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UO EMATOLOGIA E TERAPIE CELLULARI
IRCCS OSPEDALE POLICLINICO SAN MARTINO (GENOVA)

Emoglobinuria parossistica notturna: tra vecchi e nuovi anticorpi monoclonali

PNH: THE GREAT IMPERSONATOR

PNH is a rare disease, with an estimated incidence of 1.3 cases/million/year and a prevalence of 15.9 cases/million

PNH is a clonal, complement mediated hemolytic anemia, with heterogeneous manifestations (hemolityc anemia, a form of bone marrow failure, thrombophilia or all of the above), changing over time

Clinical manifestations of PNH are determined by the size of the PNH clone and the coexistence of PNH with BMF (AA, MDS)

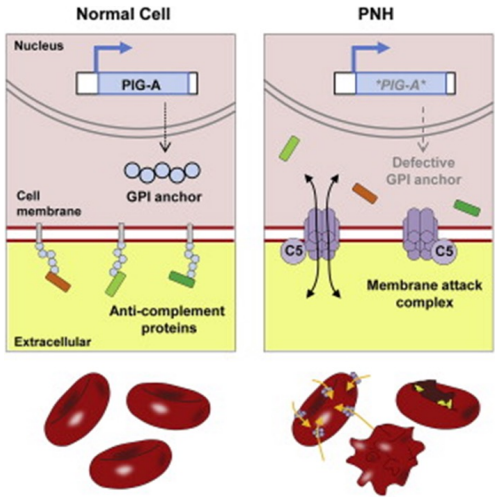
PNH: PATHOGENESIS

Complement-driven hemolytic anemia of PNH results from the clonal expansion of stem cells harboring PIG-A mutation

PIG-A is required for the biosynthesis of glycosylphosphatidylinositol (GPI) anchors

Absence of CD55 and CD59 (both GPI anchored complement regulators) leads to complement-driven RBC lysis and predisposition to thrombosis

GPI-anchor protein deficiency leads to survival advantage of PNH stem cells vs normal stem cells in the setting of autoimmunity



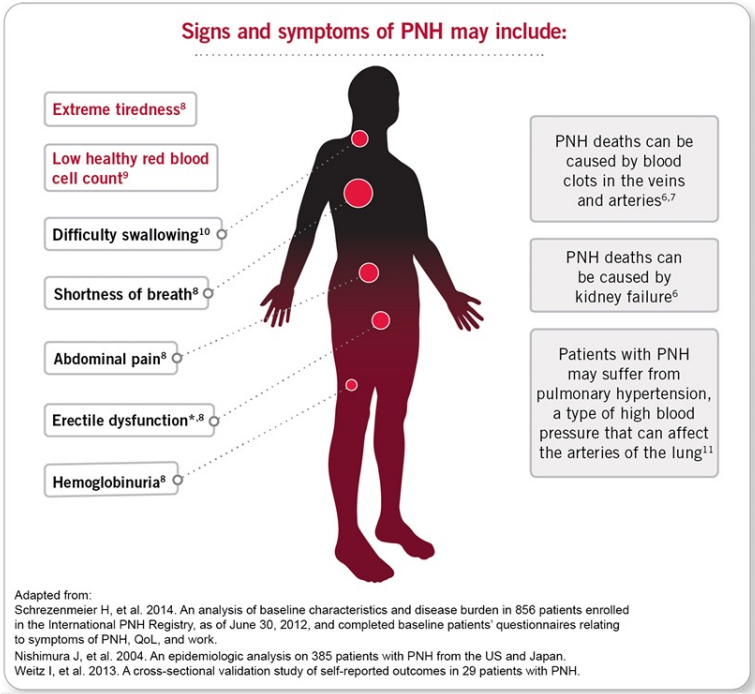
PNH **frequently evolves from acquired aplastic anemia**

PNH is **not associated with inherited forms of aplastic anemia** (dyskeratosis congenita, Fanconi anemia, Schwachman-Diamond syndrome)

Brodsky, How I treat PNH, Blood 2021

PNH: CLINICAL FEATURES

High disease activity is defined by LDH ≥1.5 x ULN and ≥1 of the following symptoms



Thrombosis accounts for 40% to 67% of the mortality from the disease

Renal failure is the cause of death in 8 to 18% of PNH patients

47% suffer from pulmonary hypertension

Free hemoglobin scavenges nitric oxyde preventing the normal relaxation of smooth muscle (abdominal and back pain, esophageal spasm, erectile dysfunction)

Scherezenmeier H, et al. Haematologica. 2014;99(5):922-929. Sharma VR. Clin Adv Hematol Oncol. 2013;11 Suppl 13(9):2-8. Roth A et al. Eur J Haematol. 2018 Jul;101(1):3-11.. Hill A, Rother RP, et al. Br J Haematol. 2010;149(3):414-425, Brodsky, How I treat PNH, Blood 2021

PNH: CLINICAL FEATURES, FOCUS ON THROMBOSIS

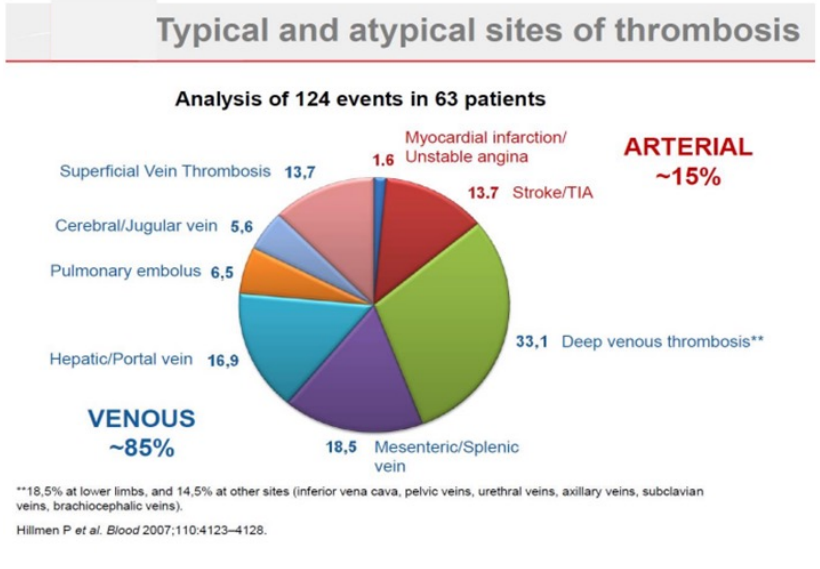
- Thrombosis is the most common cause of death in PNH (40% to 67%)

- Pathogenetic mechanism is multifactorial (intravascular hemolysis, activation of PNH platelets, possible involvement of signaling pathways that depend on the activation of complement C5…)

- Relatively rare as a presenting feature (5%), eventually occurs in up to 40% of patients with PNH

- Typically involve venous rather than arterial system, but both venous and arterial events have been reported

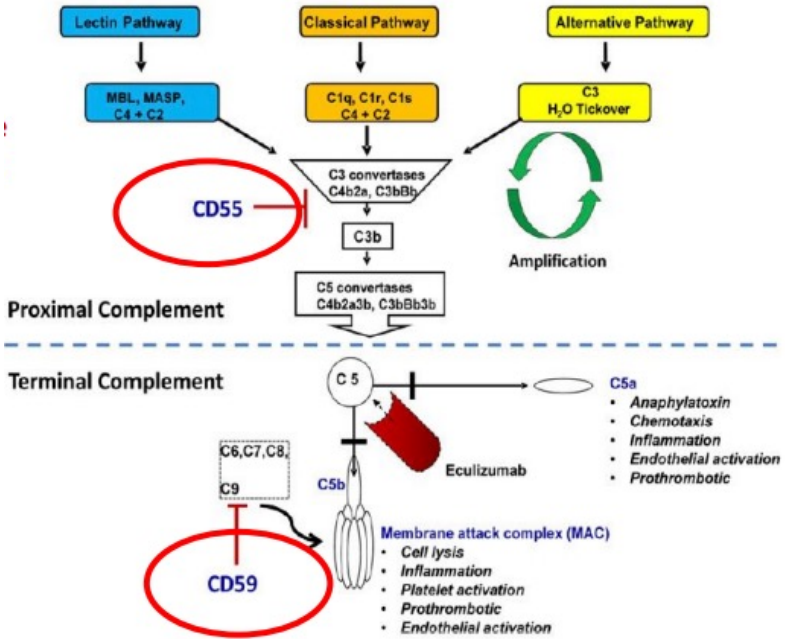
- Thrombosis in atypical locations



Hillmen P et al. Blood 2007;110(12):4123-8, Brodsky, How I treat PNH, Blood 2021; THE LATEST IN PNH: NEW TREATMENT OPTIONS AND DEALING WITH SIDE EFFECTS Anna Koget, D.O. Allegheny Health Network

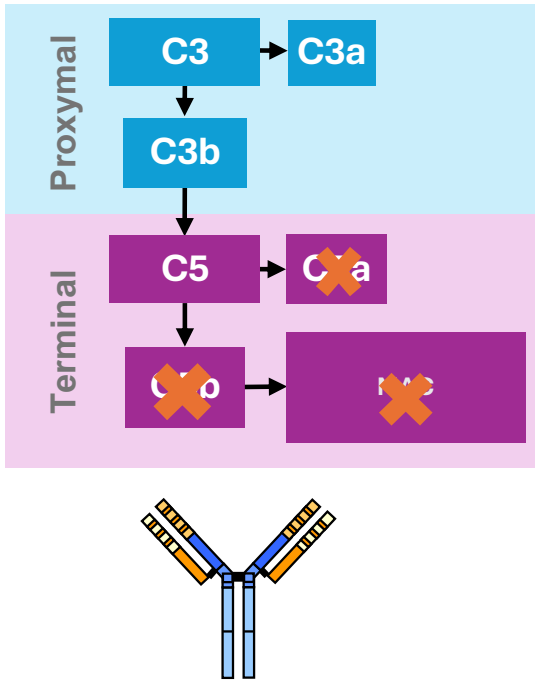
PNH: TREATMENT WITH COMPLEMENT INHIBITION

- ✓ Complement inhibitors that target terminal complement are the treatment of choice for PNH
- ✓ Eculizumab is a humanized monoclonal antibody that binds to the human C5 complement protein
- ✓ Eculizumab recombinant antibody inhibits C5 cleavage to C5a and C5b, preventing the generation of the terminal complement complex C5b-9 and thus blocking complement-mediated cell lysis and activation.



PNH: TREATMENT WITH COMPLEMENT INHIBITION

Eculizumab blocks the complement cascade, preventing chronic haemolysis



1. Walport MJ. *N Engl J Med* 2001;344(14):1058–1066;
2. Rother RP, et al. *Nat Biotechnol* 2007;25(11):1256–1264.

PNH: TREATMENT WITH COMPLEMENT INHIBITION

Eculizumab is indicated for the treatment of adults and children with paroxysmal nocturnal hemoglobinuria (PNH)

Evidence of clinical benefit is demonstrated in patients with hemolysis with clinical symptoms indicative of high disease activity, independent of transfusion history

High disease activity

Haemolysis (LDH ≥1.5 × ULN)

+

One or more of these signs/symptoms

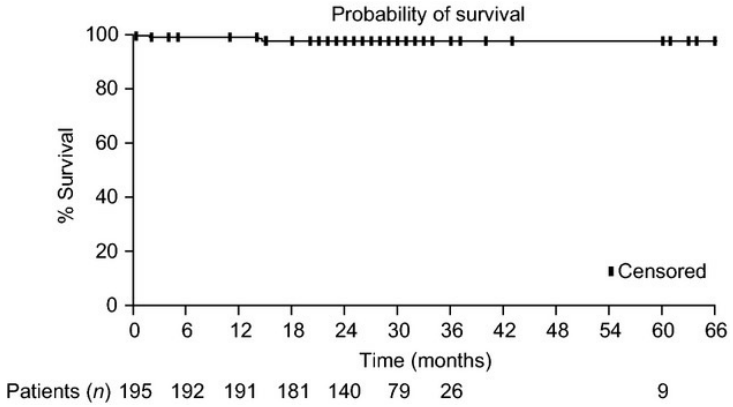
- Fatigue
- Hemoglobinuria
- Abdominal pain
- Dyspnea
- Anemia (Hb <100 g/L)
- Thrombosis
- Dysphagia
- Erectile disfunction

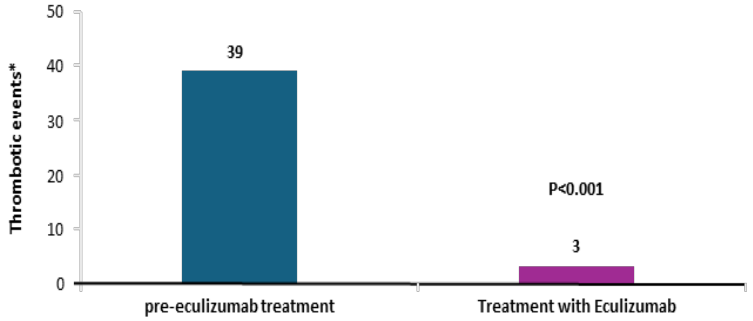
CURRENT OPTIONS FOR THE TREATMENT OF EPN

ECULIZUMAB

Eculizumab changed the natural history of PNH:

- ✓ Estimated 3-year survival 97.6%
- ✓ Reduction in LDH levels (median reduction 86.9% at 36 months)
- ✓ Venous thromboembolism (VTE) reduction of 81.8%, with 96.4% of patients not developing VTE
- ✓ Time-dependent improvement in renal function
- ✓ Increased transfusion independence by 90% from baseline, reduction CE transfused by 54.7%





Schema di dosaggio di Eculizumab per pazienti adulti affetti da EPN

Pre-trattamento		Fase di induzione				Fase di mantenimento				
Vaccinazione contro *Neisseria meningitidis* almeno 2 settimane prima dell'induzione	Settimana →	1	2	3	4	5	6	7	8	9
	Dose di Eculizumab, mg	600	600	600	600	900	X	900	X	900

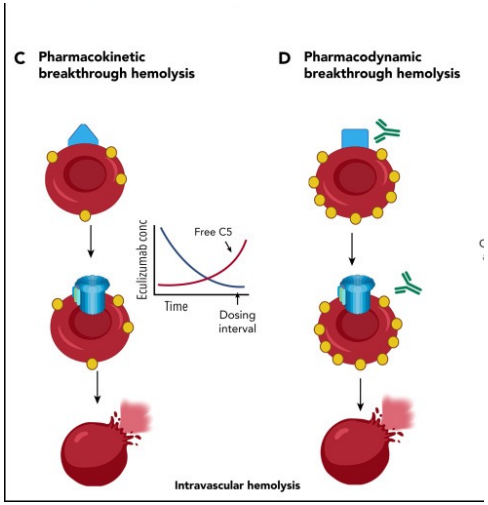
Patients should be monitored clinically and laboratorily by measuring LDH levels. **Dose adjustment** may be necessary during the maintenance phase (every 14 +/- 2 days)

*Total number of events in the 12 months prior to the start of the study or in the first 12 months of treatment. †Patients enrolled in SHEPHERD Phase 3 trial. ‡Treatment with eculizumab does not alter treatment with anticoagulants.

1. Hillmen P, et al. *Blood* 2007;110(12):4123–4128; 2. Brodsky RA, et al. *Blood* 2008;111(4):1840–1847.

PNH: CLINICAL FEATURES, BREAKTHROUGH HEMOLYSIS

- Breakthrough hemolysis (BTH)→ thrombosis
- Any complement amplifying condition (infections, traumas, surgery, pregnancy, vaccines, etc.) may result in increased hemolytic rate with:
- Worsening of anemia and possible transfusion need, dark urine, PNH symptoms, and increased risk of thrombosis
- If the patient is on Ci hemolytic flares are called BTH



	Timing	Frequency	Concomitant conditions	Free C5	Eculizumab plasma level	Intervention
Pharmacokinetic breakthrough	>7–10 days from previous dosing	Recurrent	Usually none*	Always >0.5–1 μg/mL	Inadequate	Decrease interval of dosing (10-12 days) or increase dose of eculizumab (1,200 mg)
Pharmacodynamic breakthrough	Any time	Sporadic	Infectious events (both bacterial and viral, such as common seasonal viruses) or any event leading to inflammation (i.e., surgery, possible comorbidities)	Usually ≤0.5–1 μg/mL (but it may occur with any free C5 plasma level)	Adequate	None (treat the underlying cause triggering complement activation)

Brodsky, How I treat PNH, Blood 2021

PNH: TREATMENT WITH COMPLEMENT INHIBITION

CLINICAL TRIALS AND OBSERVATIONS

Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study

KEY POINTS

- Ravulizumab every 8 weeks is noninferior to eculizumab every 2 weeks across all efficacy end points in C5 inhibitor–naive PNH patients.
- Ravulizumab provided immediate, complete, and sustained inhibition of C5 over the entire 8-week dose interval, unlike eculizumab.

- Patients with lactate dehydrogenase (LDH) ‡1.5 times the upper limit of normal and at least 1 PNH symptom were randomized 1:1 to receive ravulizumab or eculizumab for 183 days (N = 246).
- Ravulizumab was noninferior to eculizumab for both coprimary and all key secondary end points (P inf < .0001): transfusion avoidance, LDH normalization, percent reduction in LDH, change in FACIT-Fatigue score, breakthrough hemolysis, and stabilized hemoglobin

CURRENT OPTIONS FOR THE TREATMENT OF EPN

RAVULIZUMAB

blood Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study

Results: Ravulizumab demonstrated durable efficacy and good tolerability, with **complete and sustained inhibition of free C5** and **reduced incidence of BTH** up to 52 weeks, was noninferior to Eculizumab in the 4 major secondary objectives

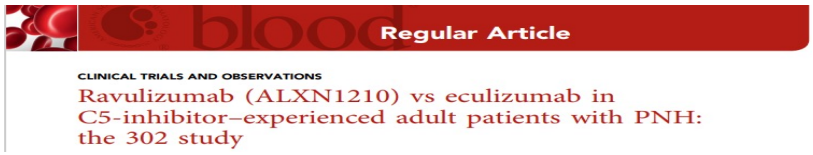
	Ravulizumab (N = 125)	Eculizumab (N = 121)	Statistic for comparison	Treatment effect	Noninferiority margin
Coprimary end points					
Transfusion avoidance rate, % (95% CI)	73.6 (65.87, 81.33)	66.1 (57.68, 74.55)	Difference in rate	6.8 (**−4.66**, 18.14)	−20%
LDH normalization, % (95% CI)	53.6 (45.9, 61.2)	49.4 (41.7, 57.0)	OR	1.19 (**0.80**, 1.77)	0.39
Key secondary efficacy end points					
LDH, least squares mean % change (95% CI)	−76.84 (−79.96, −73.73)	−76.02 (−79.20, −72.83)	Difference in % change from baseline	−0.83 (−5.21, **3.56**)	20%
FACIT-Fatigue score, least squares mean change (95% CI)	7.07 (5.55, 8.60)	6.40 (4.85, 7.96)	Difference in change from baseline	0.67 (**−1.21**, 2.55)	−5.0
Breakthrough hemolysis rate, % (95% CI)	4.0 (0.56, 7.44)	10.7 (5.23, 16.26)	Difference in rate	−6.7 (−14.21, **0.18**)	20%
Hemoglobin stabilization rate, % (95% CI)	68.0 (59.82, 76.18)	64.5 (55.93, 72.99)	Difference in rate	2.9 (**−8.80**, 14.64)	−20%

For the transfusion avoidance end point, treatment differences (95% CIs) are based on estimated differences in percent with 95% CI. For the LDH-N end point, the adjusted prevalence within each treatment is displayed. Testing of the noninf assessed by comparing the bolded limit of the 95% CI to the noninferiority margin.

Lee JW et al, Blood 2019

CURRENT OPTIONS FOR THE TREATMENT OF PNH

RAVULIZUMAB



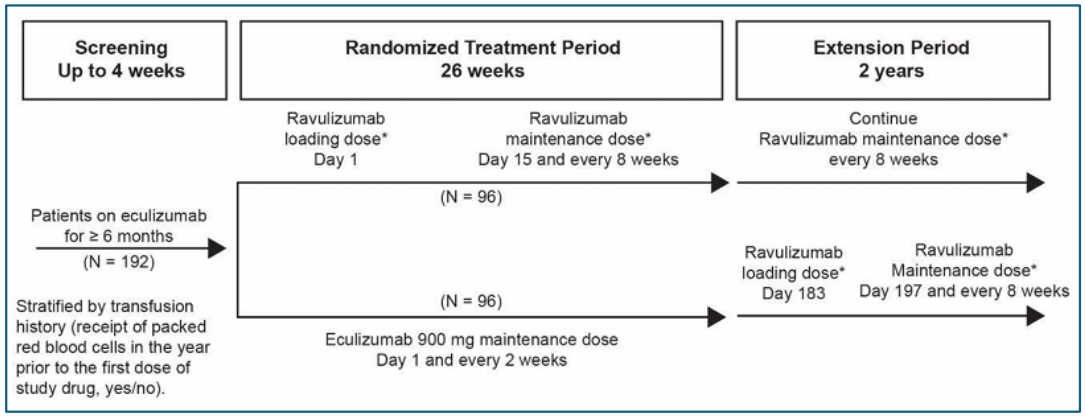
Phase III, multicenter randomized trial conducted in 49 centers in 11 countries

Primary endpoint: noninferiority in terms of efficacy (hemolysis assessed as percent change in LDH levels from baseline to day 183)

Secondary endpoints:

Percentage of patients with BTH; change from baseline in FACIT-Fatigue score; transfusion independence; percentage of patients with stabilization of Hb levels.

Study design



Kulasekararaj AG et al, Blood 2019

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CURRENT OPTIONS FOR THE TREATMENT OF PNH

RAVULIZUMAB

blood Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor–experienced adult patients with PNH: the 302 study

Results: Ravulizumab demonstrated **durable efficacy and good tolerability** in patients with clinically stable EPNs treated with Eculizumab up to 52 weeks. **4 patients** (3 in the Ravulizumab - Ravulizumab arm, 1 in the Eculizumab - Ravulizumab arm) **experienced BTH but no case was associated with an increase in C5 > 0.5 ug/mL**.

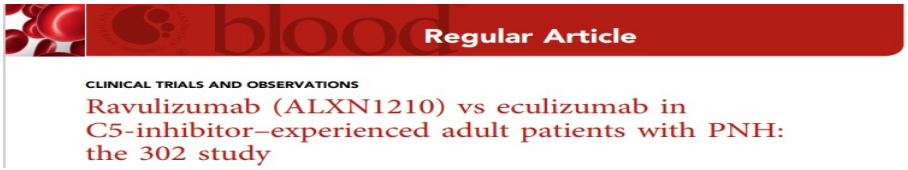
	Ravulizumab (n = 97)	Eculizumab (n = 98)	Statistic for comparison	Treatment effect	Noninferiority margin	Conclusion*
Primary end point						
LDH, least squares mean % change (95% CI)	−0.82 (−7.8, 6.1)	8.4 (1.5, 15.3)	Difference in percentage change from baseline	9.2 (−**0.42** to 18.8)	−15%	Noninferior
Key secondary efficacy end points						
Breakthrough hemolysis rate, % (95% CI)	0 (0 to 3.7)	5.1 (1.7 to 11.5)	Difference in rate	5.1 (−**8.9** to 19.0)	−20%	Noninferior
FACIT-Fatigue score, least squares mean change (95% CI)	2.0 (0.6 to 3.4)	0.54 (−0.8 to 1.9)	Difference in change from baseline	1.5 (−**0.2** to 3.2)	−3.0	Noninferior
Transfusion avoidance rate, % (95% CI)	87.6 (81.1 to 94.2)	82.7 (75.2 to 90.2)	Difference in rate	5.5 (−**4.3** to 15.7)	−20%	Noninferior
Stabilized hemoglobin rate, % (95% CI)	76.3 (67.8 to 84.8)	75.5 (67.0 to 84.0)	Difference in rate	1.4 (−**10.4** to 13.3)	−20%	Noninferior

Testing of the noninferiority hypothesis is assessed by comparing the bolded limit of the 95% CI to the noninferiority margin.
*A conclusion of noninferiority indicates that the noninferiority margin is larger or smaller than the lower or upper bound of the 95% CI indicated in boldface.

Kulasekararaj AG et al, Blood 2019

CURRENT OPTIONS FOR THE TREATMENT OF PNH

RAVULIZUMAB



Most common adverse events:
Asthenia (13.5%), upper respiratory trait infections (9.4%), headache (6.3%), nasopharyngitis (6.3%), diarrhea (6.3%), and pyrexia (6.3%) in the Ravulizumab arm - Ravulizumab

Asthenia (13.7%), headache (10.5%), upper airway infections (8.4%) and nasopharyngitis (7.4%) in the Eculizumab - Ravulizumab arm.

No cases of meningococcal infection at 52 weeks.

Table 4. Adverse events

Variable	Ravulizumab (n = 97)	Eculizumab (n = 98)
Patients with adverse events	85 (87.6)	86 (87.8)
Most common adverse events (≥5% of patients in either treatment group)		
Headache	26 (26.8)	17 (17.3)
Nasopharyngitis	21 (21.6)	20 (20.4)
Upper respiratory tract infection	18 (18.6)	10 (10.2)
Diarrhea	9 (9.3)	7 (7.1)
Pyrexia	9 (9.3)	5 (5.1)
Nausea	8 (8.2)	9 (9.2)
Constipation	7 (7.2)	5 (5.1)
Influenza-like illness	7 (7.2)	8 (8.2)
Abdominal pain	6 (6.2)	9 (9.2)
Anemia	6 (6.2)	3 (3.1)
Fatigue	6 (6.2)	6 (6.1)
Vomiting	6 (6.2)	4 (4.1)
Cough	5 (5.2)	10 (10.2)
Pain in extremity	5 (5.2)	4 (4.1)
Rhinitis	5 (5.2)	4 (4.1)
Oropharyngeal pain	4 (4.1)	9 (9.2)
Chest pain	3 (3.1)	9 (9.2)
Dizziness	3 (3.1)	7 (7.1)
Musculoskeletal pain	2 (2.1)	5 (5.1)
Dyspnea	0 (0.0)	6 (6.1)
Patients with serious adverse events	4 (4.1)	8 (8.2)
Meningococcal infections	0	0
Death	0	0
Patients with adverse events leading to withdrawal of study drug	0	0
Patients with serious adverse events leading to withdrawal of study drug	0	0

Values are reported as n (%) of patients.

Kulasekararaj AG et al, Blood 2019

CURRENT OPTIONS FOR THE TREATMENT OF PNH

RAVULIZUMAB

Indications for treatment: adult and pediatric patients with a body weight of 10 kg or more with EPN:

- in patients with hemolysis and one or more clinical symptoms indicative of high disease activity
- in patients clinically stable after treatment with Eculizumab for at least the past 6 months

Intervallo di peso corporeo (kg)	Dose di carico (mg)	Dose di mantenimento (mg)*	Intervallo di somministrazione
da ≥ 40 a < 60	2400	3000	Ogni 8 settimane
da ≥ 60 a < 100	2700	3300	Ogni 8 settimane
≥ 100	3000	3600	Ogni 8 settimane

*La prima dose di mantenimento è somministrata 2 settimane dopo la dose di carico.

Popolazione	Dose di carico per via endovenosa di ravulizumab in base al peso corporeo	Tempistica della prima dose di mantenimento per via endovenosa di ravulizumab in base al peso corporeo
Attualmente non in trattamento con ravulizumab o eculizumab	All'inizio del trattamento	2 settimane dopo la dose di carico endovenosa di ravulizumab
Attualmente in trattamento con eculizumab	Al momento della successiva dose di eculizumab programmata	2 settimane dopo la dose di carico endovenosa di ravulizumab

Important: All patients should be vaccinated against Neisseria Meningitidis (serogroups A, C, Y, W135, and B) at least 2 weeks before starting treatment with ravulizumab, otherwise perform antibiotic prophylaxis until 2 weeks after vaccination

Kulasekararaj AG et al, Blood 2019

FAILURE AFTER C5 INHIBITORS

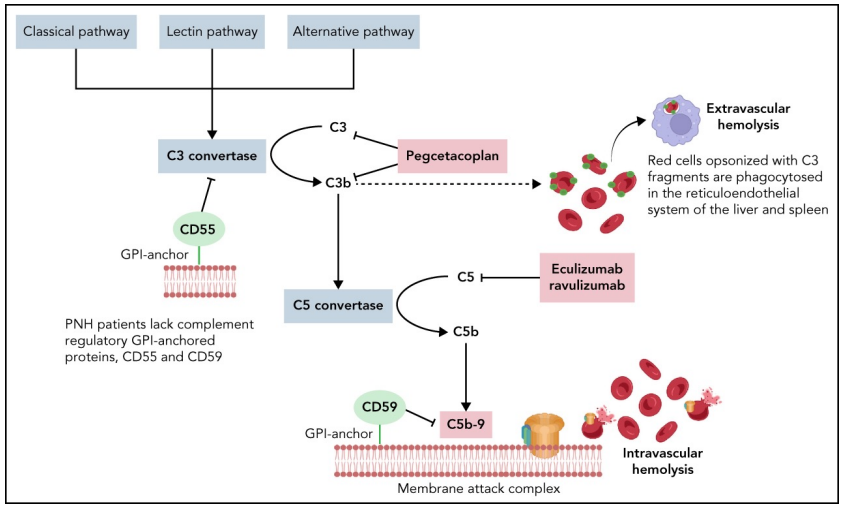
- Hemoglobin normalization occurs in 1/3 of patients; up to 1/3 of patients treated with C5 inhibitors remain transfusion dependent or have bothersome symptoms, extravascular hemolisys and mild to moderate anemia

- Factors contributing to persistence of anemia: underlying bone marrow dysfunction, residual intravascular hemolysis, extravascular C3-mediated hemolysis.

- Rare causes: intrinsic resistance to Eculizumab is associated with a C5 gene polymorphism that prevents binding to the inhibitor

- Ravulizumab, compared with Eculizumab, does not improve hematologic response although it appears to be associated with a lower risk of BTH due to pharmacokinetic issues

- Ravulizumab preferable to eculizumab due to longer half-life and more convenient administration schedule



American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Gloria F. Gerber,Robert A. Brodsky, Pegcetacoplan for paroxysmal nocturnal hemoglobinuria, Blood Adv, 2022

Hillmen P, et al. Front Immunol 2019

CURRENT OPTIONS FOR THE TREATMENT OF PNH

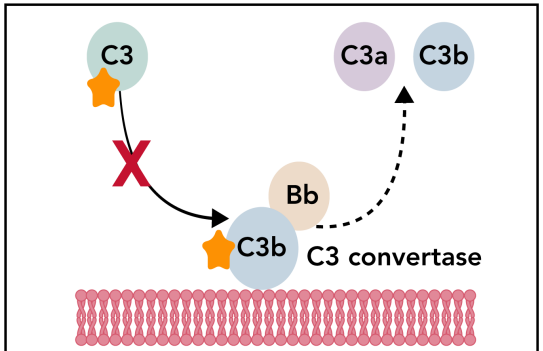
C3 INHIBITION: PEGCETACOPLAN

PEGCETACOPLAN:

Twice-weekly subcutaneous injection

2021 EMA approval for PNH patients who remain anemic despite ≥3 months of C5i

Binds to and inhibits C3 and its cleavage fragment C3b, thus attenuating both C3 mediated extravascular hemolysis and intravascular hemolysis from terminal complement activation



Pegcetacoplan (orange star) binds C3 or C3b and prevents interaction between C3 and the C3 convertase.

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Gloria F. Gerber,Robert A. Brodsky, Pegcetacoplan for paroxysmal nocturnal hemoglobinuria, Blood, 2022

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CURRENT OPTIONS FOR THE TREATMENT OF PNH

PEGCETACOPLAN

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

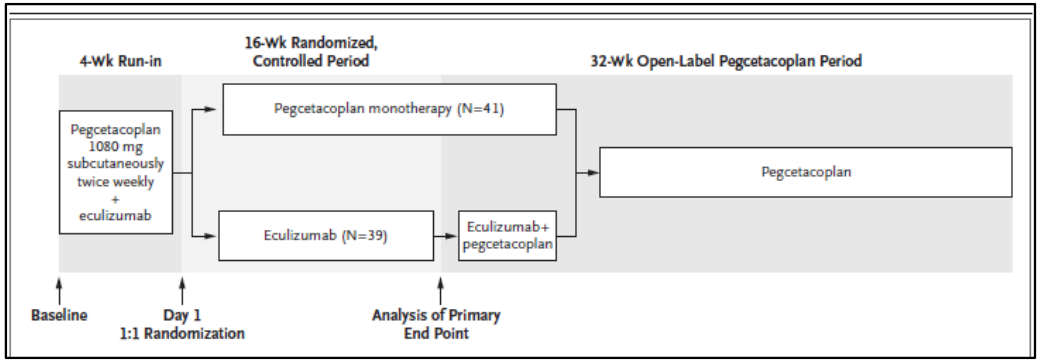
Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

PEGASUS: randomized, multicenter, 48-week phase III study conducted at 44 centers

<u>Primary ednpoint:</u> efficacy and safety of Pegcetacoplan compared with Eculizumab in patients with EPN and Hb levels less than 10.5 g/dL (mean Hb improvement from baseline to week 16)

<u>Secondary endpoints:</u> number of patients who did not require transfusion during the randomized controlled period, changes at week 16 in absolute reticulocyte count, LDH and FACIT-F score

Study design



Hillmen P et al, NEJM, March 18, 2021

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CURRENT OPTIONS FOR THE TREATMENT OF PNH

PEGCETACOPLAN

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

- ✓ Pegcetacoplan demonstrated a **mean increase of 3.84 g/dL in hemoglobin** compared with the Eculizumab-treated group of patients
- ✓ 35 patients (85%) **treated with Pegcetacoplan were transfusion independent** at week 16 vs 6 patients (15%) in the Eculizumab group ($p < 0.001$)
- ✓ Pegcetacoplan was **noninferior for both reduction in absolute reticulocyte count and reduction in LDH levels.**
- ✓ **FACIT-F score increased by 9.2 points with Pegcetacoplan and decreased by 2.7 points with Eculizumab.**
- ✓ 73% of patients treated with Pegcetacoplan had an increase in score of at least 3 points at week 16 (0% in the Eculizumab group)

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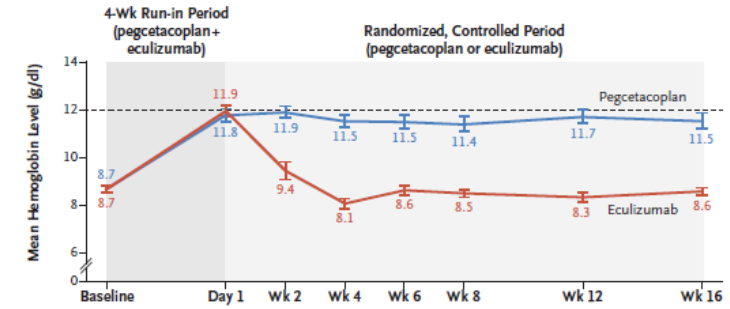

No. with Available Data								
Pegcetacoplan	41	40	40	40	39	37	38	37
Eculizumab	39	37	38	39	36	39	39	38

B

Subgroup	No. of Patients		Adjusted Change in LS Mean Hemoglobin		Difference (95% CI)
	Pegcetacoplan	Eculizumab	Pegcetacoplan	Eculizumab	
			g/dl ± SE		
Censored for transfusion events, all values after intercurrent events set to missing	41	39	2.37±0.36	−1.47±0.67	3.84 (2.33–5.34)
All available data, regardless of tranfusion events	41	39	2.66±0.25	−0.03±0.26	2.69 (1.99–3.38)
No. of transfusions in previous 12 mo					
<4	20	16	2.97±0.36	−0.01±0.49	2.98 (1.73–4.23)
≥4	21	23	2.11±0.60	−4.02±2.40	6.13 (0.79–11.48)

Hillmen P et al, NEJM, March 18, 2021

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CURRENT OPTIONS FOR THE TREATMENT OF PNH

PEGCETACOPLAN

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ORIGINAL ARTICLE

Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

Adverse events:

- Adverse events occurred in 36 patients (88%) treated with Pegcetacoplan and 34 (87%) with Eculizumab.
- The most frequent were: injection site reactions (37% vs 3%), diarrhea (22% vs 3%), BTH (10% vs 23%), headache (7% vs 23%) and fatigue (5% vs 15%)
- Infectious events occurred in 29% of patients treated with Pegcetacoplan and 26% of patients treated with Eculizumab
- **BTH was reported in 4 patients (10%) of the Pegcetacoplan arm and in 9 (23%) of the Eculizumab arm**.
- **3 of the 4 patients treated with Pegcetacoplan with BTH had > 3xULN LDH and discontinued treatment with Pegcetacoplan, switching back to Eculizumab**

Table 2. Adverse Events That Occurred during the 16-Week Randomized, Controlled Period.

Event	Pegcetacoplan (N=41)	Eculizumab (N=39)
	no. of patients (%)	
Any adverse event occurring during treatment	36 (88)	34 (87)
Adverse event in >5% of patients in either group		
Injection-site erythema	7 (17)	0
Injection-site reaction	5 (12)	0
Injection-site swelling	4 (10)	0
Asthenia	3 (7)	3 (8)
Injection-site induration	3 (7)	0
Fatigue	2 (5)	6 (15)
Pyrexia	2 (5)	2 (5)
Vaccination-site pain from any vaccine*	0	2 (5)
Back pain	3 (7)	4 (10)
Pain in arms or legs	3 (7)	1 (3)
Diarrhea	9 (22)	1 (3)
Abdominal pain	5 (12)	4 (10)
Nausea	2 (5)	2 (5)
Vomiting	0	3 (8)
Viral upper respiratory tract infection	2 (5)	2 (5)
Hemolysis	4 (10)	9 (23)
Anemia	0	5 (13)
Headache	3 (7)	9 (23)
Dizziness	1 (2)	4 (10)
Hypertension	3 (7)	1 (3)
Dyspnea	1 (2)	2 (5)
Oropharyngeal pain	0	2 (5)
Hyperbilirubinemia	0	2 (5)
Anxiety	1 (2)	2 (5)
Insomnia	0	2 (5)
Palpitations	0	2 (5)
Chromaturia	0	2 (5)
Serious adverse events occurring during treatment		
Any	7 (17)	6 (15)
Occurring in >1 patient in the pegcetacoplan group		
Hemolysis	2 (5)	1 (3)

Hillmen P et al, NEJM, March 18, 2021

LE OPZIONI ATTUALI PER IL TRATTAMENTO DELL'EPN

PEGCETACOPLAN

Indicazioni al trattamento: Farmaco approvato AIFA nel settembre 2022, indicato nel trattamento di pazienti adulti con EPN che rimangono anemici dopo trattamento con un inibitore di C5 per almeno 3 mesi.

Modalità di somministrazione:

- 2 volte alla settimana (giorni 1 e 4) mediante infusione sottocutanea di 1080 mg utilizzando una pompa per infusione a siringa disponibile in commercio in grado di dispensare dosi fino a 20 mL.

Punti in cui poter effettuare l'infusione: addome, coscia, fianchi e braccia. Alternare le sedi di infusione tra una somministrazione e l'altra. Se le sedi di infusione sono più di una, devono essere ad almeno 7,5 cm di distanza l'una dall'altra. La durata tipica dell'infusione è di circa 30 minuti (se si utilizzano due sedi) o di circa 60 minuti (se si utilizza una sola sede)

Pazienti che passano da un inibitore di C5 a Pegcetacoplan: Per le prime 4 settimane, pegcetacoplan viene somministrato due volte alla settimana per via sottocutanea con una dose di 1080 mg in aggiunta all'attuale dose di inibitore di C5 ricevuta dal paziente.

Aggiustamento della dose di Pegcetacoplan: Il regime posologico può essere modificato a 1080 mg ogni tre giorni (es., Giorno 1, Giorno 4, Giorno 7, Giorno 10, Giorno 13, e così via) nei soggetti con livelli di LDH > 2 ULN.

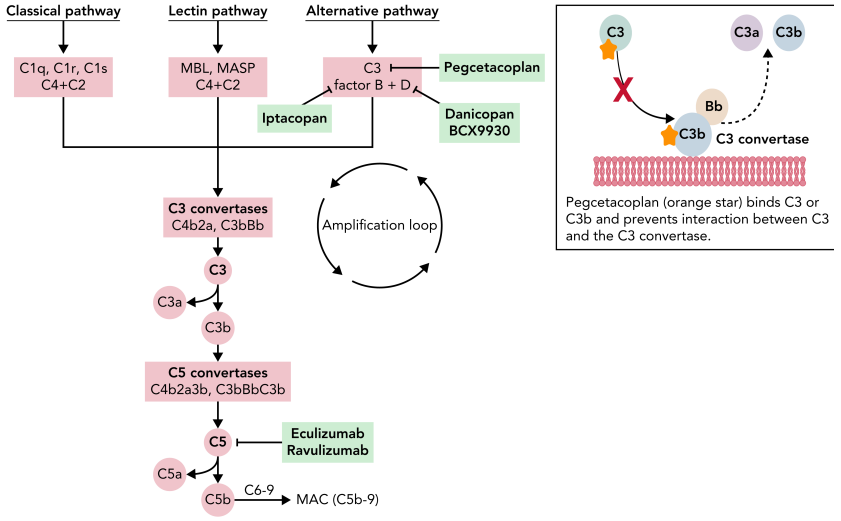
Importante: tutti i pazienti devono essere vaccinati contro S. pneumoniae, N. meningitidis di tipo A, C, W, Y e B e H. influenzae di tipo B almeno **2 settimane prima** di ricevere pegcetacoplan. Ci si deve assicurare che i pazienti con una storia vaccinale documentata siano stati vaccinati nei **2 anni precedenti** l'inizio della terapia.

NEW OPTIONS FOR THE TREATMENT OF PNH

PROXIMAL COMPLEMENT INHIBITORS

IPTACOPAN: orally available selective reversible inhibitor of complement factor B; assessed in patients with active hemolysis in patients taking eculizumab, resulted in Hb concentration improvement

DANICOPAN: oral proximal complement inhibitor of alternative pathway factor D designed to control both intra- and extravascular hemolysis; danicopan in addition to eculizumab resulted in significant increase in Hb levels and reduction in transfusion rate



Gloria F. Gerber,Robert A. Brodsky, Pegcetacoplan for paroxysmal nocturnal hemoglobinuria, Blood, 2022

Syed S, Khan R, Khurram F, Khan FH, Safi D, Safi SUD. Treatment of eculizumab refractory paroxysmal nocturnal hemoglobinuria: A systematic review about current treatment options and future direction. SAGE Open Med. 2023 Jun 22;11:20503121231181267. doi: 10.1177/20503121231181267. PMID: 37388903; PMCID: PMC10302528.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

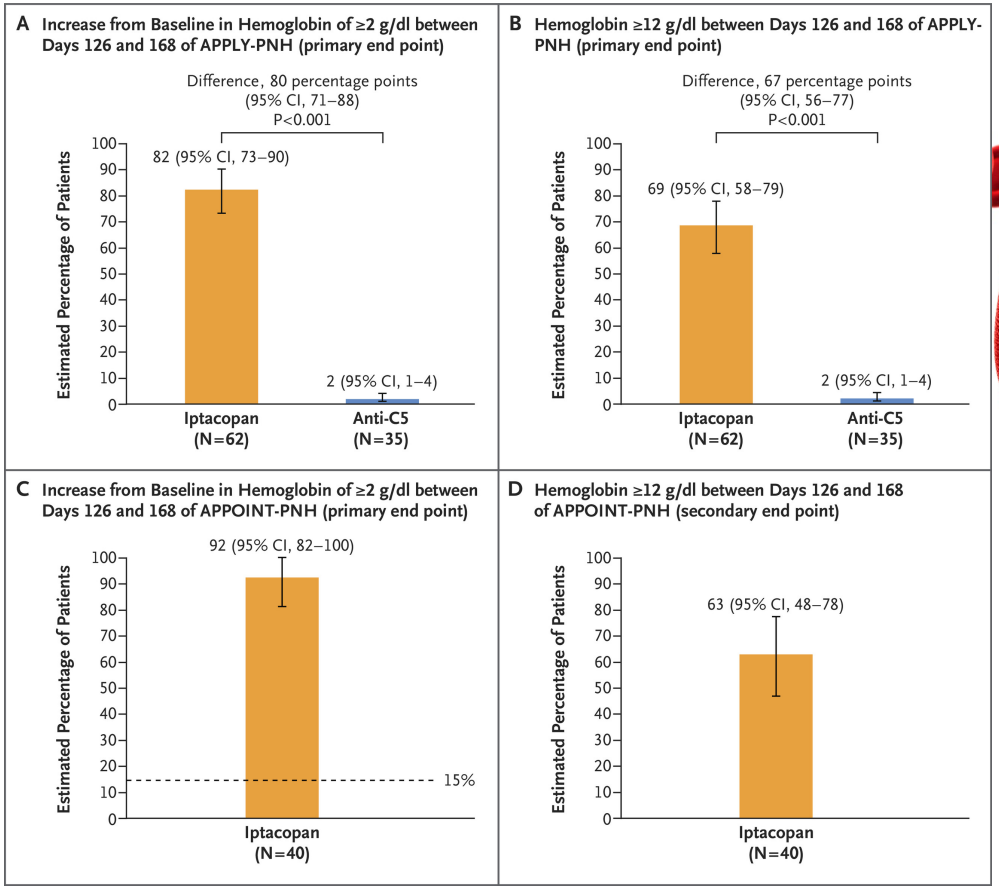
Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria

Two phase 3 trials:

*__APPLY-PNH__: patients receiving anti CD5 treatment with persistent anemia were randomized 8:5 to receive either oral iptacopan monotherapy or to continue anti-CD5

*__APPOINT-PNH__: single group of patients with hemolytic PNH who had not received complement inhibition

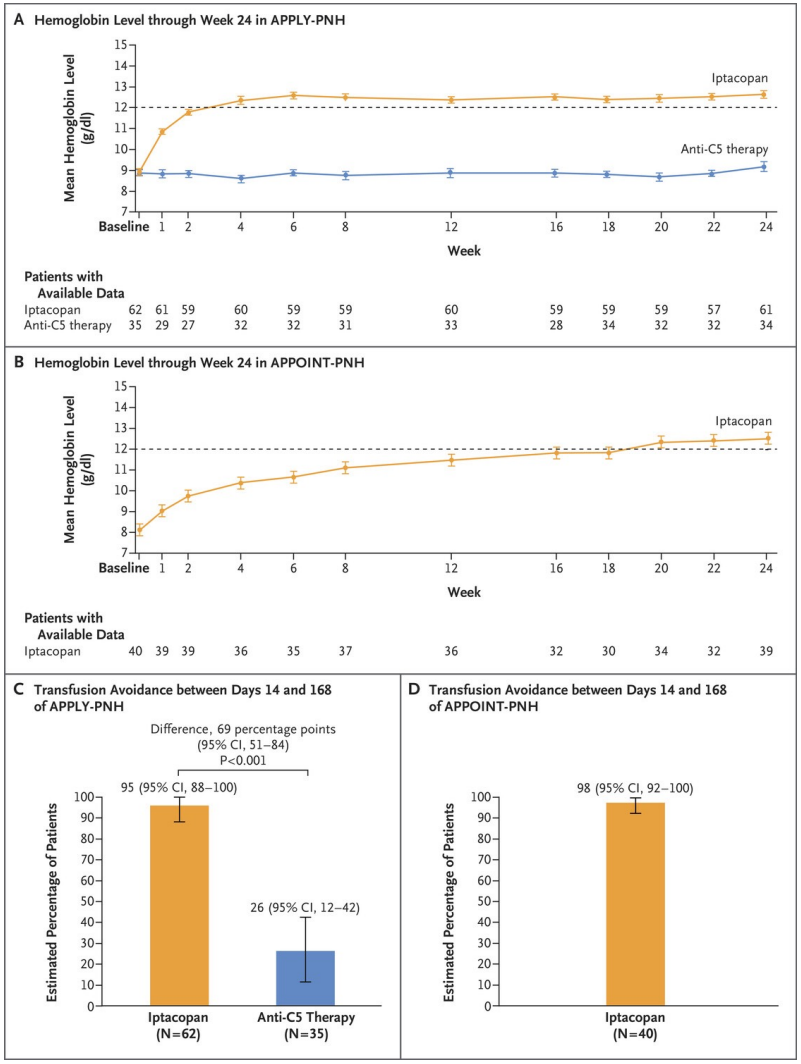
Primary endpoint for both studies:
-Increase in Hb level
-Hb level of at least 12 g/dl



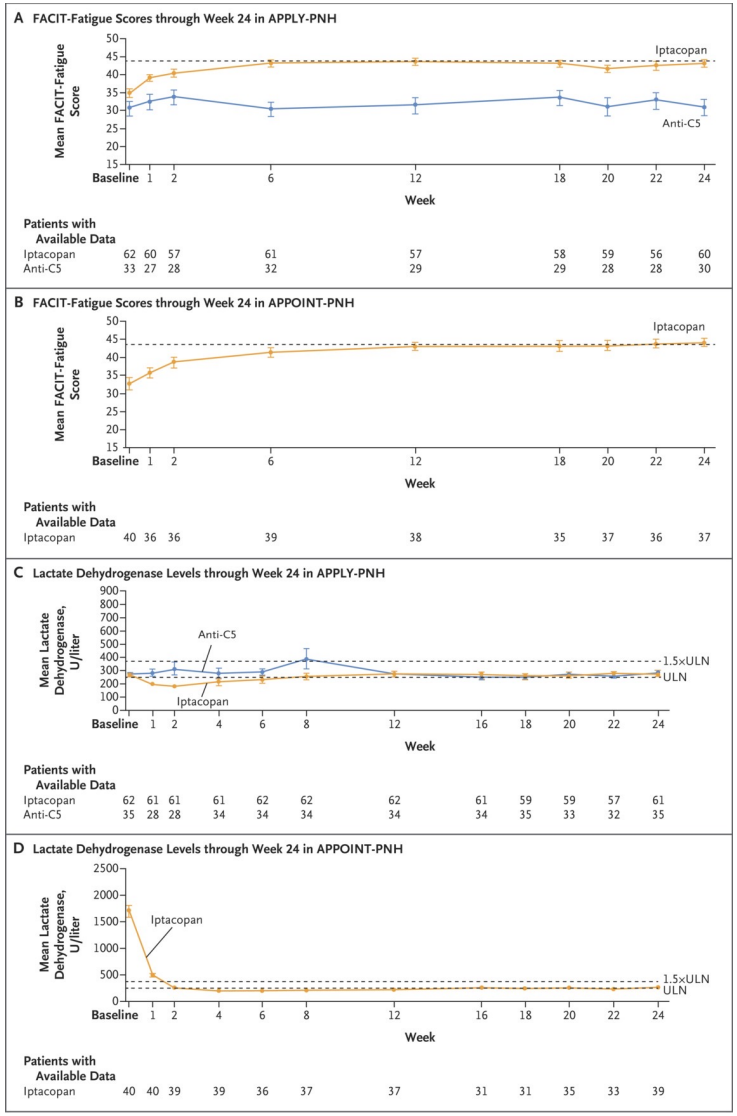
R. Peffault de Latour, Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria, N Engl J Med 2024;390:994-1008. DOI: 10.1056/NEJMoa2308695

Secondary endpoints:

*changes from baseline in the Hb levels
*transfusion avoidance
*scores on the FACIT-Fatigue survey
*absolute retyculocyte count
*percentage change from baseline in LDH levels



R. Peffault de Latour, Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria, N Engl J Med 2024;390:994-1008. DOI: 10.1056/NEJMoa2308695



Secondary endpoints:

*changes from baseline in the Hb levels

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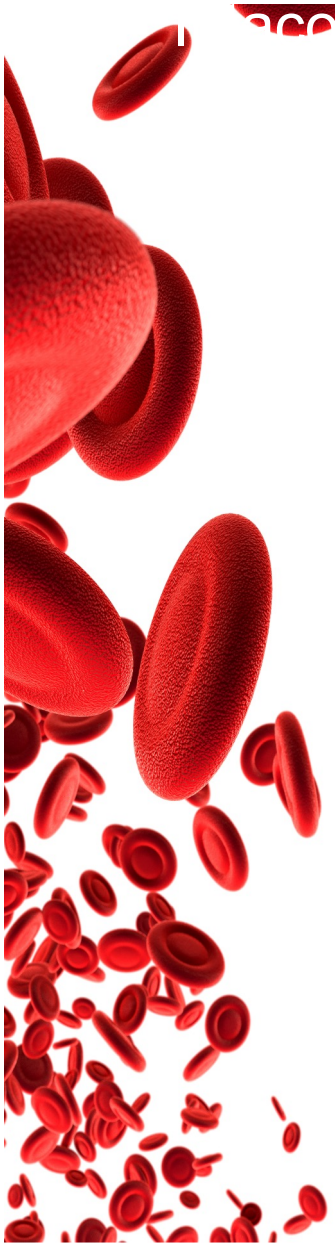


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria

Iptacopan treatment improved hematologic and clinical outcomes in anti-C5–treated patients with persistent anemia — in whom iptacopan showed superiority to anti-C5 therapy — and in patients who had not received complement inhibitors

Iptacopan: monotherapy in adult PNH patients with hemolytic anemia (200 mg bid)

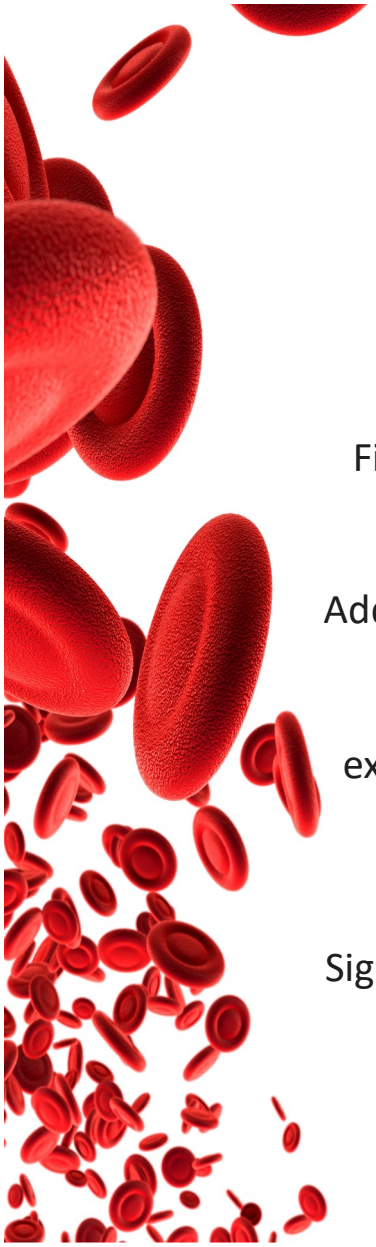
Compliance/adherence!

Table 2. Adverse Events in the 24-Week Core Treatment Periods of the APPLY-PNH and APPOINT-PNH Trials.

Event	APPLY-PNH		APPOINT-PNH
	Anti-C5 therapy (N=35)	Iptacopan (N=62)	Iptacopan (N=40)
Any adverse event	28 (80)	51 (82)	37 (92)
Severity			
Mild	13 (37)	20 (32)	26 (65)
Moderate	12 (34)	28 (45)	10 (25)
Severe*	3 (9)	3 (5)	1 (2)
Events occurring in ≥4 patients in either trial†			
Headache	1 (3)	10 (16)	11 (28)
Diarrhea	2 (6)	9 (15)	3 (8)
Nasopharyngitis	2 (6)	7 (11)	0
Nausea	1 (3)	6 (10)	2 (5)
Arthralgia	1 (3)	5 (8)	0
Coronavirus disease 2019	9 (26)	5 (8)	6 (15)
Urinary tract infection	1 (3)	5 (8)	0
Abdominal pain	1 (3)	4 (6)	2 (5)
Increase in LDH level	3 (9)	4 (6)	0
Dizziness	0	4 (6)	1 (2)
Upper respiratory tract infection	3 (9)	2 (3)	5 (12)
Breakthrough hemolysis	6 (17)	2 (3)	0

* Only one patient (in the APPOINT-PNH trial) had severe adverse events of bacterial pneumonia and chest pain.
† Shown are the most frequently occurring adverse events in the iptacopan group of the APPLY-PNH trial.

R. Peffault de Latour, Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria, N Engl J Med 2024;390:994-1008. DOI: 10.1056/NEJMoa2308695



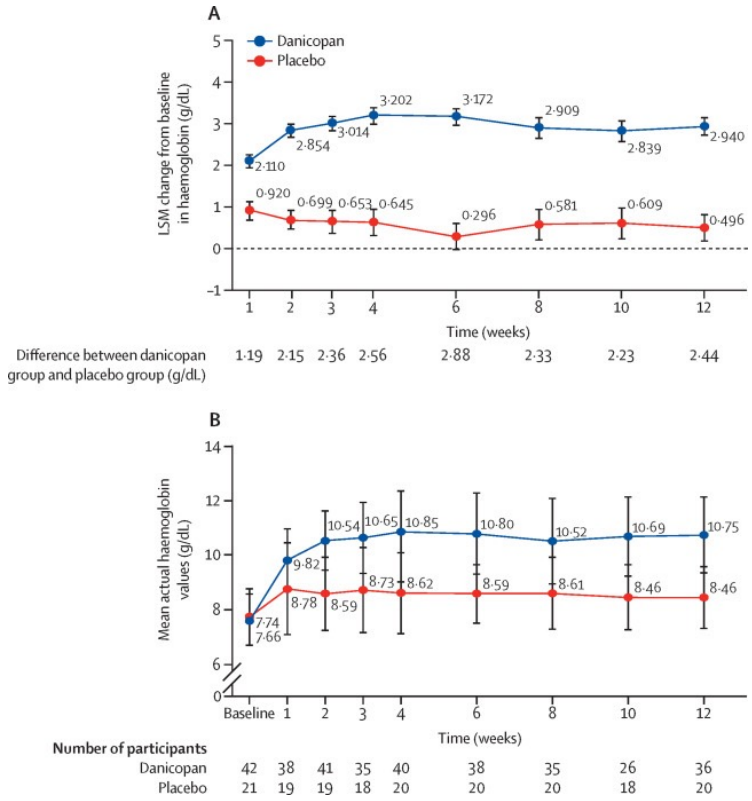
NEW OPTIONS FOR THE TREATMENT OF PNH

DANICOPLAN

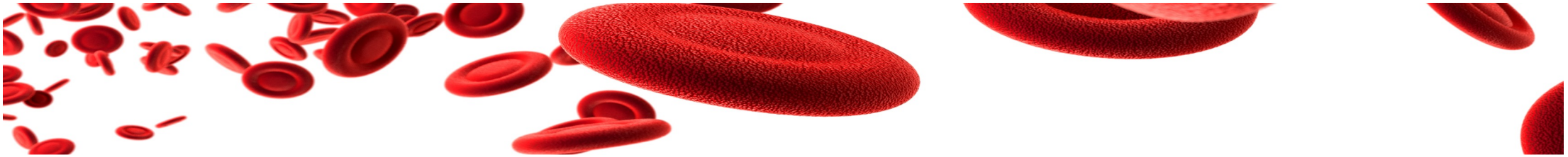
First in cass orally administered factor D inhibitor (initial dose: 150 mg 3x daily)

Addition of danicopan to ravulizumab or eculizumab in patients with paroxysmal nocturnal haemoglobinuria and clinically significant extravascular haemolysis (ALPHA): a double-blind, randomised, phase 3 trial

Significant increase of hemoglobin levels at week 12



Jong Wook Lee et al,
Addition of danicopan to ravulizumab or eculizumab in patients with paroxysmal nocturnal haemoglobinuria and clinically significant extravascular haemolysis (ALPHA): a double-blind, randomised, phase 3 trial, The Lancet Haematology, Volume 10, Issue 12, 2023,https://doi.org/10.1016/S2352-3026(23)00315-0.



COMPLEMENT INHIBITORS IN PNH: KEY POINTS

- ✓ C5 inhibition: preferred frontline treatment
- ✓ Ravulizumab is preferred to eculizumab due to rapid onset of action, dosing every 8 weeks
- ✓ Pegcetacoplan: to be considered in patients with transfusion dependence or with symptomatic anemia attributable to extravascular hemolysis despite ≥ 3 months of C5i
- ✓ Pegcetacoplan takes several weeks (4-6) to reach steady state: use may be limited in the setting of acute thrombosis
- ✓ Proximal complement inhibition (pegcetacoplan): concerns on severe BTH
- ✓ Be mindful of other causes of anemia in PNH (BMF, nutritional deficiency, relative erythropoietin deficiency, hypersplenism, transfusion-related autoantibodies)

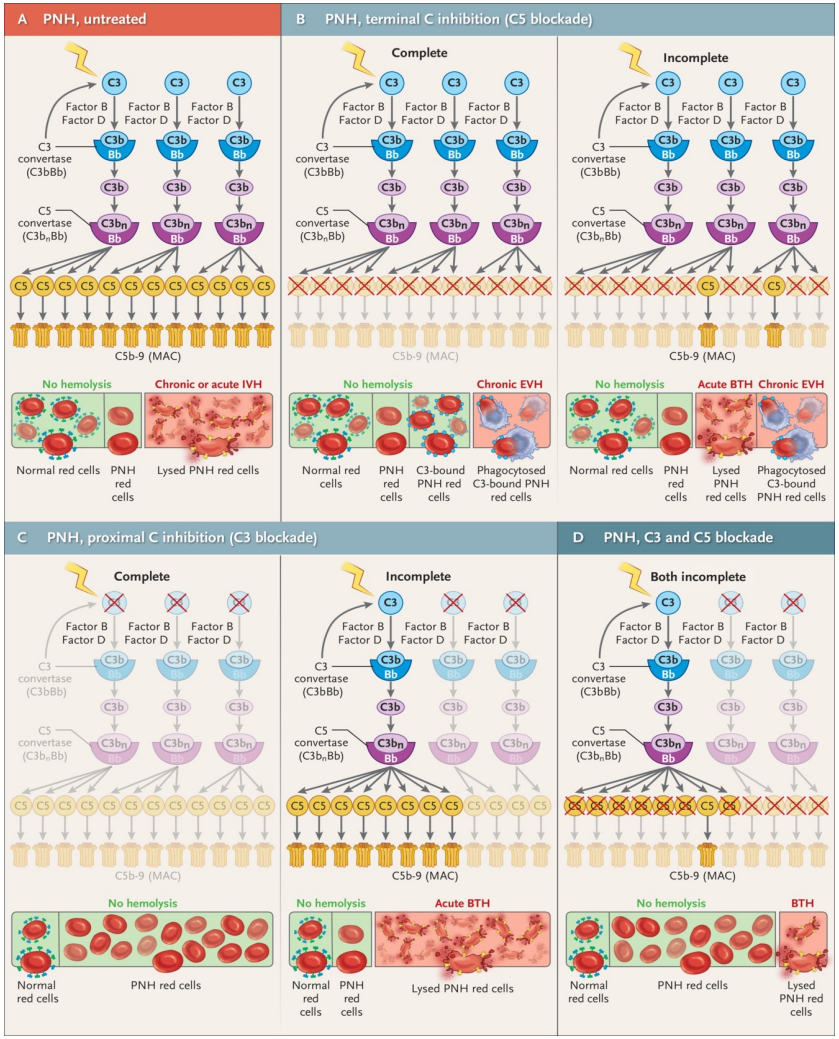
Gloria F. Gerber,Robert A. Brodsky, Pegcetacoplan for paroxysmal nocturnal hemoglobinuria, Blood, 2022

COMPLEMENT INHIBITORS IN PNH: KEY POINTS

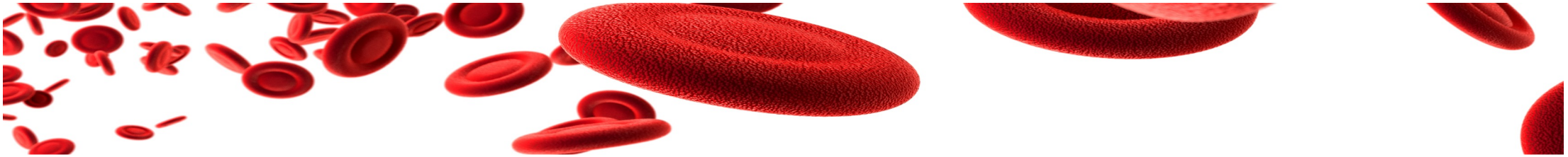
✓ Proximal complement inhibition (esp. pegcetacoplan): concerns on severe BTH

✓ Compliance

✓ Pharmacokynetic differences among different proximal inhibitors



Notaro R, Luzzatto L. N Engl J Med2022;387:160-166



COMPLEMENT INHIBITORS IN PNH: KEY POINTS

✓ Novel drugs (pegcetacoplan, danicopan, iptacopan): improved hemolysis control (intravascular and extravascular) and reduced number of side effects compared to eculizumab

✓ Danicopan/iptacopan: more convenient oral administration

✓ Proximal + terminal complement inhibition: limited risk of BTH in case of partial proximal inhibition

Syed S, Khan R, Khurram F, Khan FH, Safi D, Safi SUD. Treatment of eculizumab refractory paroxysmal nocturnal hemoglobinuria: A systematic review about current treatment options and future direction. SAGE Open Med. 2023 Jun 22;11:20503121231181267. doi: 10.1177/20503121231181267. PMID: 37388903; PMCID: PMC10302528.

GRAZIE PER L'ATTENZIONE!

UO EMATOLOGIA E TERAPIE CELLULARI
IRCCS OSPEDALE POLICLINICO SAN MARTINO (GENOVA)