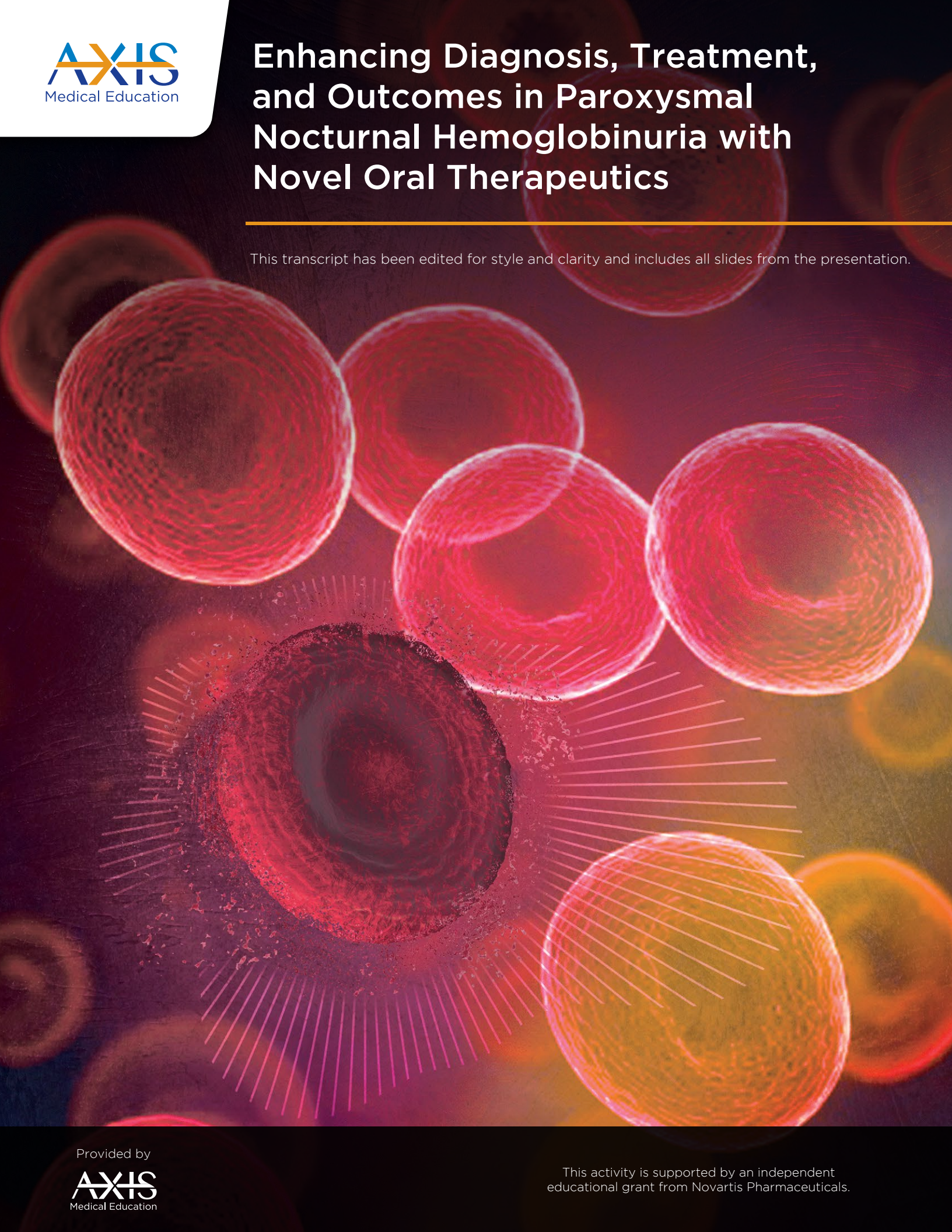


# Enhancing Diagnosis, Treatment, and Outcomes in Paroxysmal Nocturnal Hemoglobinuria with Novel Oral Therapeutics

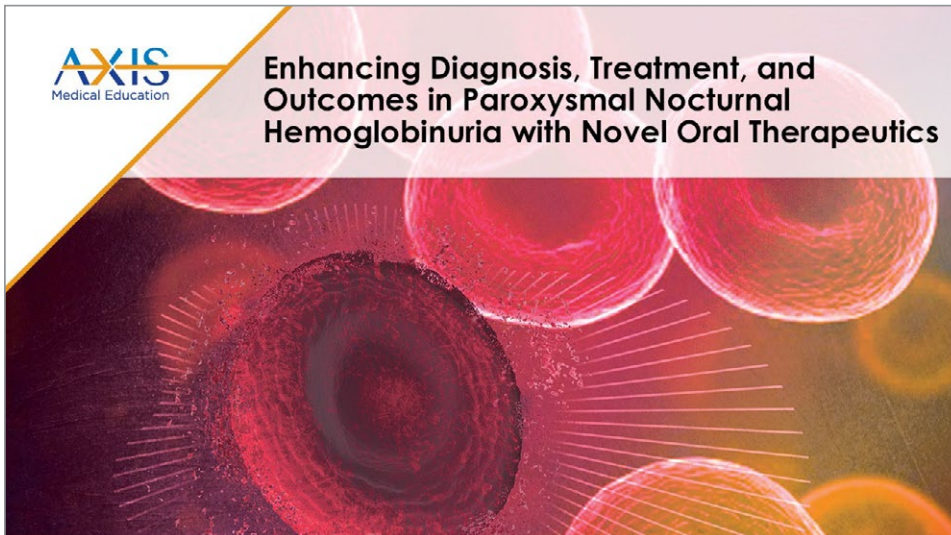
This transcript has been edited for style and clarity and includes all slides from the presentation.





# Enhancing Diagnosis, Treatment, and Outcomes in Paroxysmal Nocturnal Hemoglobinuria with Novel Oral Therapeutics

Carlos M. de Castro, MD



► **Carlos M. de Castro, MD:**  
Hello. I am Carlos de Castro. I'm a Professor of Medicine at Duke University Medical Center in the Division of Cellular Therapy and Malignant Hematology.

Today, we're going to be talking about PNH. PNH is just this fascinating disease, and now, with a bunch of new treatments that have arisen, it's a good time to be talking about this very rare disease.

## What is PNH?

- A rare (estimated incidence of 1-1.5 cases per million people) and unusual acquired hematologic disorder characterized by
  - Intravascular hemolysis
  - Bone marrow failure (cytopenias)
  - Thrombosis
- There is great clinical heterogeneity amongst patients with PNH
- A disease that has fascinated hematologists for a long time...

► It's estimated that about 1 to 1.5 cases per million people is the incidence rate. It's a very unusual disease. It is acquired; you're not born with this. And it's characterized by one of three different clinical pictures, either there's intravascular hemolysis, bone marrow failure with cytopenias, or thrombotic events, and it can be any or all three of these. There is incredible clinical heterogeneity amongst patients with PNH. Some are very asymptomatic. Others are just incredibly symptomatic. And it's fascinated hematologists for a long, long time.

AXIS  
Medical Education

Hill A, et al. *Nat Rev Dis Primers*. 2017;3:17028.

## What causes PNH?

A mutation in the PIG-A gene in hematopoietic stem cell

AND

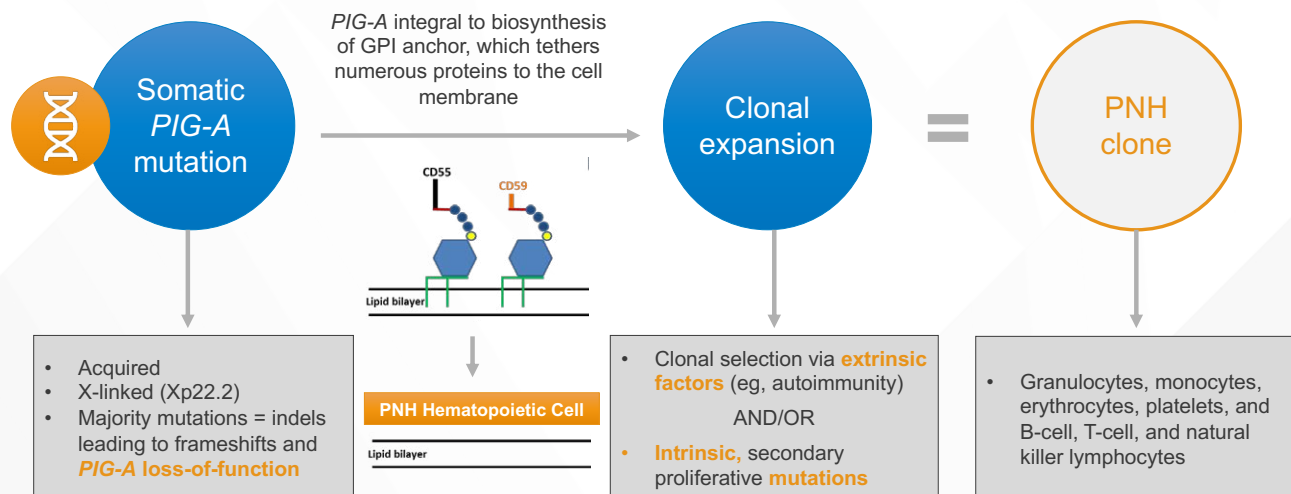
A condition that allows this mutant cell to become the dominant cell in the bone marrow (likely T-cell autoimmune attack)

► The reason PNH is so rare is that it takes two events to likely cause it. And they can occur in either order. The first event is there has to be a mutation in the what's called the PIG-A gene, which is the first step in making your GPI

anchor on hematopoietic stem cells and all their progeny. That is not an oncogenic mutation. Those cells have no growth advantage. So the second event has to be a condition that allows this mutant cell to become the dominant cell

in the bone marrow. And we feel this is likely a T cell autoimmune attack, based on evidence both from aplastic anemia, to which this disease is highly related, and also some other research evidence.

# PNH: A Rare, Acquired Hematopoietic Stem Cell Disorder



► Again, the mutation is in the PIG-A gene. It is acquired during normal hematopoiesis, when stem cells divide. The reason the PIG-A gene is involved almost 99% of the time or higher, is that it is on the X chromosome, so it only takes one single hit to knock that gene either out completely or severely down. Females have lyonized one of their X chromosomes. Males only have one X chromosome. In the other cases of all the other genes, and there's at least 20 other genes involved in making the GPI anchor, they're all on somatic chromosomes, so it would take

two hits to knock them out.

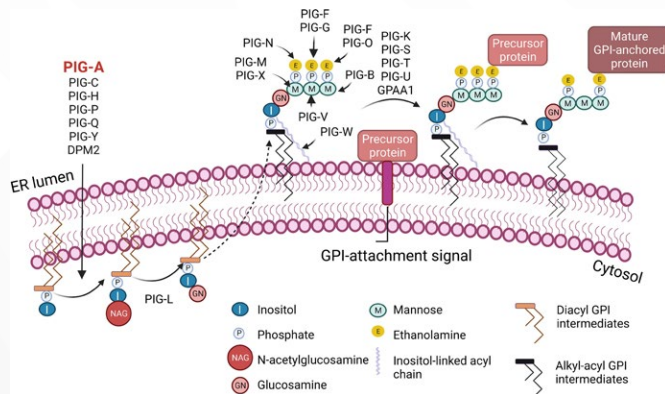
When you knock out that gene, you get a reduction in the GPI anchor and any proteins that are linked to the surface of the cells on that. There are a lot of different proteins, but the two that we know are the most important, at least in PNH, are CD55 and CD59 which protect the red cells from activated complement.

As I mentioned, something has to allow the cell to mutate it to become clonally expanded. It can be either extrinsic factors, such as immune factors, and/or intrinsic factors. Some

patients have secondary proliferative mutations, such as JAK2, that may drive clonal expansion.

And then you get what's called the PNH clone in the bone marrow. And this can involve all of your cells, granulocytes, monocytes, erythrocytes, B and T cells, natural killer lymphocytes, all of them can be involved. And we measure the clone size in the bone marrow by measuring peripheral blood, either granulocyte or monocyte clone size, using flow cytometry.

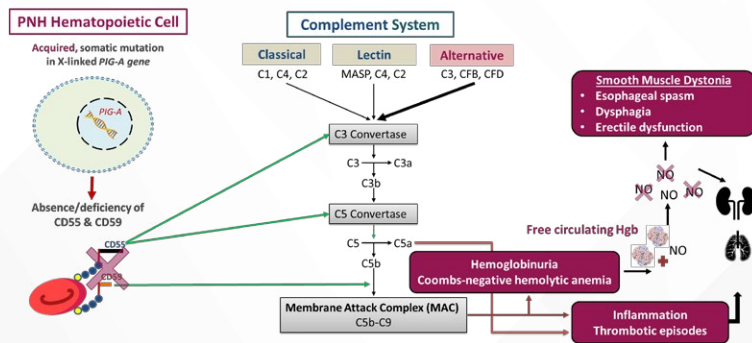
## Biosynthesis of the GPI Anchor



Golden M, et al. *Front Immunol.* 2022;12:830172.

► This is just a schematic showing you the overview or the synthesis of the GPI anchor.

## Complement Dysregulation as a Driver of PNH



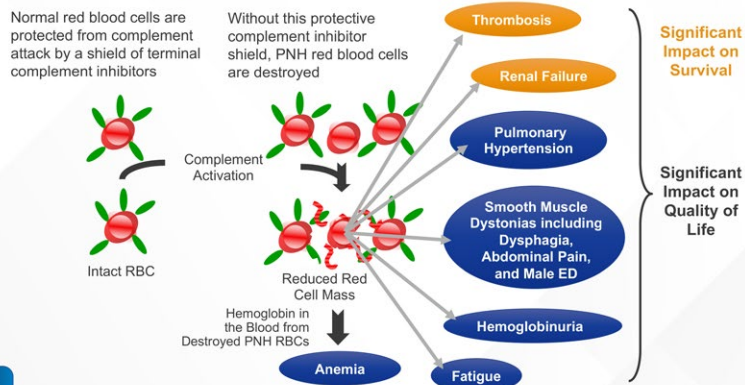
Waheed A, et al. *Blood Rev.* 2024;64:101158. Hill A, et al. *Blood.* 2013;121(25):4985-4996.

► So with the absence of CD55 and 59, whenever complement is activated, and realize it's always on to a low extent through a process called tick-over, the red cells can be lysed. And they will be lysed through the complement pathways, whether that's the alternative pathway or whether that's classical pathway. Most often it's the alternative pathway, unless they have an infection, that converges on the C3 convertase. C3 is cleaved, C3b

goes on to cleave C5 into its active forms. And this forms what's called the membrane attack complex, or MAC, with C5 through C9. That forms a pore in the cell, usually the red cells, which leads to the lysis of the red cells. If it's risk enough, you will get hemoglobinuria, spilling of hemoglobin into the urine, not hematuria. The hemolytic anemia is Coombs negative. It's important to stress that. You can have inflammation from C5a, and

likely the thrombotic episodes are related to that. The free hemoglobin that's released will cause smooth muscle dystonias, because it will squelch nitric oxide out of this blood system; that leads to esophageal spasms. Can have severe chest pain. You feel like you can't swallow. In males, they'll get erectile dysfunction. Abdominal pain and chest pain are very common, as is fatigue.

## Chronic Hemolysis is Central to the Morbidities and Mortality of PNH

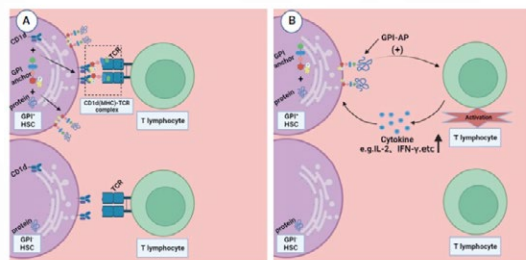


Waheed A, et al. *Blood Rev.* 2024;64:101158. Hill A, et al. *Blood.* 2013;121(25):4985-4996.

► So just in this cartoon, you see that normal red cells are protected from complement activation because of CD55 and CD59, whereas PNH red cells don't have that protection, and they will lyse whenever a complement is activated. That lysis will lead to anemia. And not only that, it will lead to hemoglobin which will squelch nitric oxide, leading to the smooth muscle dystonias we just mentioned, the hemoglobinuria, the fatigue. Long term, people can get pulmonary hypertension, renal failure, and we think that it, in part, plays a role in thrombotic events. All of these can have a significant impact on quality of life, and, more importantly, on survival.

## PNH: Bone Marrow Failure Due to T Cell Mediated Attack

Two possible ways that T lymphocytes are involved in the pathogenesis of immune escape. (A) CD1d presents GPI molecule as antigen to T lymphocytes and then activates them, these T lymphocytes kill the GPI<sup>+</sup>HSC; however, the GPI<sup>+</sup>HSC can escape from this attack. (B) GPI-AP mediates the activation of T lymphocytes and promotes the release of its cytokines (e.g., IL-2), then T lymphocytes kill HSCs expressing GPI-Aps; however, HSCs do not express GPI-Aps escape from this effect. Figures were created in BioRender.com



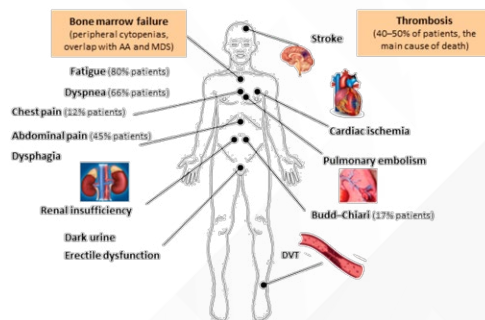
Li C, et al. *Front Immunol.* 2021;12:777649.

► I mentioned before that we think that there's a T cell-mediated attack as the second step that has to occur. That can occur before you even have a PNH mutation, that there is some attack on the bone marrow, mediated by the T lymphocytes, similar to what we see in aplastic anemia.



## The Clinical Picture of PNH

- Hemolysis due to complement activation
  - Anemia and fatigue
  - Hemoglobinuria, kidney damage
  - Nitric oxide trapping >> Esophageal spasm, abdominal pain, pulmonary hypertension, impotence, fatigue?
- Thrombosis – possibly due to complement activation
  - Unusual sites of blood clots
- Bone marrow failure
  - Decreased blood counts (cytopenias)



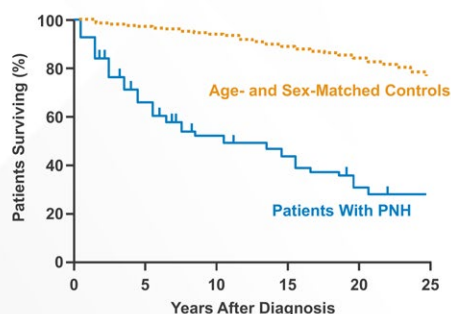
► So the clinical picture of PNH is as follows. You get hemolysis due to complement activation. From that, you get anemia and fatigue. You get hemoglobinuria. Acutely, you can have kidney damage if that hemoglobinuria is severe. Chronically, you can get kidney damage from the deposition of hemosiderin in the kidneys. The nitric oxide trapping or squelching leads to all sorts of symptoms. There can be thrombosis, usually in unusual sites, such as the liver, the spleen, the mesenteric vessels, or it can be typical DVTs or even arterial clots. And then you have the bone marrow failure with decreased blood counts or cytopenias, which is not too uncommon in PNH.

## PNH – Presenting Symptoms Can Be Heterogenous

Clinical Signs or Symptoms	Incidence (%)
Thrombosis	40
Anemia	89
Bone marrow failure	10-45
Fatigue, impaired QoL	96%
<b>Hemoglobinuria</b>	<b>26</b>
Abdominal pain	57
Dysphagia/Swallowing difficulty	41
Erectile dysfunction	47

► Shown here are just the clinical signs and symptoms that we see with PNH. They can be very heterogeneous. Fatigue is probably the most common symptom we see, and that's a very subjective symptom, as you all are aware. Hemoglobinuria, at least in this one registry study was only in 26% of patients who presented. Now this was out of Asia, where bone marrow failure is more common. So hemoglobinuria, we estimate to be at least in 40% of patients when they present.

## Significant Mortality in PNH Pre-Complement Inhibitor Therapy



- 5 year mortality: **35%**
- Diagnosed at all ages - median time from diagnosis to death: **10-15 yrs**

AXIS  
Medical Education

Hillmen P, et al. *N Engl J Med*. 1995;333:1253-1258.

► And you can see here, PNH was not a good disease to have prior to our current treatments, with average survivals that ranged from 13 to 17 years, depending on which study you looked at. And since the median age of diagnosis is in the 30s, it was never a great disease to have when you tell a 30-year-old you may live on average 15 more years. The problem is the only curative therapy was a bone marrow transplant, which itself carries a 20% mortality risk, and it's hard to want to transplant somebody who may be asymptomatic and doing well and may live 13 or 15 years. So we always had difficulty with recommending transplant for these patients, and we don't do that anymore, now that we have complement therapy, as I'll show you.

## Diagnosis of PNH

- PNH continues to be primarily a clinical diagnosis, which can be confirmed by laboratory analyses
- Signs and symptoms are highly variable and may mirror other conditions
- Most common symptoms at presentation are not unique to PNH
  - Hemolytic anemia, often requiring transfusions
  - Fatigue
  - Dyspnea
  - Abdominal pain or dysphagia

**<40% of patients receive diagnosis within 12 months, 24% of all PNH diagnoses take 5 years or longer<sup>1</sup>**

AXIS  
Medical Education

PNH, paroxysmal nocturnal hemoglobinuria.  
Dacie JV, Lewis SM. *Semin Haematol*. 1972;9(3):3-23.  
1. Bektaş M, et al. *J Manag Care Spec Pharm*. 2020;26(12-b Suppl):S8-S14.

► The diagnosis of PNH was always tricky. Because it's such a rare disease, most doctors have never heard of it, or if they had a course in med school, they may have mentioned it. They don't remember that at all because they've never seen a case. Less than 40% of patients actually receive a diagnosis within 12 months of symptoms, and up to 24% take 5 years or longer from the time symptoms are occurring. It is primarily a clinical diagnosis, which is confirmed by a blood test. You send off for what's called a PNH screen, as we'll talk about later.

The signs and symptoms are obviously highly variable and can mirror other conditions. Fatigue is incredibly common with so many things. Fatigue in PNH is not the first thing that comes to mind.



## Clinical Indicators of Hemolysis

- Elevated reticulocyte number
- Elevated LDH
- Reduced haptoglobin
- Elevated bilirubin
- Positive urine hemosiderin (intravascular hemolysis only)
- Positive urine/serum free hemoglobin (intravascular hemolysis only)

► Clinical indications of hemolysis include an elevated reticulocyte count, elevated LDH levels, reduced haptoglobin levels, elevated bilirubin levels. If a urine hemosiderin test is done, it's positive in intravascular hemolysis. We can also do a urine or serum free hemoglobin, and that's positive if it's intravascular also.



## Types of Hemolytic Anemia

- Intrinsic
  - Membrane/cytoskeletal abnormalities -- HS
  - Enzyme defects -- G6PD, PK
  - Hemoglobin defects -- thalassemia, sickle cell
  - **PNH**
- Extrinsic
  - Non-immune
    - Increased shear -- artificial valves
    - DIC, TTP, HUS/aHUS
  - Immune -- autoimmune hemolytic anemia (AIHA)
    - Cold antibody -- cold AIHA [cold agglutinin disease (CAD), cold agglutinin syndrome (CAS)]
    - Warm antibody -- **warm AIHA (wAIHA)**
  - Mixed

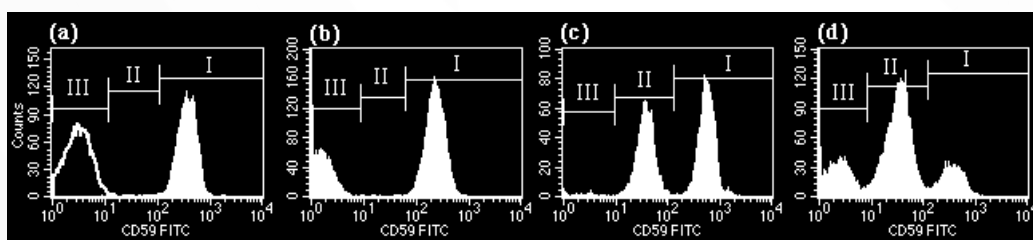
► Just to recall about the types of hemolytic anemia that occurs, there can be intrinsic defects to the red cells. This includes congenital diseases such as hereditary spherocytosis, where you have a membrane or cytoskeletal abnormality, enzyme defects such as G6PD deficiency or pyruvate kinase deficiency, hemoglobinopathy, such as thalassemia or sickle cell. And then the only one that is an acquired disease in this list is paroxysmal nocturnal hemoglobinuria, which we're talking about.

Extrinsic to the red cell, you can have both immune and non-immune causes. Non-immune causes include things such as DIC or TTP, artificial valves, especially when they're leaky, or immune causes, of which warm antibody immune hemolytic anemia is the most common form of hemolysis that we see, and those are patients who are Coombs positive or DAT positive.



## Flow Cytometry: Diagnostic Test for PNH

- Perform on peripheral blood
- Test both granulocytes and erythrocytes<sup>1</sup>
  - Erythrocytes alone are not sufficient due to hemolysis and the dilution effect of transfusions
- Use monoclonal antibodies against GPI-anchored proteins, such as CD59 or CD55<sup>1,2</sup>
- PNH blood cells (PNH clone) are cells missing GPI-anchored proteins



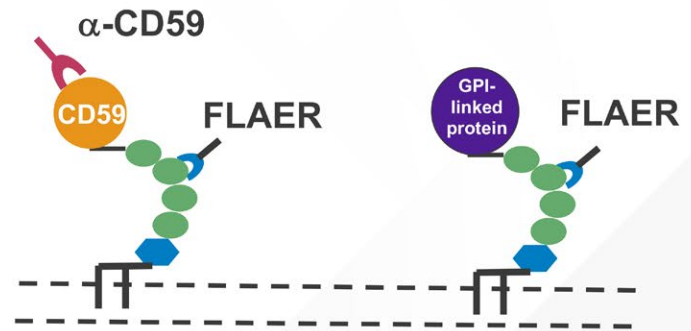
► The diagnostic test for PNH, as I mentioned, is a blood test. It should not be done on bone marrow because of nonspecific binding of antibodies. You test both white cells and red cells, in part because the red cells are lysing rapidly, you may not detect the disease. We use monoclonal antibodies against GPI-anchored proteins such as CD59 or CD55. And what we're looking for are cells

that are missing GPI-anchored proteins. And you see here in Panel A, that's a negative control antibody in that left-hand panel, where we see just this blank line. And here is a normal patient who has all of their red cells expressing CD59. Panel B shows a typical patient with PNH, where they have a population of cells that is completely missing CD59. And anything above 1% is

considered PNH by diagnosis, whereas they have a normal population of red cells that are expressing CD59. Panel C shows a patient who has partial deficiency, what we call type II cells, in CD59. And then Panel D is a patient with a biclonal population of cells, one that is completely lacking type III and one that is partially lacking type II.

## Fluorescent AERolysin (FLAER)

- FLAER binds to the GPI-anchor itself, rather than to a single protein such as CD55 or CD59
- FLAER provides much greater signal noise and better accuracy than an antibody against a single target



► The FLAER test is another assay that's done using the same sort of flow cytometry panel. They have taken the aerolysin protein from the *Aeromonas* bacteria and labeled it with a fluorescein

label, and it binds directly to the GPI anchor itself. So you're not looking for a specific antigen, you're going right for that GPI anchor. And because of that, you get a higher signal of the noise ratio and a higher

sensitivity and specificity. But it can only be done on the white cells. The red cells have non-specific binding to this protein, so you can't use it there.



## Significance of PNH Clone Size

- ~1/3 of patients with PNH clones have classical PNH with hemolysis and increased thrombotic risk
  - Larger clone size (usually >50% PNH WBCs)
  - Complement inhibitors improve outcomes in these patients
- The other two-thirds have subclinical PNH or PNH overlapping with AA/BMF
  - Patients typically with smaller clone sizes (<30%), no clinical hemolysis or symptoms
  - Unlikely to benefit from complement inhibitors, treatment directed at BMF
  - Some patients with moderate clone sizes, clinical hemolysis, and symptoms may benefit from complement inhibitors
  - Continued screening (~annually of PNH clone size); classical PNH can evolve from AA and progressive BMF requiring treatment for AA can occur in classical PNH
- PNH clones commonly occur in BM failure, typically smaller clones (<30%)
  - Presence of a PNH clone can distinguish an acquired aplastic anemia from inherited bone marrow failure
- Very small, polyclonal PNH populations can arise in normal individuals (2-4 per 100,000 cells)



Babushok DV. *Hematology Am Soc Hematol Educ Program*. 2021(1):143-152. DeZern AE, et al. *Eur J Haematol*. 2014;92(6):467-470. Shah YB, et al. *Blood Adv*. 2021;5(16):3216-3226.

► Now, let me just deal with clone size briefly. About 1/3 to 40% of patients have classical PNH with clone sizes that are usually larger, usually greater than 50%. And that results in a lot of hemolysis and increased thrombotic episodes. And these are the patients that we need to treat with complement inhibitors. The rest of the patients have either PNH which overlaps with a bone marrow failure syndrome with cytopenias; they will not benefit from complement inhibitors, because that's a T cell-mediated process, and

treatment should be directed using immunosuppressive therapy. These patients still can clot, and some of these patients may still have hemolysis, and if detected, they will benefit from complement inhibitors. They typically have smaller clone sizes, less than 30%, and there are some patients who have what's called subclinical PNH, where your clone size is less than 10%, and you really have no symptoms and no hemolysis, and they don't benefit from any treatment at all.

PNH clones do occur in bone marrow failure, such as MDS or aplastic anemia, usually with small clone sizes. They may evolve into true hemolytic PNH and the clone size may increase. Very, very small polyclonal PNH populations can be detected in normal individuals. Presumably, they've not had anything that allows these cells to become the dominant cell in the bone marrow, and in many cases, these spontaneously will regress and go away.

## Who Should Be Screened For PNH?

- Patients with “**CATCH**”
  - Unexplained **C**ytopenias
  - **A**plastic anemia (or a history of)
  - Unexplained **T**hrombosis
  - **C**oomb’s negative hemolytic anemia
  - **H**emoglobinuria



Parker C, et al. *Blood*. 2005;106:3699-3709. Borowitz MJ, et al. *Cytometry B Clin Cytom*. 2010;78:211-230. Canadian PNH Network. <https://www.pnhnetwork.ca/patient-screening>

- Who should be screened for PNH? Patients who have the acronym, CATCH, which comes from my Canadian colleagues, with unexplained Cytopenias; Aplastic anemia or a history of aplastic anemia, and these patients need to be screened yearly; unexplained Thrombosis, especially in a young person, and especially if it's in an unusual site; patient with Coombs-negative hemolytic anemia should be screened; and patients with Hemoglobinuria should be screened.

# PNH: Current and Emerging Therapies

- Complement inhibition –
  - FDA Approved
    - > Eculizumab
    - > Ravulizumab
    - > Crovalimab
    - > Pegcetacoplan
    - > Iptacopan
    - > Danicopan (+ C5 inhibitor)
- In clinical trials
  - Pozelimab + cemdisiran
  - OMS906
  - KP104
- Supportive care remains important
- Role of prophylactic anticoagulation very unclear
- Allogeneic HCT has a very limited role
- Treatment goals
  - Correct anemia<sup>1</sup>
  - Reduce fatigue<sup>2</sup>
  - Reduce risk of thrombosis, pulmonary hypertension, renal damage<sup>3,4</sup>



1. Martí-Carvajal AJ, et al. *Cochrane Database Syst Rev*. 2014;CD010340.
2. Cançado RD, et al. *Hematol Transfus Cell Ther*. 2020;S2531-137930079-1.
3. Hill A, et al. *Br J Haematol*. 2012;158:409-414.
4. Griffin M, et al. *Ther Adv Hematol*. 2017;8:119-126.

► We're going to move now to treatment, which is the most active area, as we now have six drugs that are FDA approved for complement inhibition in PNH, and they're listed there. There are more in clinical trials, which is hard to believe that we still need more drugs, but there is room for improvement in treating PNH. Supportive care is always important in these patients. If they need a blood transfusion, you give them a blood transfusion. If they need iron,

you give them iron, etc.

The role for prophylactic anticoagulation in PNH is very unclear. What we learned before complement inhibition is that anticoagulants really didn't work well in preventing clots, once you'd had a clot, so putting them on prophylaxis may just increase their bleeding risk without giving them any benefit.

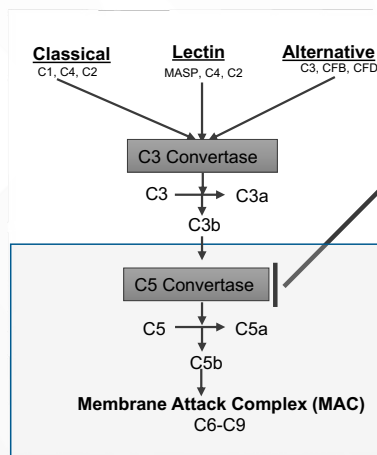
Allogeneic stem cell, which is the only curative therapy for this disease, now has a very limited role, in part

because the survivals have improved so dramatically with complement inhibition. Really allogeneic transplant is only used for patients with severe bone marrow failure that doesn't respond to immunosuppressive therapy.

The treatment goals now are to correct anemia, reduce fatigue and other symptoms, certainly reduce the risk of thrombosis and of all the long term complications of PNH.



# First-Line C5 Complement Inhibitors for PNH



Terminal complement inhibitors target complement protein C5 preventing its cleavage, formation of the MAC, and MAC-mediated intravascular hemolysis

They also suppress C5a, which reduces inflammation and thrombosis

	Approval Year	Target	Administration	Half-life	Indication
Eculizumab	2007	C5	Intravenous/2 weeks	~12 days	Adults with PNH
Ravulizumab	2018, 2021 (adults, pediatric)	C5	Intravenous/4-8 weeks	~49 days	Adult and pediatric PNH patients
Crovalimab	2024	C5	SubQ / 4weeks	~53 days	Adult and pediatric (≥ 13 years) PNH patients



CF, complement factor, MASP, mannan-binding lectin-associated serine protease.  
 Parker CJ. *Hematology Am Soc Hematol Educ Program*. 2016(1):208-216. Bektas M, et al. *J Manag Care Spec Pharm*. 2020;26(12-b Suppl):S3-S8.  
 Waheed A, et al. *Blood Rev*. 2024;64:101158. Röth A, et al. *Blood*. 2020;135(12):912-920.

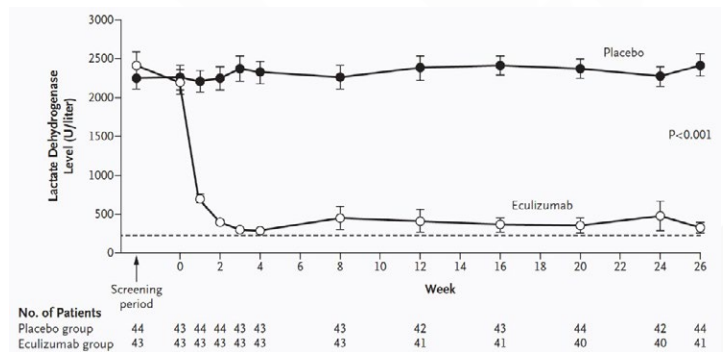
► We can divide our complement inhibitors now into two groups. The first group is the distal or C5 inhibitors, which were started back in 2007 is when eculizumab was approved. It targets C5; it's a monoclonal antibody that's been humanized. It was given initially as a

weekly loading dose for 4 weeks and then moved on to intravenously every 2 weeks. It was approved in 2007 for adults with PNH and made a dramatic, dramatic improvement in these patients, as I'll show you in the next slide. The other two drugs, ravulizumab, is a modified form of eculizumab

with a longer half-life. It was approved in 2018. And then this last year, crovalimab, which binds to a separate epitope or a different epitope, was FDA approved, and it's given subcutaneously every 4 weeks.

# Eculizumab: Summary of Clinical Efficacy

- Significantly reduced **hemolysis**, the underlying cause of morbidity and mortality in PNH
  - 86% reduction in hemolysis**<sup>1</sup>
  - 92% reduction in thrombotic events<sup>2</sup>
  - 73% reduction in need for transfusions<sup>1</sup>
  - Significant reduction in fatigue and improvement in QoL measures<sup>3</sup>
  - AEs similar to placebo
- Does not treat PNH-associated bone marrow failure
- May not completely restore Hgb



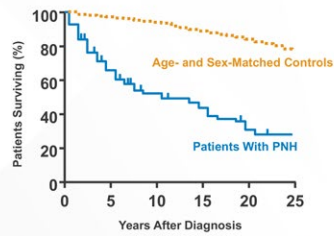
**Degree of Intravascular Hemolysis as Measured by Mean LDH Levels, Baseline to Week 26 (Phase 3 Trial)<sup>1</sup>**

► It, in many studies that were done, significantly reduced hemolysis within 2 weeks of giving the drug. LDH levels fell dramatically, as shown in this diagram, to near, but not quite normal levels, and we'll come back to talk about that. So there was an 86%

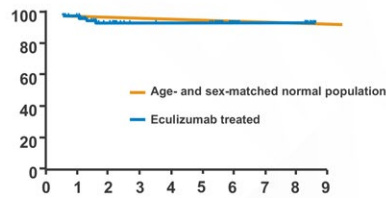
reduction in hemolysis, as measured by LDH levels, a 92% reduction in thrombotic events, which is very dramatic, not 100% but very close to it, a 73% reduction in need for transfusions, marked improvements in fatigue and quality of life measures, and

the adverse events were very similar to placebos. This drug does not treat PNH-associated bone marrow failure and usually does not completely restore hemoglobin levels, as we'll show you.

## Eculizumab Has a Major Impact on Survival in PNH



Survival comparable to age and gender-matched control population out to 8 years



- 96% (76/79) patient survival
  - No difference in mortality in patients on eculizumab vs healthy population ( $P = .46$ )

► One thing we learned with the dramatic drop in thrombotic events, which used to be the number one cause of death in PNH patients, was the marked impact in survival in these patients to near normal levels, as shown in this study by Richard Kelly that was published in *Blood* in 2011. And several other subsequent studies have shown this same effect on survival.

## Eculizumab Warning

- Eculizumab increases the risk of meningococcal infections
  - Vaccinate patients with a meningococcal vaccine at least 2 weeks prior to receiving the first dose of SOLIRIS®
  - Revaccinate according to current medical guidelines for vaccine use
  - Monitor patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary

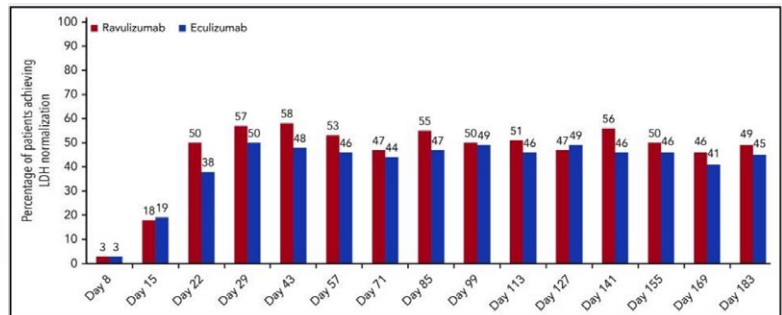
**WARNING: SERIOUS MENINGOCOCCAL INFECTION**

► All these drugs, because they inhibit complement C5, carry a black box warning that you need to vaccinate these patients against meningococcus, and we'll come back to vaccinations later on. The black box warning says you should vaccinate at least 2 weeks prior to receiving the first dose of eculizumab. You revaccinate according to current medical guidelines for vaccine use, which at least is every 5 years. And you'd educate these patients and give them a card to carry for warnings about meningococcal infections. So if they present to their ER, they can give it the doctor who may have never heard of PNH or this treatment, and can quickly start therapy with antibiotics.



## Terminal Complement Inhibitors - Ravulizumab

- Modifications to the eculizumab monoclonal antibody led to ravulizumab which had a longer half life.
- Two studies (301 – complement inhibitor treatment naïve, and 302 – prior eculizumab treatment) compared ravulizumab to eculizumab. Both studies showed that ravulizumab was non-inferior to eculizumab across all end-points.
- Ravulizumab provided immediate, complete, and sustained C5 inhibition over the 8 weeks period.
- Still need to vaccination against Meningococcus.



**Proportion of patients achieving LDH-N over time in the ravulizumab and eculizumab treatment groups**


► So modifications to the eculizumab monoclonal antibody led to ravulizumab, which has a longer half-life with more sustained high levels of C5 inhibition. There were two studies that were done on this drug, one in complement inhibitor-naïve patients, and the other in patients who were on eculizumab. And that one

compared to ravulizumab to eculizumab. Both of these studies were noninferiority studies, and both showed that ravulizumab was noninferior to eculizumab across all the endpoints that were studied. We can't claim it's superior, but we do know that it's certainly much more convenient to give this drug every 8 weeks

than every 2 weeks. And because it provides a higher level of C5 inhibition over that period, you probably get less breakthrough hemolysis events. You still need to vaccinate against meningococcus with this antibody, and that's true for all the complement inhibitors.

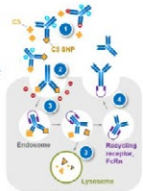
## Emerging Complement Inhibitors: Terminal inhibitors - Crovalimab

- Novel anti-C5 monoclonal antibody engineered using Sequential Monoclonal Antibody Recycling Technology (SMART-Ig).
- It is recycled within the circulation, enabling sustained complement inhibition through low-dose, subcutaneous administration every four weeks.

 Crovalimab is a novel **anti-C5 recycling monoclonal antibody**<sup>1,2</sup> with a long-half life, high solubility, and high bioavailability, which allows for **low-volume, Q4W SC injection**

**Mechanism of action**<sup>3</sup>

- 1 High-affinity binding
- 2 Preferential antibody uptake (proprietary innovative engineering)
- 3 Acid-sensitive binding and antigen degradation
- 4 Antibody recycling by FcRn engineering



Adapted from Igawa T, Biochim Biophys Acta 2014.

**Phase III COMMODORE studies in PNH**

**COMMODORE 2** (NCT04434092)<sup>4</sup>


- Global **C5-naïve** patients (N=204)
- **Randomized** 2:1 to receive crovalimab or eculizumab
- Pediatric patients were enrolled in a descriptive arm to receive crovalimab

**COMMODORE 3** (NCT04654468)<sup>5,6</sup>

- Chinese **C5-naïve** patients (N=51)
- **Single arm**

**COMMODORE 1** (NCT04432584)<sup>7</sup>

- Global **C5-experienced** patients (N=89)
- **Randomized** 1:1 to receive crovalimab or eculizumab
- Select patients<sup>8</sup> were enrolled in a descriptive arm to receive crovalimab

 Here, we report **pooled safety data** for crovalimab and eculizumab from the 3 open-label, multicenter, **Phase III COMMODORE studies**

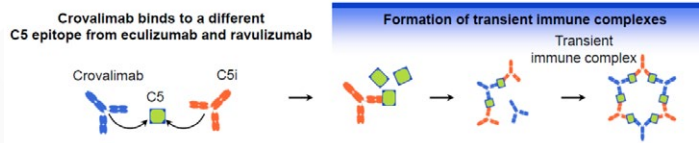
► Finally, crovalimab is out there. It is a novel anti-C5 monoclonal antibody that was engineered using what was called smart technology so it bypasses the liver and has a long half-life, and you can use small volumes. Because of that, you can give

it subcutaneously in smaller volumes. And the hope was that you could actually take this home and administer at home for patients. Three studies led to its FDA approval last year, COMMODORE 1, COMMODORE 2, and COMMODORE 3, which you

can see were either in C5 treated or in C5 inhibitor-naïve patients. This drug also was done in patients up to above the age of 13, or it is FDA approved for above the age of 13, so some pediatric patients.

## Transient Immune Complex Reactions Resolved in Around Two Weeks

- In patients switching from other C5is to crovalimab, or from crovalimab to other C5is, transient immune complexes form between crovalimab, C5, and the other C5i. These complexes may lead to a one-time transient immune complex reaction in a fraction of switch patients<sup>1</sup>
- Across COMMODORE 1 and 2, transient immune complex reactions occurred in 33 of 185 patients (18%)



- The median time to onset of the transient immune complex reaction was 1.6 weeks (range, 0.7–4.4) and the median duration of the resolved transient immune complex reactions was 1.9 weeks (0.4–34.1)<sup>2,3</sup>; some clinical symptoms were ongoing at clinical cutoff

► One thing we learned when giving this there was an overlap when you had the C5 inhibitor still in your system and crovalimab. And because they bind to different epitopes, you could get these immune complexes that formed, which were very worrisome. Clinically, however, they just led to rash, which was limited to a few weeks, and outside of a little bit of itching, really did not cause any clinical problems, including no renal failure or other problems like that.

## Limits of C5 Targeting Therapy

- Despite benefits of targeting C5, responses to eculizumab and ravulizumab are heterogeneous[a]
  - Most patients exhibit continuous low-level hemolysis
  - 25-35% still require RBC transfusions
- Eculizumab prevents intravascular hemolysis, unmasks low-level extravascular hemolysis[b]
  - Occurs through opsonization of PNH red cells by C3 fragments, leading to extravascular cell clearance
  - This effect may contribute to low-level hemolysis and RBC transfusion requirements

► Now, despite all of these C5 inhibitors being very, very good drugs, and its survival improving markedly, and symptoms improving, patients were still having suboptimal responses. Most patients continue to show a low level of hemolysis, 25 to 35% still required red cell transfusions. And what we learned is that eculizumab, though it blocks C5 and prevents its cleavage, C3 was still being cleaved and activated, and C3 fragments were coating these PNH red cells because they had no way of removing them, because of the lack of the GPI active proteins. And that would eventually lead to uptake in the spleen and liver and the reticuloendothelial cells, and extravascular hemolysis to various levels in patients.



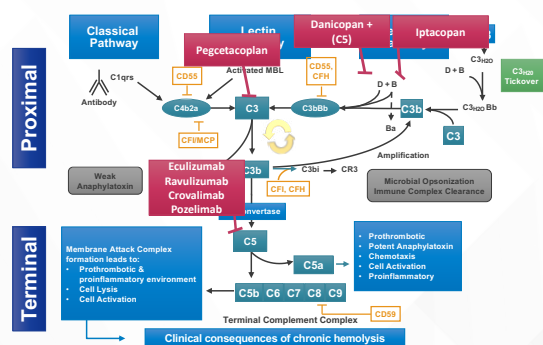
## PNH – Treatment with Eculizumab Suboptimal Responders

- About 5-20% of PNH patients show a sub-optimal response (continued hemolysis and/ or transfusion need) to eculizumab.
- Potential etiologies
  - Poor production (bone marrow failure)
  - Dosing
  - C5 Polymorphism (Asian population)
  - C3 coating of red cells

► Some of these patients, it could be severe enough. And we estimated that 5 to 20% of patients on C5 inhibitors had a suboptimal response due to most often C3 coding of the red cells.

AXIS  
Medical Education

## Complement Activation: Current and Emerging Targets



► This led then to studies of the proximal pathway of C3 factor D and factor B inhibition, as shown in this slide.

AXIS  
Medical Education

Figueras JE, Densen P. Clin Microbiol Rev. 1991;4:359-395.  
Zipfel PF, et al. Front Immunol. 2019;10:2166.  
Ricklin D, et al. Nat Rev Nephrol. 2018;14:26-47.

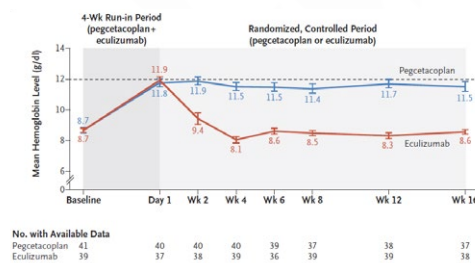
## Proximal Complement Inhibitors

Agent	FDA Approval	MOA	Administration	Indication	REMS Program
Pegcetacoplan	May 2021	Pegylated pentadecapeptide that targets C3	Subcutaneous/ 2x weekly  **on-body injector approved in October 2023	Adult patients with PNH	Yes
Danicopan	May 2024	Factor D inhibitor	Oral three times a day  With a C5 inhibitor	Adult patients with PNH	Yes
Iptacopan	December 2023	Factor B inhibitor	Oral given BID with or without food	Adult patients with PNH	Yes

► And we now have three FDA approved drugs that target those three factors. Pegcetacoplan was the first, which was FDA approved in May of 2021. It is given subcutaneously twice a week, for all adult patients with PNH. Danicopan is a factor D inhibitor that's given orally three times a day, and it has to be given with a C5 inhibitor, so you are not getting rid of your IV therapy with this. Iptacopan is an oral factor B inhibitor that is used as a monotherapy, and it's given twice a day.

## PEGASUS Trial

- PEGASUS is a phase 3, randomized, multicenter trial comparing Pegcetacoplan to Eculizumab in PNH patients on eculizumab with an Hgb <10.5
- Primary endpoint was the change in Hgb at week 16.
- Pegcetacoplan was superior to eculizumab in improving Hgb levels and other clinical outcomes.
- Adverse events include injection site reactions, diarrhea (mild), and breakthrough hemolysis



► So let's talk first about pegcetacoplan. The PEGASUS was the phase 3 registry trial comparing pegcetacoplan to eculizumab in patients who were on eculizumab with a hemoglobin less than 10.5, a suboptimal responder, in a sense. During the first 4 weeks, all patients received both drugs together. So you see that rise in hemoglobin from 8.7 to 11.8-11.9 range. And then they were randomized to receiving either eculizumab alone or pegcetacoplan alone. And the primary endpoint of this was a change in the hemoglobin at week 16. And what you see here is that patients on eculizumab therapy fell right back to their baseline hemoglobin, whereas those in pegcetacoplan maintain this effect of staying in the close to normal range around 12.

## PEGASUS: Safety Outcomes

- Breakthrough hemolysis reported in 13 patients (9 eculizumab, 4 pegcetacoplan)
- 3 patients in pegcetacoplan group discontinued due to TEAE of hemolysis
  - Included 1 SAE
- Injection site reactions: mostly mild
  - None led to change in dose or study discontinuation
- Diarrhea mostly mild (1 moderate)
  - No dose changes due to diarrhea

**Table 2. Adverse Events That Occurred during the 14-Week Randomized, Controlled Period.**

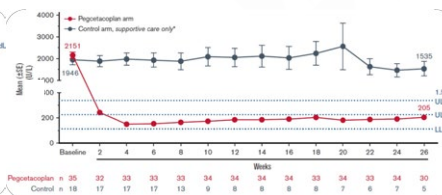
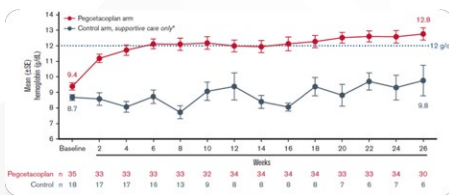
Event	Pegcetacoplan (N=41)	Ecuzumab (N=39)
Any adverse event occurring during treatment	36 (88)	34 (87)
Adverse event in ≥5% of patients in either group		
Injection-site erythema	7 (17)	0
Injection-site reaction	5 (12)	0
Injection-site swelling	4 (10)	0
Asthenia	3 (7)	3 (8)
Injection-site induration	3 (7)	0
Vaginitis	2 (5)	4 (10)
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	3 (7)	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	1 (2)	1 (3)
Dyspnea	1 (2)	2 (5)
Oropharyngeal pain	0	2 (5)
Hypokalemia	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 ≥2 patients in the pegcetacoplan group		
Hemolysis	2 (5)	1 (3)

\*Patients were required to receive vaccinations against *Neisseria meningitidis* types A, C, W, Y, and B, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B within 2 years before receiving the first dose of pegcetacoplan or within 14 days after the first dose. Hillmen P, et al. *N Engl J Med*. 2021;384(11):1028-1037.

There were a few adverse events, including injection site reaction, since it's a sub-q drug, diarrhea which was mild and self-limited, and some episodes of breakthrough hemolysis, although the number of breakthrough hemolysis events were actually higher in the eculizumab arm than in the pegcetacoplan arm. Again, safety outcomes are shown here. The breakthrough hemolysis occurred in 13 patients, 9 who were on the eculizumab arm, 4 on the pegcetacoplan arm, 3 patients had to discontinue it because we didn't know what to do if they had hemolytic anemia. We put them back on the C5 inhibitor. We now have a study out there showing that if you give an extra dose of pegcetacoplan, you can abrogate that breakthrough hemolysis.

## PRINCE Trial: Pegcetacoplan Controls Hemolysis in Complement Inhibitor-Naïve Patients With Paroxysmal Nocturnal Hemoglobinuria

Coprimary end points	Pegcetacoplan arm (n = 35)	Control arm supportive care only* (n = 18)	Difference 95% CI	P value
Hemoglobin stabilization, n (%)†	30 (86.7)	6 (33)	79.1 (52.2, 106.0)	<.0001
CFB in LDH levels, LS mean (SE), U/L‡	-1870.5 (101.0)	-400.1 (313.0)	-1470.4 (-2113.4, -927.3)	<.0001



PRINCE was a study done with the same drug in naive patients, complement inhibitor-naïve patients. And you show here again that rise in hemoglobin to above 12 with a low LDH. And these patients' reticulocyte counts fell. Everything looked very good for this drug. So it's now FDA approved and given primarily to patients with extravascular hemolysis or suboptimal response to C5 inhibitors, but it can be used up front in some patients.

Wong RSM, et al. *Blood Advances*. 2023;7:2468-2478.

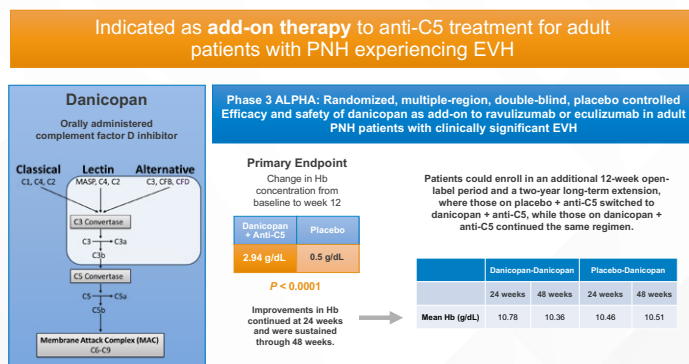
## Proximal Complement Inhibitors: Danicopan

	FDA Approval	MOA	Administration	Indication	REMS Program
Danicopan	May 2024	Factor D inhibitor	Oral three times a day With a C5 inhibitor	Adult patients with PNH	Yes

- ▶ Danicopan is the oral factor D inhibitor that was FDA approved in May of last year, given orally three times a day with a C5 inhibitor. They did not want to try it without that. In part, they were worried about breakthrough hemolysis on just a single agent.

AXIS  
Medical Education

## Proximal Complement Inhibitors – Danicopan

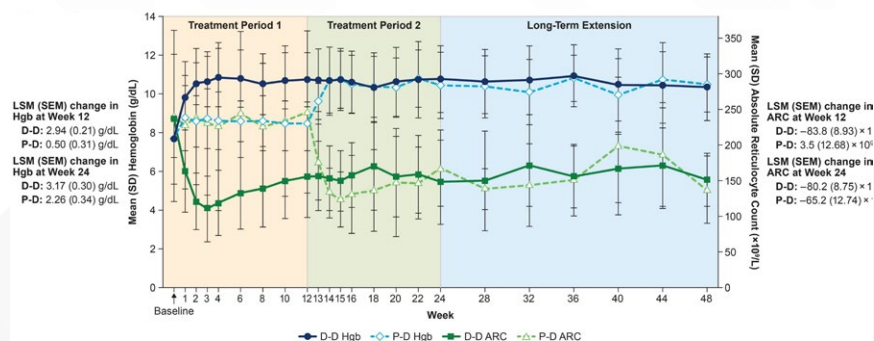


- ▶ And you see here again, the primary endpoints were co-endpoints of either a hemoglobin rise of greater than 2 g/dL, or a hemoglobin rise to above 12. And you see that that did occur in the majority of patients treated with danicopan plus a C5 inhibitor as compared to placebo.

AXIS  
Medical Education

EVH, extravascular hemolysis, Hb, hemoglobin.  
Lee JW, et al. *Lancet Haematol*. 2023;10(12):e955-e965. Kulasekararaj A, et al. *ASH* 2023. Abstract 576.

## Change in Hemoglobin and Absolute Reticulocyte Count During 48 Weeks of Treatment



► Again, dramatically, on this graph, where you see patients treated with danicopan plus the C5 inhibitor versus those just on the C5 inhibitor alone in the green line, that patients' hemoglobin levels rose to above 10 when they were below 8 in the baseline for these patients, and this was sustained out greater than 48 weeks. So it provides another option for treating patients.

## Proximal Complement Inhibitors: Iptacopan

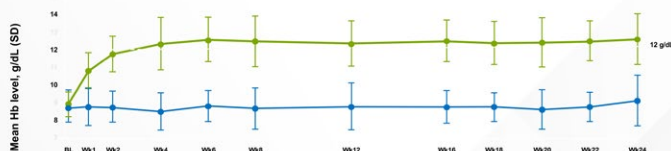
	FDA Approval	MOA	Administration	Indication	REMS Program
Iptacopan	December 2023	Factor B inhibitor	Oral given BID with or without food	Adult patients with PNH	Yes

► And finally, we have iptacopan, which is a factor B inhibitor, oral monotherapy given twice a day to adult patients with PNH.



## Iptacopan: APPLY-PNH Clinical Trial

- APPLY-PNH is an open-label, randomized, multicenter, Phase III trial investigating iptacopan monotherapy in PNH patients with residual anemia despite SoC therapy.
- Two primary endpoints - Hematological response defined as an increase from baseline in Hb of  $\geq 2$  g/dL in the absence of RBC transfusions and hematological response defined as Hb  $\geq 12$  g/dL in the absence of RBC transfusions.
- Oral iptacopan monotherapy led to a significant majority of patients achieving clinically meaningful Hb increases and Hb  $\geq 12$  g/dL, associated with a higher rate of transfusion independence and reduced patient-reported fatigue, compared with SoC



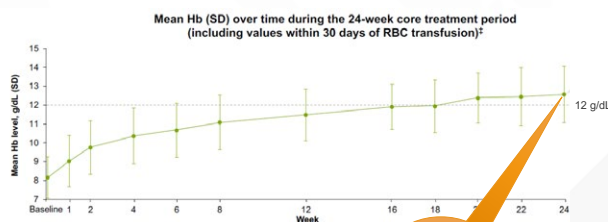
AXIS  
Medical Education

de Latour RP, et al. *N Engl J Med*. 2024;390:994-1008.

► APPLY and APPOINT were the two studies that were done, phase 3 studies. APPLY is in C5 inhibitor-treated patients. APPOINT is in treatment-naïve patients. Again, co-endpoints of a rise of greater than 2 or hemoglobin level greater than 12. And these were both met in the significant majority of patients compared to those that stayed on the C5 inhibitor alone. There was marked improvements in transfusion and independence, fatigue compared to standard of care.

## Iptacopan: APPOINT-PNH Clinical Trial

- APPOINT-PNH is a Phase 3, multinational, multicenter, open-label, single-arm study of iptacopan in treatment-naïve PNH patients.
- 92.2% achieved a 2.0 g/dL increase in Hgb levels from baseline without transfusion at week 24
- 62.8% achieved a Hgb level of  $> 12.0$  g/dL
- 97.6% achieved transfusion independence by week 24
- All secondary endpoints all met
- No episodes of BTH



Mean Hb level  
at 24 weeks:  
**12.56 g/dL**  
(SD 1.49)

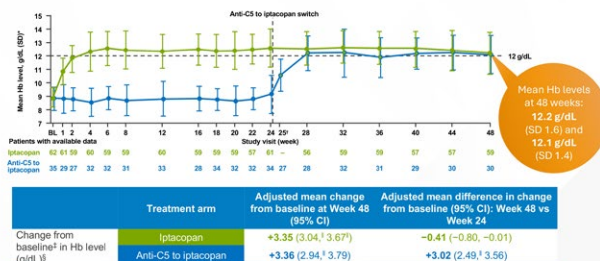
► And this is just the APPOINT study showing the same thing, hemoglobin levels rising to near normal levels.

AXIS  
Medical Education

Risitano AM, et al. *EBMT* 2023. Abstract OS12-06.

## Proximal Complement Inhibitors – Iptacopan 48-Week Data

Increases in Hb and a mean normal/near-normal Hb level were maintained in the iptacopan arm and rapidly achieved in the anti-C5-to-iptacopan arm upon treatment switch

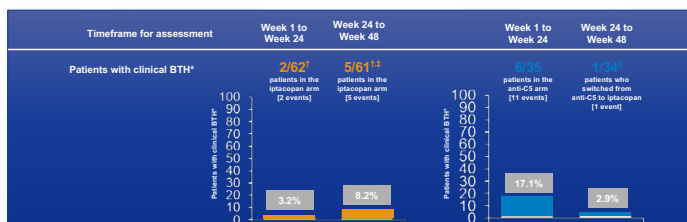


► We have data out for the same drug for over 48 weeks, showing, again, a sustained response to the iptacopan given orally, it doesn't go away. And the side effects, again, have been very good with this drug. Everything looking good.

**AXIS**  
Medical Education

<sup>†</sup>Events that met the prespecified criteria in the protocol for clinical BTH. All hemolytic events were also reported as TEAEs, irrespective of whether they met the criteria for clinical BTH. <sup>‡</sup>One of the patients in the iptacopan arm had an event of clinical BTH in the randomized treatment period and a second event of clinical BTH in the extension period. Therefore, overall, six of 62 patients in the iptacopan arm had clinical BTH. <sup>§</sup>Of 62 patients in the iptacopan arm, 61 entered the extension period. <sup>||</sup>Of 35 patients who were randomized to the anti-C5 arm, 34 switched to iptacopan monotherapy in the extension period. The patient who had clinical BTH after switching to iptacopan did not have clinical BTH during anti-C5 treatment in the randomized treatment period.

## Proximal Complement Inhibitors – Iptacopan 48-Week Data Breakthrough Hemolysis (BTH)



- The **overall adjusted annualized rate of clinical BTH\*** since initiation of iptacopan monotherapy, including iptacopan-treated patients in both treatment arms, was **0.11** (95% CI 0.05, 0.23)
- All clinical BTH events\* reported during iptacopan monotherapy in APPLY-PNH were **mild or moderate** in severity and **resolved without iptacopan discontinuation**; one patient received a single dose of eculizumab per the decision of their investigator<sup>1</sup>

► The one thing I will say about iptacopan, and we'll have to wait with more time to see if this true, but the number of breakthrough hemolysis events, that is, you get a complement-activated event, like an infection, and you can get breakthrough hemolysis with all these drugs, but it seemed to be lower with iptacopan. There is no head-to-head study to compare these, but historically, the number of breakthrough events with iptacopan seemed to be a little bit lower.

**AXIS**  
Medical Education

<sup>†</sup>Events that met the prespecified criteria in the protocol for clinical BTH. All hemolytic events were also reported as TEAEs, irrespective of whether they met the criteria for clinical BTH. <sup>‡</sup>One of the patients in the iptacopan arm had an event of clinical BTH in the randomized treatment period and a second event of clinical BTH in the extension period. Therefore, overall, six of 62 patients in the iptacopan arm had clinical BTH. <sup>§</sup>Of 62 patients in the iptacopan arm, 61 entered the extension period. <sup>||</sup>Of 35 patients who were randomized to the anti-C5 arm, 34 switched to iptacopan monotherapy in the extension period. The patient who had clinical BTH after switching to iptacopan did not have clinical BTH during anti-C5 treatment in the randomized treatment period.

1. de Latour RP, et al. Blood. 2023;142(suppl1):1338.

# Adverse Events and Management

- Lipids<sup>1</sup>
  - Patients on proximal inhibitors should have lipid monitoring at least every 6 months
- Vaccinations<sup>2</sup>
  - All patients receiving complement inhibitors should receive Meningitis vaccines (both ACWY and B)
  - Proximal inhibitor patients should receive pneumococcal vaccine, consider HiB vaccine
  - Timing of vaccination (vaccines can activate complement)
- Infections<sup>2</sup>
  - All infections should receive immediate antibiotics
  - Stopping complement inhibitor not recommended (despite FDA label)
- Extravascular hemolysis<sup>3,4</sup>
  - Only seen in patients on C5 inhibitors
  - Labs show elevated reticulocyte count, mildly elevated LDH, variable elevation in bilirubin, and may show weak DAT +
  - If anemic or symptomatic, consider switching to a proximal inhibitor



1. de Latour RP, et al. *N Engl J Med*. 2024;390:994-1008. 2. Hill A, et al. *Nat Rev Dis Primers*. 2017;3:17028. 3. Risitano AM, et al. *Blood*. 2009;113(17):4094-4100. 4. McKinley CE, et al. *Blood*. 2017;130:3471.

▶ With all these patients, we have to watch out for hyperlipidemia. It's not clear why they can get that. It's mild, and in most patients, it was managed easily with either diet modifications and/or with increasing their dose of statins. All patients have to be vaccinated against meningitis, as mentioned. In addition, if you're on a proximal inhibitor, you should receive the pneumococcal vaccine and possibly the Hemophilus influenza vaccine.

Vaccines can activate complements, so we have to be careful with that if you're not on a C5 inhibitor or a proximal inhibitor. And it's been recommended in some cases that we actually give prophylactic antibiotics, start the treatment with the complement inhibitor, and then vaccinate right away, so we can avoid that hemolysis. Infection should all receive immediate antibiotics. Stopping complement inhibitors is not recommended,

even if you have an infection. The FDA label, for example, says, hey, if you get a serious infection, consider stopping it. But the reality is, if you do that, you're going to see a lot more hemolysis. And extravascular hemolysis is a complication that we just talked about, and in those cases, we should probably switch to a proximal inhibitor.

## Adverse Events and Management

- Breakthrough hemolysis<sup>1</sup>
  - Usually related to a Complement Activating Event such as an infection (viral or bacterial)
  - Except for pegcetacoplan<sup>2</sup>, there is no clinical data to support any recommendation
  - Expert panel recommendations<sup>3</sup>
  - My recommendations
    - > Continue current complement inhibitor and consider giving an extra dose
    - > Consider short course of steroids
- Thrombosis<sup>1</sup>
  - Thrombotic episodes are now rare but can still happen
  - Treat with thrombolytics and anticoagulants
  - No data to know if switching to another complement inhibitor helps

AXIS  
Medical Education

1. Hill A, et al. *Nat Rev Dis Primers*. 2017;3:17028. 2. Griffin M, et al. *Blood Advances*. 2024;8:1776-1786. 3. Dingli D, et al. *Hematology*. 2024;29(1):2329030.

► Breakthrough hemolysis is usually related to complement-activating events such as infection or bacteria. Except for pegcetacoplan, we don't really have clinical guidelines to help do this. There is recommendations from an expert panel, although it is a little bit scattered all over the place in terms of what they recommend. I recommend continuing the current complement inhibitor they're on. You obviously treat the infection or whatever complement event there is – complement-activated event there is and consider giving an extra dose of whatever they're on, which is what we do with pegcetacoplan. Thrombotic events need to be treated with thrombolytics and anticoagulants as indicated. You have to be careful for bleeding. There is no data if you are on a complement inhibitor, if switching to another component inhibitor will help prevent another clot.

## Complement Inhibition for PNH: Which One Should We Use?

- Now have 6 FDA approved complement inhibitors for PNH, more may be on the way
- Some target terminal pathway, others the proximal pathway
- Two are oral, others given IV or subQ at various intervals
- All are very well tolerated with few side effects
- Patients need to be alert for infections, especially meningococcal infections
- Some may be better at achieving a higher hemoglobin level
- Breakthrough hemolysis is still an issue for all drugs
- Other considerations: side effects, rate of thrombosis, cost and insurance coverage, compliance
- Choosing the right therapy may take consultation with a center that specializes in PNH

AXIS  
Medical Education

► How to choose which one to use is not easy. It takes somebody who knows all the drugs well to discuss with the patient, asking the patients what they would prefer is one method. But obviously there are side effects to all these drugs, and you need to know which one is best for the patient. We have to consider side effects, rate of thromboses, the cost of these drugs, they're all very expensive, whether insurance will cover them, and we have to make sure the patients can be compliant, especially if they're on an oral drug, because if you stop or miss a dose, you can quickly go into a hemolytic flare. All these drugs are well tolerated, with few side effects. And choosing the right therapy might take consultation with a center that specializes in PNH.

## PATIENT CASE



### 41-YEAR-OLD-WOMAN

#### Initial Presentation:

- She initially presented 20 years ago with shortness of breath and heavy menstrual periods. She was found to be markedly pancytopenic.

#### Initial Workup and Treatment:

- W/U including a bone marrow biopsy showed aplastic anemia. She was treated with ATG and cyclosporine with complete count recovery. A bone marrow biopsy one year later was normocellular.

#### Case Evolution:

- She did well until 8 years ago when she noticed fatigue.

#### Workup and Treatment:

- Labs 8/22/16 showed WBC 3.4, Hgb 5.7, Hct 17.5, platelets 142K
- Referred to her local hematologist. BM biopsy showed 40-45% cellular marrow with erythroid hyperplasia. Normal FISH, normal cytogenetics.
- Peripheral blood flow cytometry was + for PNH.
- She was started on eculizumab on 9/12/2016



- ▶ We have a couple of cases that we'll present in our grand rounds series to talk about how to treat patients with PNH and give you examples. And I think they're very interesting.

Patient C is a 41-year-old female. She initially presented 20 years ago with shortness of breath and heavy bleeding from her menses. She was found to be markedly pancytopenic, and she

had a workup including a bone marrow biopsy, which revealed aplastic anemia. She was treated with ATG and cyclosporine, and had a complete count recovery and a bone marrow biopsy a year later was normocellular, so she had a wonderful response. She was followed until about 8 years later, when she began having fatigue. She came in and had marked anemia with a hemoglobin of 5.7. Other

counts were a little bit low, but not bad. She was referred to her local hematologist who did a bone marrow biopsy and she was cellular. She did not have aplastic anemia. She did not have MDS. And he was smart enough to do a peripheral blood flow cytometry for PNH, which was positive. She got started on eculizumab in September of 2016, and did okay.



## PATIENT CASE



### 41-YEAR-OLD-WOMAN

#### Workup:

- CBC 1/13/2017 showed WBC 3.8, Hgb 9.4, HCT 28, platelets 188K, LDH 268
- Evaluated for a bone marrow transplant, not felt to be a candidate

#### Case Evolution:

- She still didn't feel great, required transfusions q 3 months despite increasing dose of eculizumab to 1200 mg q 2 weeks.

#### Workup and Treatment:

- Switched to ravulizumab in Dec 2020
- Referred to Duke in June 2021
- WBC 5.8, Hgb 7.6, Hct 23, platelets 247K, LDH 263, T bili 7.1, normal transaminases, Retic 20.60%

#### Case Evolution:

- Felt to be sub-optimal responder, likely due to C3 coating of her red cells and extravascular hemolysis

#### Treatment:

- Started on Iptacopan January 2024
- Still feels well with stable blood counts

#### Current Status:

- Patient C was last seen in clinic on 10/20/2024
- Absolutely no complaints
- WBC 6.0, Hgb 14.8, Hct 45, platelets 183K, LDH 145, T bili 1.2, Retic 1.12%
- Still feels well with stable blood counts

► Her hemoglobin rose to 9.4 but it wasn't great, and she was still having fatigue, and her LDH was still not completely normal. The local hematologist actually referred her for a bone marrow transplant, and the transplant team said she was not felt to be a candidate. I don't know the reasons why. She was still not feeling great, and she was requiring transfusions about every 3 months, despite increasing the dose of eculizumab. And she eventually got switched to ravulizumab in December of 2020. And about a year later, she was still not having a great response, and was

referred to our center. Her hemoglobin was 7.6 as you see there. White cells and platelets were normal. Her LDH was just slightly elevated. Her bilirubin was markedly elevated, and she had a retic count that was sky high – or a retic percentage that was sky high. At that time, we felt she was a suboptimal responder, likely due to the C3 coating of her red cells and extravascular hemolysis. We started her on iptacopan in January of 2024, shortly after it got FDA approved. We last saw her last October. Actually, we've seen her since then. She has absolutely no complaints. Her hemoglobin is

now normal at 14.8. Her LDH is normal, her retic count is normal, her bilirubin is normal, and she feels very well with stable blood counts. This is a great example of what's called a suboptimal responder to C5 inhibitor therapy due to extravascular hemolysis, who then responds to a proximal complement inhibitor.

And she still feels well with very stable blood counts, and is doing quite well.

With that, I would like to thank you so much for your attention for this interesting activity, and I hope you learned a good bit.

## REFERENCES

- Babushok DV. When does a PNH clone have clinical significance?. *Hematology Am Soc Hematol Educ Program*. 2021;2021(1):143-152.
- Bektas M, Copley-Merriman C, Khan S, Sarda SP, Shammo JM. Paroxysmal nocturnal hemoglobinuria: patient journey and burden of disease. *J Manag Care Spec Pharm*. 2020;26(12-b Suppl):S8-S14.
- Bektas M, Copley-Merriman C, Khan S, Sarda SP, Shammo JM. Paroxysmal nocturnal hemoglobinuria: role of the complement system, pathogenesis, and pathophysiology. *J Manag Care Spec Pharm*. 2020;26(12-b Suppl):S3-S8.
- Borowitz MJ, Craig FE, Digiuseppe JA, et al. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. *Cytometry B Clin Cytom*. 2010;78(4):211-230.
- Brodsky RA, Mukhina GL, Li S, et al. Improved detection and characterization of paroxysmal nocturnal hemoglobinuria using fluorescent aerolysin. *Am J Clin Pathol*. 2000;114(3):459-466.
- Brodsky RA, Young NS, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2008;111(4):1840-1847.
- Canadian PNH Network. Accessed July 20, 2020. <https://www.pnhnetwork.ca/en.html#patient-screening>
- Cançado RD, Araújo ADS, Sandes AF, et al. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. *Hematol Transfus Cell Ther*. 2021;43(3):341-348.
- Colden MA, Kumar S, Munkhbileg B, Babushok DV. Insights into the emergence of paroxysmal nocturnal hemoglobinuria. *Front Immunol*. 2022;12:830172.
- Dacie JV, Lewis SM. Paroxysmal nocturnal haemoglobinuria: clinical manifestations, haematology, and nature of the disease. *Ser Haematol*. 1972;5(3):3-23.
- de Latour RP, Kulasekararaj A, Scheinberg P, et al. Clinical breakthrough hemolysis (BTH) during monotherapy with the oral factor B inhibitor iptacopan is generally not severe and managed without treatment discontinuation: 48-week data from the phase III APPLY-PNH and APPOINT-PNH trials in paroxysmal nocturnal hemoglobinuria (PNH). *Blood*. 2023;142(Supplement 1):1338.
- de Latour RP, Röth A, Kulasekararaj AG, et al. Oral iptacopan monotherapy in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2024;390(11):994-1008.
- DeZern AE, Symons HJ, Resar LS, Borowitz MJ, Armanios MY, Brodsky RA. Detection of paroxysmal nocturnal hemoglobinuria clones to exclude inherited bone marrow failure syndromes. *Eur J Haematol*. 2014;92(6):467-470.
- Dingli D, De Castro Iii C, Koprivnikar J, et al. Expert consensus on the management of pharmacodynamic breakthrough-hemolysis in treated paroxysmal nocturnal hemoglobinuria. *Hematology*. 2024;29(1):2329030.
- Figuerola JE, Densen P. Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev*. 1991;4:359-395.
- Griffin M, Kelly RJ, Panse J, et al. Management of acute breakthrough hemolysis with intensive pegcetacoplan dosing in patients with PNH. *Blood Adv*. 2024;8(7):1776-1786.
- Griffin M, Munir T. Management of thrombosis in paroxysmal nocturnal hemoglobinuria: a clinician's guide. *Ther Adv Hematol*. 2017;8(3):119-126.
- Hall SE, Rosse WF. The use of monoclonal antibodies and flow cytometry in the diagnosis of paroxysmal nocturnal hemoglobinuria. *Blood*. 1996;87(12):5332-5340.
- Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. *Nat Rev Dis Primers*. 2017;3:17028.
- Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood*. 2013;121(25):4985-4996.
- Hill A, Rother RP, Arnold L, et al. Eculizumab prevents intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria and unmasks low-level extravascular hemolysis occurring through C3 opsonization. *Haematologica*. 2010;95(4):567-573.
- Hill A, Sapsford RJ, Scally A, et al. Under-recognized complications in patients with paroxysmal nocturnal haemoglobinuria: raised pulmonary pressure and reduced right ventricular function. *Br J Haematol*. 2012;158(3):409-414.
- Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 1995;333(19):1253-1258.
- Hillmen P, Muus P, Dührsen U, et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2007;110(12):4123-4128.
- Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2021;384(11):1028-1037.
- Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2006;355(12):1233-1243.
- Jalbert JJ, Chaudhari U, Zhang H, Weyne J, Shammo JM. Epidemiology of PNH and real-world treatment patterns following an incident PNH diagnosis in the US. *Blood*. 2019;134(Supplement\_1):3407.
- Kelly RJ, Hill A, Arnold LM, Brooksbank GL, et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. *Blood*. 2011;117(25):6786-6792.
- Kulasekararaj A, Griffin M, Piatek CI, et al. Danicopan as add-on therapy to ravulizumab or eculizumab versus placebo in patients with paroxysmal nocturnal hemoglobinuria and clinically significant extravascular hemolysis: phase 3 long-term data. Abstract presented at: American Society of Hematology Annual Meeting & Exposition; San Diego, California. December 9-12, 2023. Abstract 576.
- Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood*. 2019;133(6):540-549.
- Lee JW, Griffin M, Kim JS, 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. *Lancet Haematol*. 2023;10(12):e955-e965.
- Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood*. 2019;133(6):530-539.

## REFERENCES

- Li C, Dong X, Wang H, Shao Z. The role of T lymphocytes in the pathogenesis of paroxysmal nocturnal hemoglobinuria. *Front Immunol*. 2021;12:777649.
- Luzzatto L, Risitano AM. Advances in understanding the pathogenesis of acquired aplastic anaemia. *Br J Haematol*. 2018;182(6):758-776.
- Martí-Carvajal AJ, Anand V, Cardona AF, Solà I. Eculizumab for treating patients with paroxysmal nocturnal hemoglobinuria. *Cochrane Database Syst Rev*. 2014;(10):CD010340.
- McKinley CE, Richards SJ, Munir T, et al. Extravascular hemolysis due to C3-loading in patients with PNH treated with eculizumab: defining the clinical syndrome. *Blood*. 2017;130(Suppl 1):3471.
- Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood*. 2005;106(12):3699-3709.
- Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):208-216.
- Ricklin D, Mastellos DC, Reis ES, Lambris JD. The renaissance of complement therapeutics. *Nat Rev Nephrol*. 2018;14(1):26-47.
- Risitano AM, Han B, Ueda Y, et al. Oral complement factor B inhibitor iptacopan monotherapy improves hemoglobin to normal/near-normal levels in paroxysmal nocturnal hemoglobinuria patients naïve to complement inhibitors: phase III APPOINT-PNH trial. Abstract presented at: 49th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT); Paris, France; April 23-36, 2023. Abstract OS12-06.
- Risitano AM, Notaro R, Marando L, et al. Complement fraction 3 binding on erythrocytes as additional mechanism of disease in paroxysmal nocturnal hemoglobinuria patients treated by eculizumab. *Blood*. 2009;113(17):4094-4100.
- Röth A, Fu R, He G, et al. Safety of crovalimab versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria (PNH): pooled results from the phase III COMMODORE 1, COMMODORE 2, and COMMODORE 3 studies. Abstract presented at: American Society of Hematology Annual Meeting; San Diego, California; December 9-12, 2023. Abstract 575.
- Röth A, Maciejewski J, Nishimura JI, Jain D, Weitz JI. Screening and diagnostic clinical algorithm for paroxysmal nocturnal hemoglobinuria: Expert consensus. *Eur J Haematol*. 2018;101(1):3-11.
- Röth A, Nishimura JI, Nagy Z, et al. The complement C5 inhibitor crovalimab in paroxysmal nocturnal hemoglobinuria. *Blood*. 2020;135(12):912-920.
- Shah YB, Priore SF, Li Y, et al. The predictive value of PNH clones, 6p CN-LOH, and clonal TCR gene rearrangement for aplastic anemia diagnosis. *Blood Adv*. 2021;5(16):3216-3226.
- Subías Hidalgo M, Martín Merinero H, López A, et al. Extravascular hemolysis and complement consumption in paroxysmal nocturnal hemoglobinuria patients undergoing eculizumab treatment. *Immunobiology*. 2017;222(2):363-371.
- Waheed A, Shammo J, Dingli D. Paroxysmal nocturnal hemoglobinuria: Review of the patient experience and treatment landscape. *Blood Rev*. 2024;64:101158.
- Wong RSM, Navarro-Cabrera JR, Comia NS, et al. Pegcetacoplan controls hemolysis in complement inhibitor-naïve patients with paroxysmal nocturnal hemoglobinuria. *Blood Adv*. 2023;7(11):2468-2478.
- Zipfel PF, Wiech T, Rudnick R, Afonso S, Person F, Skerka C. Complement inhibitors in clinical trials for glomerular diseases. *Front Immunol*. 2019;10:2166.

### **About AXIS Medical Education, Inc.**

AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, web-based, and print-based educational activities for healthcare professionals. AXIS provides convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 75 years of experience in adult learning theory, curriculum design/implementation/assessment, continuing education accreditation standards, and medical meeting planning and logistics. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities.

AXIS employs an experienced team of medical and scientific experts, medical writers, project managers, meeting planners, and logistics professionals. This team is dedicated to meeting the unmet educational needs of healthcare professionals, with the goal of improving patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. To that end, AXIS partners with other organizations and accredited providers to offer added expertise and assist in expanding access to our educational interventions. AXIS also partners with numerous patient advocacy organizations to provide recommended patient education and caregiver resources in specific disease areas. AXIS finds value in these partnerships because they complement our core clinical curriculum with validated and relevant supplemental resources for busy clinicians and their patients.

The mission of AXIS is to enhance the knowledge, skills, competence, and performance of the interprofessional healthcare team to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led certified educational activities designed to foster lifelong learning that is applicable to clinical practice and patient-centered care.

To learn more and to see our current educational offerings, visit us online at [www.AXISMedEd.com](http://www.AXISMedEd.com).

