH through study week 26. All 17 patients achieved LDH reduction to below the clinically-significant threshold of LDH ≤1.5 x ULN.
- All but one patient achieved control of intravascular hemolysis (LDH ≤1.5 x ULN) at week 2, and all but one patient achieved normalization of LDH (LDH ≤1.0 x ULN) at week 4.
- Importantly, one patient who is a carrier of a C5 variant known to be resistant to blockade by eculizumab/ravulizumab demonstrated rapid and sustained normalization of LDH.
- No AEs or serious AEs leading to treatment discontinuation were reported.
- Overall, pozelimab administered SC once weekly led to the inhibition of intravascular hemolysis in patients with active PNH and was generally well-tolerated.
- ***Clinical pearl: Pozelimab appears to be a well-tolerated, efficacious therapy that led to a quick and sustained reduction in LDH levels.***

Characteristics of Patients with Classic PNH With vs Without Anticoagulation

	Classic PNH with anticoagulation	Classic PNH without anticoagulation	OR	P
LDH U/L, median	1803	1628	1.00	.342
Platelets, x 10^3 /μ, median	159	147	1.00	.218
Granulocyte clone size %, median	96	95	1.02	.195
Clone type III % Mixed %	 63.2 36.8	 60.0 40.0	.87	.831
LDH ≥ 1.5 x ULN	94.7	92.0	1.56	.721
Thrombosis %	0	20	.51	.038

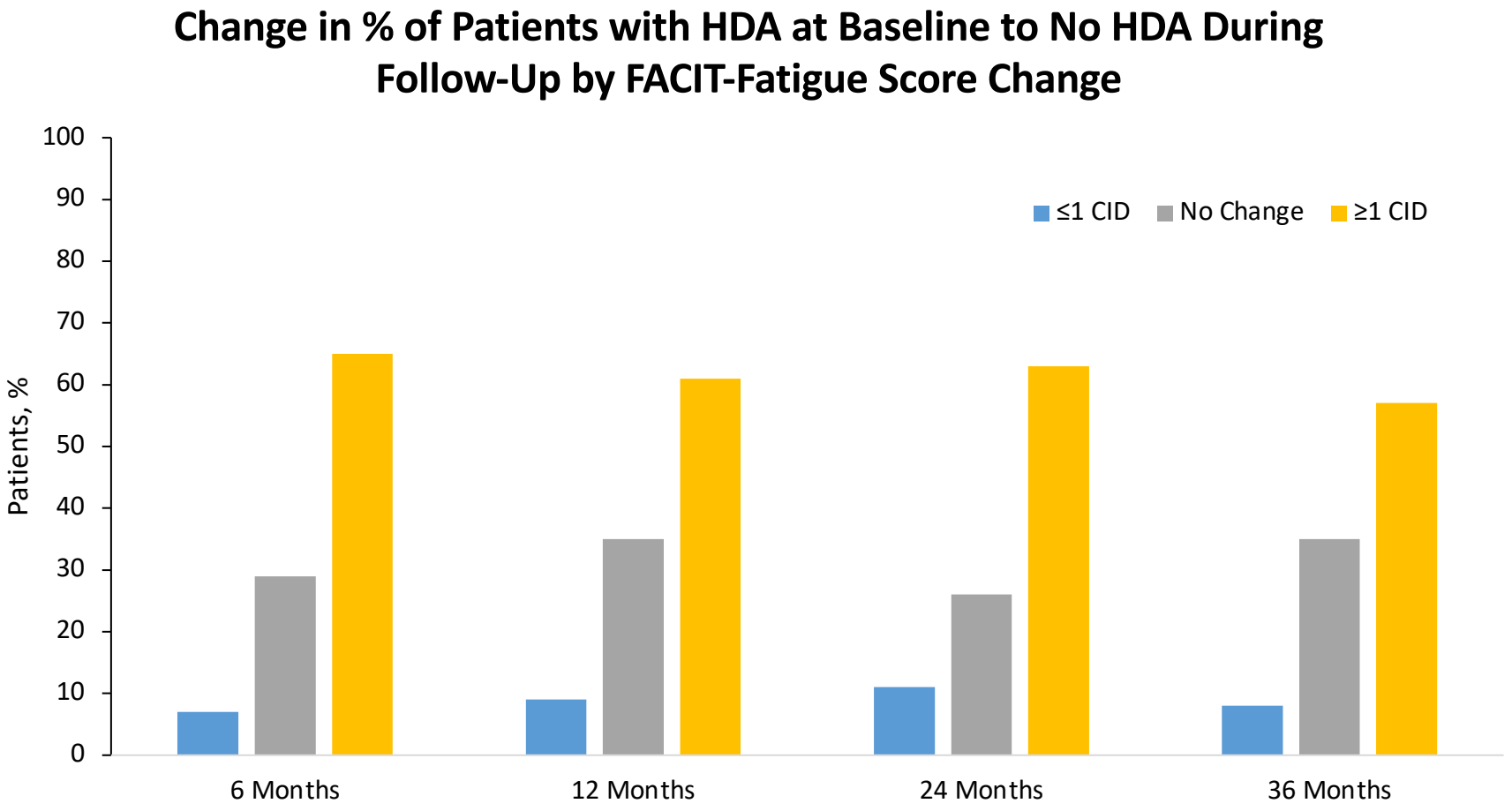
Jang JH et al. Pozelimab, a Human Monoclonal Antibody Against Complement Factor C5, Provided Inhibition of Intravascular Hemolysis in Patients with Paroxysmal Nocturnal Hemoglobinuria. *Blood.* 2021; 138 (supply 1): 1128. *Table recreated by author from published abstract.*

Clinically Important Difference for FACIT-Fatigue Scale

- Fatigue is a common symptom associated with PNH.
- The Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-Fatigue) is validated for use in patients with PNH and has been used extensively both in clinical trials and in the International PNH Registry.
- No disease-specific CID for FACIT-Fatigue has been estimated in patients with PNH.
- The objective of Cella and colleagues' analysis was to determine the FACIT-Fatigue CID for patients with PNH using distribution- and anchor-based approaches and real-world data from the International PNH Registry.
- They found the use of 5 points as the CID for FACIT-Fatigue in individual patients with PNH, which, although not necessarily the minimal value, is close to the range of CIDs reported in other diseases (3–5 points).
- This finding, obtained from a real-world dataset with a large number of patients, helps establish an important metric for assessment of the meaningful treatment response of patients with PNH.

Cella D et al. Clinically Important Difference for the FACIT-Fatigue Scale in Paroxysmal Nocturnal Hemoglobinuria: A Derivation from International PNH Registry Patient Data. *Blood.* 2021; 138 (supply 1): 1952.

Clinically Important Difference in FACIT-Fatigue Scale



Cella D et al. Clinically Important Difference for the FACIT-Fatigue Scale in Paroxysmal Nocturnal Hemoglobinuria: A Derivation from International PNH Registry Patient Data. *Blood.* 2021; 138 (supply 1): 1952. *Figure recreated by author from published abstract.*

Summary

PNH is a rare, acquired blood disease characterized by hemolytic anemia, bone marrow failure, and thrombosis.

ASH 2021 was held December 11-14, 2021 in Atlanta with option to attend the event virtually via livestream.

Abstracts published in *Blood*

Three FDA approved drugs for PNH – pegcetacoplan, eculizumab, and ravulizumab – continue to show clinically meaningful benefits for patients with PNH.

Data presented for two treatments in development – iptacopan and pozelimab – suggests these agents appear to be safe and efficacious in patients with PNH.