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Facing clinical challenges associated with paroxysmal nocturnal haemoglobinuria (PNH)

Practice aid for PNH education

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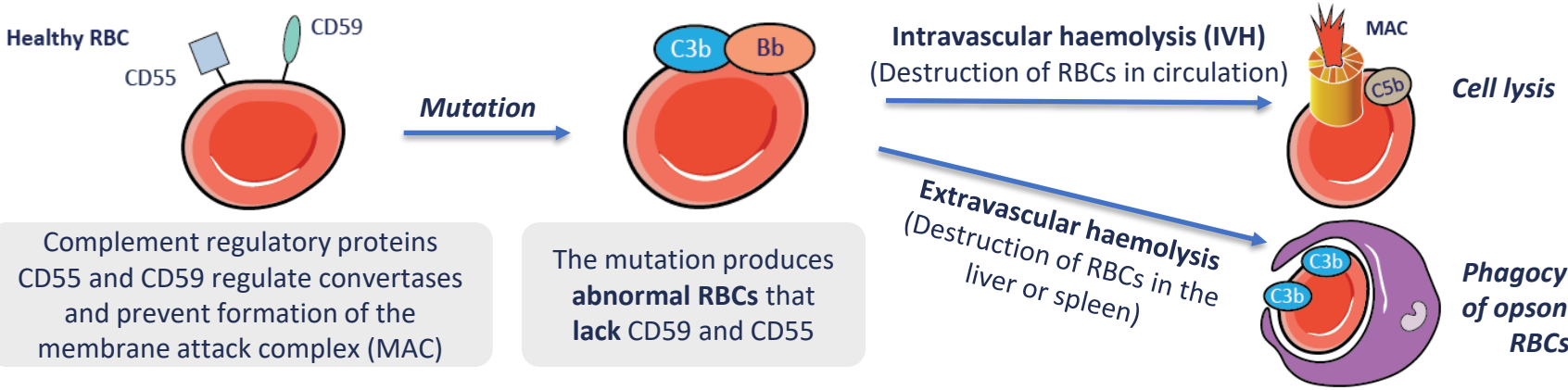
What is paroxysmal nocturnal haemoglobinuria?[1–3]

PNH is a rare, chronic, acquired, haematologic disease caused by a variety of somatic mutations in the ***PIGA* gene**



Complement regulatory proteins CD55 and CD59 regulate convertases and prevent formation of the membrane attack complex (MAC)

The mutation produces **abnormal RBCs** that **lack** CD59 and CD55

Symptoms of PNH[1,4]

Highly heterogeneous presentation but common symptoms include:

- Fatigue
- Haemoglobinuria
- Renal dysfunction
- Dyspnoea
- Abdominal pain
- Other: Erectile dysfunction, dysphagia and thrombosis

Diagnosing PNH[4–7]

In primary care settings:

- Blood tests to detect haemolysis:
  - Hb levels (low)
  - Reticulocyte count (high)
  - Bilirubin (high), LDH (high) and haptoglobin (low) levels
  - Coombs test (negative)
- Unexplained abdominal pain: Refer for ultrasound scan to screen for thrombosis

Specialist haematology settings:

- FLAER-based flow cytometry
  - Confirms deficiency of CD55 and CD59

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Supportive measures and complement inhibitor therapy for PNH

Common supportive measures include: Oral iron and folic acid supplementation; occasionally iron/RBC transfusions[8]

Indicators for use of complement therapy include: Symptomatic haemolysis requiring transfusions and the presence of thrombosis[8]

Drug name	Administration	SmPC indications
Eculizumab[9] C5 Inhibitor	 IV, Q2W	Adults and children with PNH: • Evidence of clinical benefit is demonstrated in pts with haemolysis and clinical symptom(s) indicative of high disease activity, regardless of transfusion history
Ravulizumab[10] C5 Inhibitor	 IV, Q8W	Adult and children with PNH with a body weight ≥10 kg: • In pts with haemolysis with clinical symptom(s) indicative of high disease activity • In pts who are clinically stable after having been treated with eculizumab for at least the last 6 months
Pegcetacoplan[11] C3 Inhibitor	 SC, BW	Adults with PNH who are anaemic after treatment with a C5 inhibitor for ≥3 months

Blue drug names represent terminal CIs and green represent proximal CIs.

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Complement inhibitor therapy for PNH

Drug name	Phase III pivotal trials	Primary efficacy outcomes	Summary of safety profile
Eculizumab[9] C5 Inhibitor	• TRIUMPH (C04-001) • SHEPHERD (C04-002)	• TRIUMPH: Significantly greater proportion of pts with stabilized Hb levels from BL to week 26 ($p<0.001$) and TA ($p<0.001$) vs placebo [9,12] • SHEPHERD: Significant reduction in LDH levels from BL to week 26 ($p<0.001$) [9,13]	• Adverse reactions reported in ≥10% pts: Headache* • Most serious AEs: Meningococcal sepsis*
Ravulizumab[10] C5 Inhibitor	• 301-study (CI-naïve pts) • 302-study (eculizumab pre-treated pts)	• 301 study: Non-inferior to eculizumab for TA* and LDH normalization from day 29–183 [10,14] • 302 study: Non-inferior to eculizumab for percentage change in LDH from BL to day 183 [10,15]	• Adverse reactions reported in ≥10% pts: Diarrhoea, nausea, nasopharyngitis, headache, upper respiratory tract infection, pyrexia, fatigue† • Most serious AEs: Meningococcal infection and meningococcal sepsis†
Pegcetacoplan[11] C3 Inhibitor	PEGASUS study (APL2-302)	Significantly greater change in Hb levels from BL to week 16 with pegcetacoplan vs eculizumab ($p<0.0001$) [11,16]	• Adverse reactions reported in ≥10% pts: Upper respiratory tract infection, diarrhoea, haemolysis, abdominal pain, headache, fatigue, pyrexia, cough, urinary tract infection, vaccination complication, dizziness, pain in extremity, arthralgia, back pain, nausea‡ • Most commonly serious AEs: Haemolysis and sepsis‡

Blue drug names represent terminal CIs and green represent proximal CIs.

*Data from the following studies: Asthma (C07-002), aHUS (C08-002, C08-003, C10-003, C10-004), Dermatomyositis (C99-006), gMG (C08-001, ECU-MG-301, ECU-MG-302), Neuromyelitis Optica Spectrum Disorder (ECU-NMO-301), IMG (C99-004, E99-004), PNH (C02-001, C04-001, C04-002, C06-002, C07-001, E02-001, E05-001, E07-001, M07-005, X03-001, X03-001A), Psoriasis (C99-007), RA (C01-004, C97-001, C99-001, E01-004, E99-001), STEC-HUS (C11-001) and SLE (C97-002). †Data from PNH and aHUS clinical trials and from post-marketing experience. ‡Data from clinical studies APL2-302, Study 202, Study 204 and Study CP0514 in PNH.

PNH therapy precautions and monitoring recommendations[9-11]

Vaccinations prior to treatment

Eculizumab[9] and ravulizumab[10]

- It is recommended that pts initiate immunizations according to current guidelines prior to treatment
- All pts must be vaccinated against *Neisseria meningitidis* ≥2 weeks prior to receiving treatment, unless the risk of delaying therapy outweighs the risk of developing a meningococcal infection
- Pts who initiate treatment <2 weeks after receiving a meningococcal vaccine must receive antibiotic treatment for 2 weeks after vaccination
- Pts <18 years old must be vaccinated against *Haemophilus influenzae* and pneumococcal infections

Pegcetacoplan[11]

- All pts must be vaccinated against *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae* according to local guidelines ≥2 weeks prior to receiving treatment, unless the risk of delaying therapy outweighs the risk of developing an infection
- If immediate therapy is indicated, the required vaccines should be administered as soon as possible and the patient treated with appropriate antibiotics until 2 weeks after vaccination

Signs of infection[9–11]

- Monitor for signs of infection and act immediately if infection is suspected
- Antibiotics should be administered if necessary

Monitoring for haemolysis[9–11]

- Eculizumab: Monitor 1 hour post infusion for signs of IVH, and adjust dose within the 14±2 day dosing schedule if needed. After treatment discontinuation, monitor for ≥8 weeks
- Ravulizumab: Monitor 1 hour post infusion for signs of IVH and for ≥16 weeks after treatment discontinuation
- Pegcetacoplan: Monitor regularly for signs of haemolysis and for ≥8 weeks after treatment discontinuation

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Emerging treatments for PNH in phase III development[17]

Drug	Administration	Phase III trial
ABP 959 Eculizumab biosimilar	 IV	**DAHLIA (completed):** Efficacy and safety vs eculizumab
BCD-148 Eculizumab biosimilar	 IV, BW*	**NCT04060264 (completed):** Efficacy, safety and immunogenicity
SB12 Eculizumab biosimilar	 IV, Q2W*	**NCT04058158 (completed):** Efficacy, safety, PK, and immunogenicity vs eculizumab
Crovalimab C5 inhibitor	 SC, Q4W	• **COMMODORE 1/ COMMODORE 2:** Efficacy and safety vs eculizumab in CI pre treated (COM1) and CI-naive pts (COM2) • **COMMODORE 3:** Efficacy, safety, PK and PD in CI-naive pts
Nomacopan C5 inhibitor	 SC, daily	• **CAPSTONE (completed)**: Efficacy and safety of nomacopan plus SOC • **CONSERVE (terminated)**: Long-term safety and efficacy
Pozelimab C5 inhibitor	 SC, QW	• **ACCESS-1:** Efficacy and safety of pozelimab plus cemdisiran vs ravulizumab in CI-naive pts† • **ACCESS-2:** Efficacy and safety of pozelimab plus cemdisiran vs continued eculizumab or ravulizumab‡ • **NCT04162470 (completed):** Long-term safety, efficacy and tolerability
Danicopan Factor D inhibitor	 PO, daily	• **ALPHA:** Efficacy as add-on treatment to a C5 inhibitor in pts with EVH • **NCT05389449:** Long-term safety and efficacy as add-on treatment to a C5 inhibitor
Iptacopan Factor B inhibitor	 PO, BID	• **APPOINT-PNH:** Efficacy and safety in CI-naive pts • **NCT04747613:** Long-term safety and tolerability • **APPLY-PNH:** Efficacy and safety in pts with residual anaemia despite anti-C5 treatment

Blue drug names represent terminal CIs and green represent proximal CIs.
*Maintenance therapy dosing regimen. †CI-naive pts or pts who have not received CI treatment within 6 months.
‡All pts were treated with eculizumab or ravulizumab prior to screening.

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Abbreviations and References

Abbreviations

AE, adverse event; aHUS, atypical haemolytic uremic syndrome; BID, twice daily; BL, baseline; BW, biweekly; C3bBb, C3 convertase; CD, cluster of differentiation; CI, complement inhibitor; COM1, COMMODORE 1; COM2, COMMODORE 2; EVH, extravascular haemolysis; FLAER, fluorescein-labelled proaerolysin; gMG, generalized myasthenia gravis; Hb, haemoglobin; IMG, idiopathic membranous glomerulonephritis; IV, intravenous; IVH, intravascular haemolysis; LDH, lactate dehydrogenase; MAC, membrane attack complex; PD, pharmacodynamics; PK, pharmacokinetics; PNH, paroxysmal nocturnal haemoglobinuria; PO, oral administration; pts, patients; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QW, weekly; RA, rheumatoid arthritis; RBC, red blood cell; SC, subcutaneous; SmPC, summary of product characteristics; SOC, standard of care; STEC-HUS, *Escherichia coli*-associated haemolytic uremic syndrome; TA, transfusion avoidance.

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