Harnessing the Power of the Complement Pathway: Evolving Treatments and Improving Outcomes in PNH

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Dr. de Castro: Hello and welcome to this educational session entitled *Harnessing the Power of the Compliment Pathway, Evolving Treatments and Improving Outcomes in PNH*. I'm Carlos de Castro, I'm a Professor of Medicine at Duke University.

Dr. Patel: Hi, my name is Bhumika Patel. I'm an Associate Professor at the Prisma Health Cancer Institute in Greenville, South Carolina. We look forward to teaching you guys about PNH in this educational session.

Learning Objectives

- Outline the function of the complement system cascade, focusing on the role of the terminal and proximal complement pathways in PNH disease pathogenesis
- Align the therapeutic rationale for inhibition of C5, C3, factor B and factor D in PNH with safety and efficacy data for currently available and emerging novel agents that target each
- Summarize practice considerations for PNH therapies that are either approved or in clinical trials, including benefits, risks of infection and complement inhibition, monitoring, and management
- Apply clinical decision-making approaches to challenging PNH cases

Dr. de Castro: The learning objectives for this session are outlined here and you can read through them.

Translating Biology into Clinical Practice:

The Complement Pathway and Current Standard of Care in PNH

Dr. Patel: So, we'll be talking about translating biology into clinical practice, the complement pathway, and the current standard of care in PNH.

Paroxysmal Nocturnal Hemoglobinuria

PNH is an acquired hemolytic anemia that arises from a somatic mutation in the PIGA gene in hematopoietic stem cell, which causes defective synthesis of the GPI anchor proteins, leading to the development of PNH and associated clinical manifestations

Characterized by chronic intravascular hemolysis due to the action of the complement on abnormal RBCs lacking CD55 and CD59. PNH RBCs lyse more readily in the presence of activated complement.

PNH can be classified:

- Classical PNH
- PNH in the context of BMF
- Subclinical PNH

Brodsky RA. *Blood*. 2014;124(18):2804-2811.

PNH is an acquired hemolytic anemia that arises from a somatic mutation in the PIGA gene in the hematopoietic stem cell, which causes defective synthesis of the GPI anchor proteins leading to the development of PNH and its associated clinical manifestations.

It's characterized by chronic intravascular hemolysis due to the action of the complement on the abnormal red blood cells that are lacking the CD55 and CD59 regulatory proteins in which PNH red blood cells are lysed more readily in the presence of complement activation.

PNH can be classified in three categories. We call it classical PNH, where there is only PNH that you are worried about, where there is chronic intravascular hemolysis.

Then you have small PNH clones that could be in the presence of bone marrow failure syndrome, such as aplastic anemia, and you can see them in some circumstances in myelodysplastic syndrome.

And subclinical PNH, where there is PNH clones detected in the setting where they are not clinically active, but something that we do monitor in clinical practice or may evaluate for.

Epidemiology

- Incidence: 1 - 1.5 cases/million people
- Likely underestimated due to underdiagnosis
- May be slightly more common in females, and may occur more frequently in Asia vs US and Europe
- PNH may be diagnosed at any age; median age is 30's

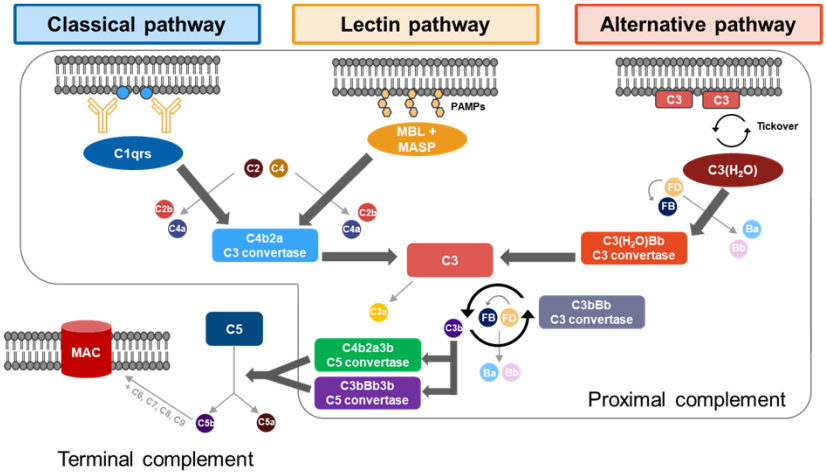
Griesser C, et al. *TH Open*. 2020;4(1):e36-39.;Yu F, et al. *Int J Hematol*. 2016;103(6):649-654.; Hill A, et al. *Nat Rev Dis Primers*. 2017;3:17028.; Nishimura JL, et al. *Medicine* (Baltimore). 2004; 83(3):193-207.

We can't talk about PNH without talking about the rarity of it. Its incidence is 1 to 1.5 cases in a million people likely underestimated due to underdiagnosis and delayed diagnosis.

It may be slightly more common in females and may occur more frequently in Asia versus the United States and Europe.

PNH may be diagnosed at any age, but usually the median age of diagnosis for PNH is around the age of 30.

Complement System



- Complement is a group of more than 40 proteins in the blood and on the cell surface
- Complement is an immune surveillance system
  - First line of defense against various microorganism
  - Involved in immunological and inflammatory responses
- Many different events can activate complement including trauma, infection, stress, etc.
- In PNH, activated complement will attack red cells causing them to "lyse" (burst)

Adapted from Zhang R, et al. *Cancer Cell Int*. 2019;19:300.; Figueroa JE, et al. *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.; Merle NS, et al. *Front Immunol*. 2015;6:257.; Ricklin D, et al. *Nat Immunol*. 2010;11(9):785-797.

Another important basic foundation of understanding PNH is the complement system. The complement system is composed of greater than 40 proteins in the blood and on the surface of cells.

It is the immune surveillance systems for humans. And so, for what's important to take away from the complement system it's our first line of defense against various microorganisms and is involved in our immunological and inflammatory responses.

So, each part of our complement system plays an important role, proximal and the terminal does. And that is important to keep in mind in fighting off certain organisms such as our encapsulated organisms. Many different events can activate our complement system including trauma, infection, and stress.

PNH is a dysregulation of the complement system because of the lack of CD55 and 59, which leads to red blood cells to lyse more actively and causes the complement system to be more activated.

Consequences of Complement in PNH

- Intravascular hemolysis
  - Anemia-elevated LDH, D-dimer, low haptoglobin, negative direct Coombs test, and elevated/decrease reticulocyte count
  - Iron def anemia
  - End organ damage (CKD, pulmonary HTN)
- Thrombosis
- Cytopenias - leukopenia or thrombocytopenia
- Poor quality of life
- Symptoms at presentation are not unique to PNH
  - Hemolytic anemia, often requiring transfusions
  - Fatigue
  - Dyspnea
  - Abdominal pain or dysphagia
- Early mortality and morbidity

The consequences of the complement system in PNH include chronic intravascular hemolysis in which we see anemia, where you will find clinical serological markers of positive for elevated LDH, D-dimers, low haptoglobin, and you'll find a negative direct Coombs test. I would think about this in a clinical setting where you have an individual who has anemia and active hemolysis. And this is what type of clinical indicators you may see when you're suspecting PNH. And you may see an elevated or decreased reticulocyte count, especially if there's a concern for underlying bone marrow failure.

Intravascular hemolysis in PNH can lead to iron deficiency anemia.

In uncontrolled complement activation in intravascular hemolysis in patients with untreated PNH can lead to end organ damage such as chronic kidney disease, pulmonary hypertension. And as we know, one of the most feared complications of PNH is thrombosis.

Other clinical markers that you are worried about in PNH are, you may see some mild leukopenia and thrombocytopenia.

Consequences of Complement in PNH

- Intravascular hemolysis
  - Anemia-elevated LDH, D-dimer, low haptoglobin, negative direct Coombs test, and elevated/decrease reticulocyte count
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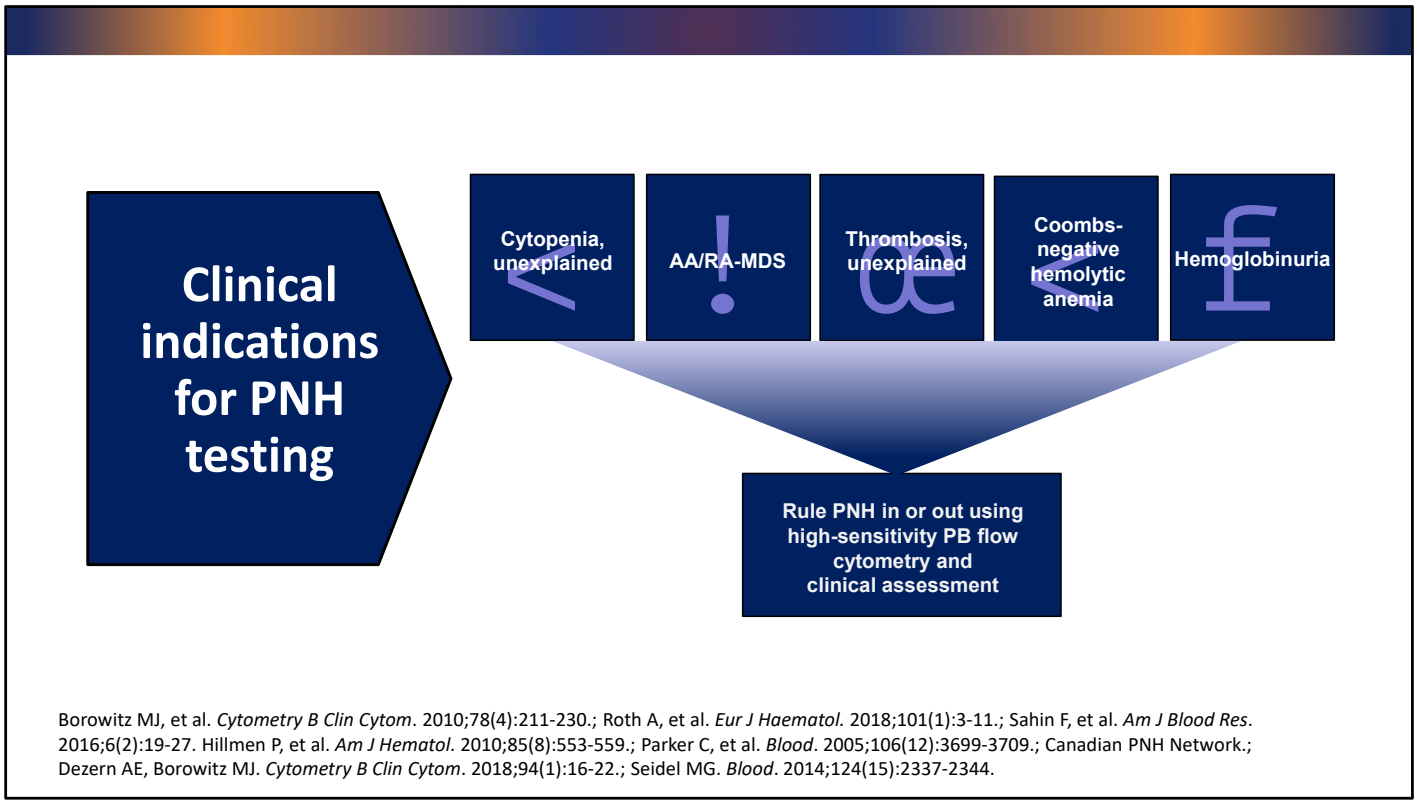
  - Abdominal pain or dysphagia
- Early mortality and morbidity

Individuals diagnosed with PNH may have also poor quality of life because of the chronic intravascular hemolysis leading to anemia.

Symptoms at presentation are not unique to PNH, which is why it's important to keep PNH in your differential, when you have cytopenias of unclear etiology or hemolysis of unclear etiology, which is Coombs negative, think about PNH.

So, symptoms may be hemolytic anemia, often requiring transfusions, fatigue, dyspnea, abdominal pain or dysphasia. Because of the lack of specificity of symptoms with PNH, a lot of patients, there's a delay to diagnosis, which is why sometimes keeping it in your differential will help you in diagnosing these patients more readily and making sure you're promptly diagnosing them and also making sure they're promptly treated in the appropriate fashion, if clinically indicated.

Untreated PNH can lead to early mortality and morbidity, which is one of the most feared complications is the risk of thrombosis along with end organ damage and other symptomology as we've discussed. So, keep it in your differential because it'll help in assessing, you know, when you're thinking about PNH, these are some of the symptoms and clinical parameters you may find, but also the thing is, think about it in your differential when you're clinically assessing patients.



Borowitz MJ, et al. *Cytometry B Clin Cytom*. 2010;78(4):211-230.; Roth A, et al. *Eur J Haematol.* 2018;101(1):3-11.; Sahin F, et al. *Am J Blood Res*. 2016;6(2):19-27. Hillmen P, et al. *Am J Hematol.* 2010;85(8):553-559.; Parker C, et al. *Blood*. 2005;106(12):3699-3709.; Canadian PNH Network.; Dezern AE, Borowitz MJ. *Cytometry B Clin Cytom*. 2018;94(1):16-22.; Seidel MG. *Blood*. 2014;124(15):2337-2344.

One of the most, one common theme I use, like the catchphrase has been great to use utilizing clinical practice for me especially, and I think a lot of other clinicians across the United States is when in doubt, I test for PNH.

When there's cytopenias of unexplained etiology, there's aplastic anemia for sure that we teach for acquired aplastic anemia, we test for PNH at diagnosis and we monitor them routinely. In certain subtypes of MDS, we test for PNH. Thrombosis that's unexplained, we test for PNH and then Coombs negative hemolytic anemia, as we discussed and hemoglobinuria.

These are common clinical indicators where I think about PNH, and where PNH is a test that can be run easily off the peripheral blood with high sensitivity flow cytometry. So, keeping it in your differential really is helpful in these set scenarios and I think is it keeps it on, make sure that you can test for it easily too. You don't require bone marrow biopsy at the beginning unless it’s otherwise clinically indicated in the setting of bone marrow failure. But I think this is an easy test that can be utilized by clinicians in all practices when in doubt in any of these clinical instances.

Diagnosis

- High sensitivity flow cytometry with FLARE on peripheral blood
  - Increase sensitivity to detect small abnormal populations, because monocytes and granulocytes have shorter half lives and numbers not affected by transfusions, analysis of GPI anchored proteins on neutrophils or monocytes is preferred
- FLARE assay binds selectively with high affinity to GPI anchor of most cells lineages, most useful to assay the GPI anchor on granulocytes

Type 1 – no deficiency

Type 2 – partial deficiency of CD55/59

Type 3 – complete deficiency of CD55/59

Hall SE, et al. *Blood*. 1996;87:5332-5340.; Parker C, et al. *Blood.* 2005;106:3699-3709.; Brodsky RA, et al. *Am J Clin Pathol*. 2000;114:459-466.

So, as we alluded to, using the catchphrase, you test for high sensitivity flow cytometry. So, high sensitivity flow cytometry with FLARE on the peripheral blood is the gold standard for testing for PNH. It has the increased sensitivity to detect at small abnormal populations because monocytes and granulocytes have shorter half-lives and numbers are not affected by transfusions. And analysis of GPI anchor proteins on the neutrophils or monocytes is preferred. FLARE assay binds selectively with high affinity GPI anchor of most cell lineages and most useful to the GPI anchor on granulocytes.

So, certain reports of, when you get these reports back from flow cytometry, will tell you there's either no PNH clone, which is type 1.

Type 2 where there's partial deficiency of a type 2 PNH clone. So, you may have only some of your cells are losing CD55, 59.

And then type 3 is where there's complete loss of CD55 and 59 deficiency in that setting because you don't have those GPI anchor proteins. So, keep in mind, type two and type three can be clinically relevant. That's when you need to be, you know, looking at other clinical parameters also. This is, the larger the clone, the increased risk of thrombosis, which has been seen in multiple studies. So, it's important to know how to assess the clone, how to make sure in its appropriate clinical context, but also making sure you're addressing that and treating it promptly in the appropriate setting.

Current Standard of Care for PNH

- Complement inhibition
  - C5 inhibitors
    - ✓Eculizumab or ravulizumab
  - C3 inhibitor
    - ✓Pegcetacoplan
  - Factor B
    - ✓Iptacopan
- Supportive care
  - Transfusions for anemia
    - ✓Treat iron overload if progressive
  - Role of anticoagulation very unclear
  - ESA therapy, treated for IDA, IST in the setting of AA
- Allogeneic HSCT has a very limited role

- Treatment goals
  - Improve anemia
  - Reduce fatigue and improve quality of life
  - Reduce risk of thrombosis and end organ damage

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

So, the current standard of care for PNH. So, once the diagnosis is made, so, we know the first FDA approved therapy for PNH was eculizumab subsequently followed by ravulizumab, which is our C5 inhibitors. Subsequently, we had the C3 inhibitor approved, pegcetacoplan and most recently we had the factor B iptacopan approved, which is an oral factor B inhibitor. These treatments have literally changed the treatment paradigm for PNH, from eculizumab to where we are today. And these have decreased mortality and morbidity and helped change clinical practice for our patients where there was not, outside of supportive care, there was not many treatment options prior to eculizumab for our patients with PNH. Each of these treatment modalities have their different mechanism of action. As we know, C5 inhibitors are terminal complement inhibitors, C3 inhibitors are proximal complement inhibitors, and the oral factor B is also a proximal inhibitor. And in conjunction with complement inhibition when we're treating our patients for PNH, we are thinking about supportive care. There's individuals that may still require transfusions despite optimal therapy. So, you may have to treat iron overload if progressive.

The role of anticoagulation is also very unclear because of the fact that there's some of these patients where they present and they may have a clot. And in the optimal setting for PNH, how long do you continue anticoagulation for these patients? Usually in the upfront setting, I do anticoagulate patients to make sure they're stabilized depending on, you know, how their clinical scenario. If they're unstable, anticoagulation is preferred while you're getting treated these patients with their complement inhibition therapy.

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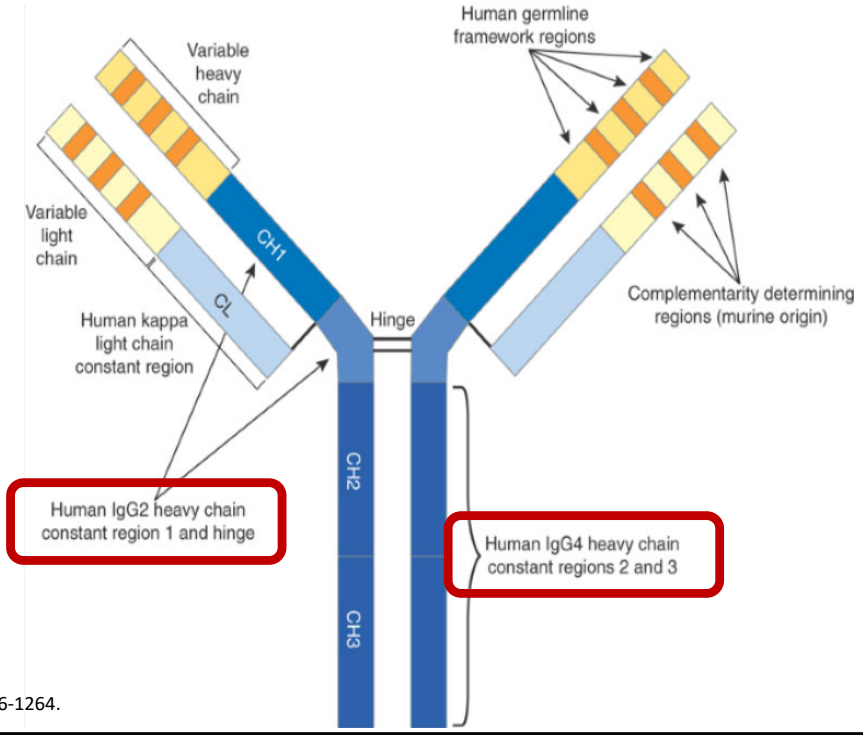
You may consider using erythropoietin stimulating agents because of the fact that you may, they may have a lack of erythropoietin stimulating the bone marrow to produce red blood cells. So, that will help in producing red blood cells, especially in the setting of chronic kidney disease, you may think about that. You may have to treat iron deficiency anemia with the setting of iron deficiency. And in the setting of aplastic anemia for PNH, you may think about immunosuppressive therapy. So, there's a small cohort, I would say about like 20% or 10 to 20% or less.

You see patients with AAPNH, and these patients, you may have to treat the PNH along with the aplastic anemia. So, you may think about immunosuppressive therapy with that, such as a cyclosporine, ATG, in the appropriate clinical scenario.

Allogeneic transplant is very rarely utilized in patients with classical PNH, but you may consider in patients with AAPNH, depending on how their response is to therapy and their clinical scenario, their age, and other clinical parameters that you may consider for these patients and our treatment goals for patients with PNH is to improve anemia, reduce fatigue, improve the quality of life, but reduce the risk of thrombosis and end organ damage.

Terminal Complement Inhibitors Eculizumab (Anti-C5 Antibody)



Rother RP, et al. *Nature Biotechnology.* 2007;25:1256-1264.

So, you know, you can't talk about PNH without talking about the first FDA-approved therapy for PNH was eculizumab, which is an anti-C5 antibody. Eculizumab was the first in class humanized anti-C5 monoclonal antibody, which has very high affinity binding for a human C5. And each eculizumab C5 molecule binds to two C5 proteins, and it was the first therapy that was specifically targeted to complement mediated hemolysis.

Eculizumab is unique among the humanized monoclonal antibodies because germline human framework accelerator sequences were used to minimize the immunogenicity.

And the human Ig2 and 4 heavy chains constant regions were used to eliminate the ability of the antibody to bind to the FC receptors and activate the complement.

Eculizumab Clinical Trials

- Pilot study
  - Phase 2, open label study
  - 11 patients
  - 12 weeks
- TRIUMPH
  - Phase 3, double-blind, placebo-controlled, randomized, multi-center trial
  - Patients: history of ≥4 transfusions/ year + platelet count >100,000
  - Treatment: eculizumab or placebo, 26 weeks
- SHEPHERD
  - Phase 3, open-label multi-center trial
  - Broader, more diverse patients
    - Lower transfusion requirements
    - Thrombocytopenia
    - Platelet count >30,000
  - Treatment: eculizumab, 12 months
- All patients in the Pilot study, TRIUMPH and SHEPHERD studies were eligible to enroll in the extension trials to receive eculizumab
- Eculizumab significantly reduced the hemolysis and the underlying cause of morbidity and mortality in PNH

Hillmen P, et al. *N Engl J Med.* 2004;350:552-559.; Hillmen P, et al. *N Engl J Med*. 2006;355:1233-1243.; Hillmen P, et al. *Blood*. 2007;110:4123-4128.; Brodsky RA, et al. *Blood*. 2008;111:1840-1847.

And first time eculizumab was evaluated was in a pilot study, which was a phase two study open label study that included about 11 patients and was 12 weeks long.

Subsequently, this was followed by the TRIUMPH study, which was a phase three double blind placebo controlled randomized multi-center study. To be eligible, patients had to have a history of four or more transfusions a year, a platelet count of greater than 100,000. And patients received either Solaris or placebo for 26 weeks.

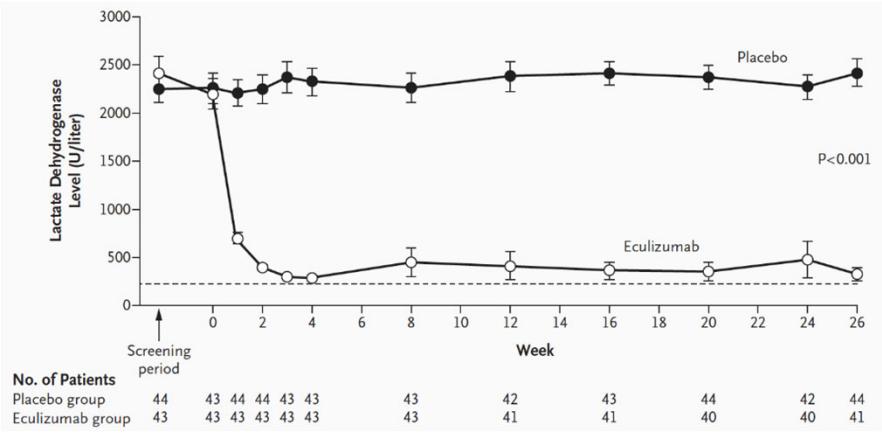
The subsequent other study was the SHEPHERD study, which was a phase three open label multi-center study in a broader, more diverse patient population. And in this study, it included patients with lower transfusion requirements, including patients with thrombocytopenia, where the platelet cutoff was greater than 30,000. And patients were treated with Soliris for 12 months.

The TRIUMPH and SHEPHERD study were designed to establish a safety and efficacy of eculizumab in patients with PNH and combined were the basis for Soliris approval and support the prescribing information for eculizumab for patients with PNH. All patients in the pilot, TRIUMPH, and SHEPHERD trials were eligible to enroll in the extensions trials including the placebo-treated patients in TRIUMPH who are now receiving Soliris.

So what this eculizumab showed, just to give a summary, is significantly reduced the hemolysis and the underlying cause of morbidity and mortality in PNH.

Eculizumab: Summary of Clinical Efficacy

- Significantly reduced hemolysis, the underlying cause of morbidity and mortality in PNH
  - 86% reduction in hemolysis[1]
  - 92% reduction in thrombotic events[2]
  - 73% reduction in need for transfusions[1]
  - Significant reduction in fatigue and improvement in QoL measures[3]
  - AEs similar to placebo
- Does not treat PNH-associated bone marrow failure and may not completely resolve the anemia



Degree of Intravascular Hemolysis as Measured by Mean LDH Levels, Baseline to Week 26 (Phase 3 Trial)[1]

1. Hillmen P, et al. *N Engl J Med.* 2004;350:552-559 2. Hillmen P, et al. *N Engl J Med*. 2006;355:1233-1243. 3. Hillmen P, et al. *Blood*. 2007;110:4123-4128. Brodsky RA et al. *Blood*. 2008;111:1840-1847.

There was 86% reduction in hemolysis, as we can see when you compare the placebo to eculizumab in the LDH marker, which is a marker of intravascular hemolysis.

There was 92% reduction in thrombotic events, 73% reduction in the need for transfusions and significant reduction in fatigue and improvement in quality of life measures.

Adverse events were similar to placebo.

But keep in mind, eculizumab does not treat the PNH-associated bone marrow failure and does not completely correct the defect that's at the stem cell. But it does help you control the intravascular hemolysis and this associated complications in individuals with PNH.

C5 inhibitors (Eculizumab and Ravulizumab)

- Binds the complement component C5, thereby inhibiting terminal complement activation, decreases hemolysis of RBCs and tendency of thrombosis, but does not fix the defect in hematopoiesis
  - Up to a third of patients can experience symptomatic anemia or remain transfusion dependent
  - Reduces intravascular hemolysis not extravascular hemolysis
- Vaccinate 2 weeks prior to treatment with meningococcal vaccines due to risk of meningitis (*Neisseria*) secondary to complement inhibition then revaccinate every 3-5 years
  - In urgent situations prophylactic antimicrobial therapy can be started while initiating therapy

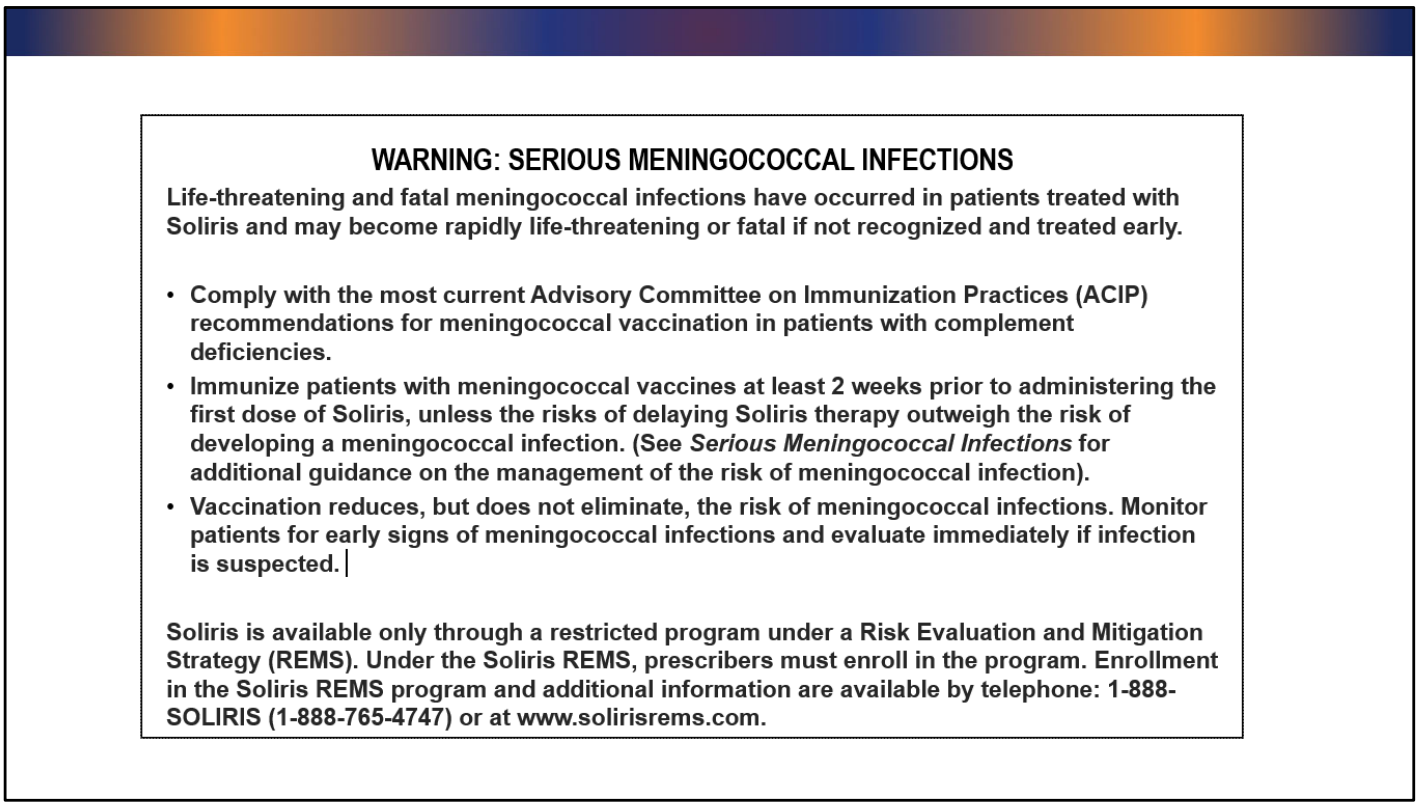
Subsequently, as we're wanting to improve on the care for patients with PNH, we have ravulizumab, which was approved. And ravulizumab is another C5 terminal complement inhibitor which binds to the complement component C5, inhibiting the terminal complement activation, decreases hemolysis of the red blood cells, that decreases the risk of thrombosis, but does not fix again the defect at the hematopoiesis.

Up to a third of patients treated with C5 inhibitor experienced symptomatic anemia and transfusion dependency, despite optimal therapy with eculizumab and ravulizumab.

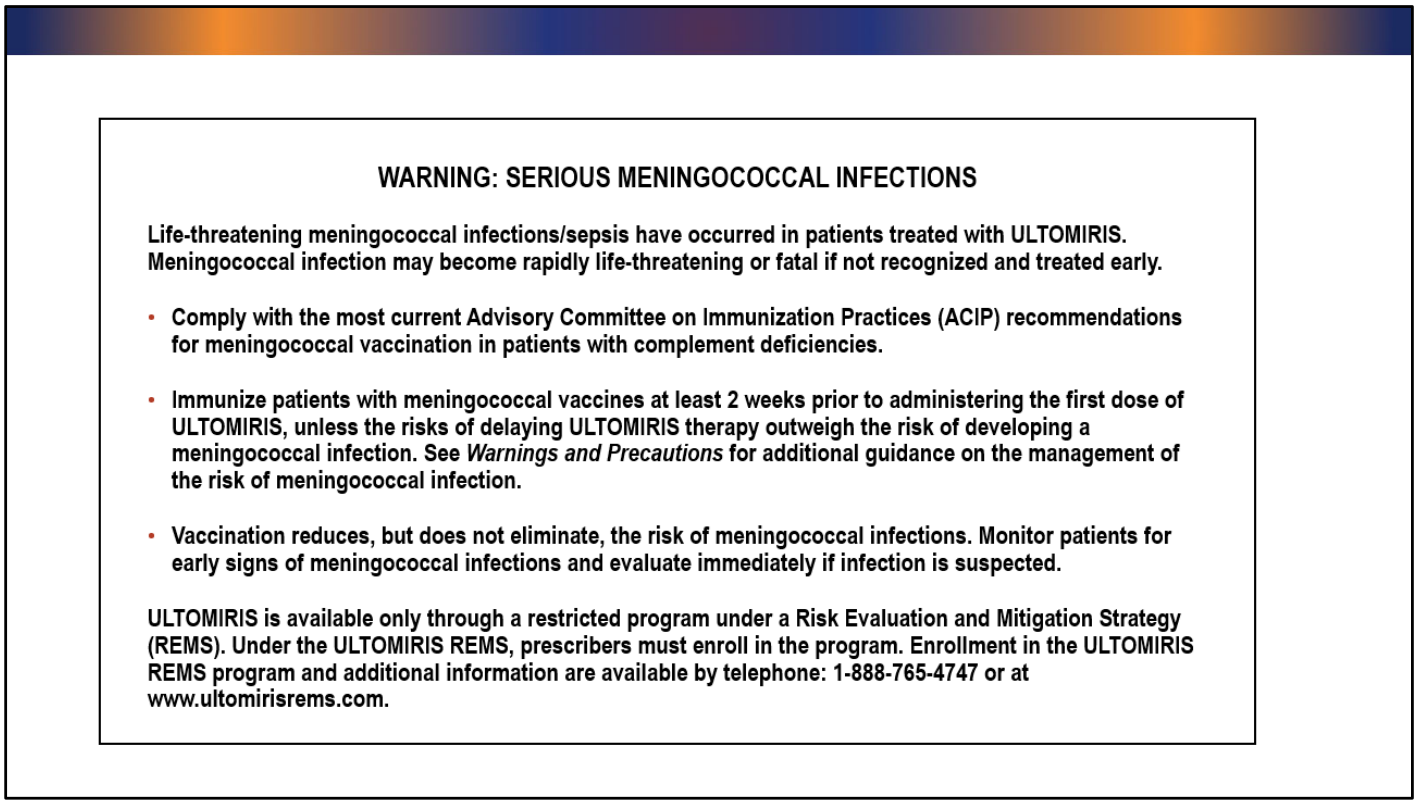
Both of these agents, eculizumab and ravulizumab, reduced intravascular hemolysis, but does not address extravascular hemolysis, which is a component that we see commonly in patients treated with C5 inhibitors. And this is C3b-mediated.

What's important in prior to initiating therapy with C5 inhibitors is you want to vaccinate these patients two weeks prior to the treatment with your encapsulated organism, which is your meningococcal vaccines, because there is a risk of 0.5 to 1% risk of meningitis in patients treated with complement inhibition, which stresses the importance of making sure patients are vaccinated prior to initiation of therapy.

However, in urgent clinical scenarios, you can use prophylactic antimicrobial therapy to get therapy started in patients that are hemodynamically stable or need clinically, urgently need to be treated for their PNH.



Here are the black box warnings for both eculizumab and ravulizumab, which stresses the importance, why it's important for clinical practitioners to make sure that they vaccinate their patients prior to initiation therapy for PNH, and also making sure it's two weeks prior and following the most recent ACIP guidelines so that way you're continuing to follow your patients that are being actively treated with complements C5 inhibitors you're following through on their immunizations subsequently after they've been started on therapy. Because we do want to mitigate that risk. Even though the risk is small, the risk is still there and we want to make sure we protect our patients.



WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a meningococcal infection. See *Warnings and Precautions* for additional guidance on the management of the risk of meningococcal infection.**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.**

ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS REMS, prescribers must enroll in the program. Enrollment in the ULTOMIRIS REMS program and additional information are available by telephone: 1-888-765-4747 or at www.ultomirisrems.com.

Similarly, there's another black box warnings with ravulizumab as we've previously discussed. So we want to make sure that, you know, all clinical providers that are prescribing PNH drugs are enrolled in REMS programs. So, the thing is, they go through extensive training to make sure that they're qualified to prescribe it and they know how to monitor patients for these. They educate their patients about the risk of meningitis, but also they're following through on their most recent immunization guidelines.

Summary

- There will be choices for therapies to discuss with your patients
  - Terminal vs proximal complement inhibitors FDA approved
    - ✓Terminal: eculizumab and ravulizumab
    - ✓Proximal: pegcetacoplan and iptacopan
  - Personalizing therapy
  - Follow the most recent ACIP guidelines for vaccinations prior to initiation of therapy with terminal and proximal inhibitor due to the risk of serious infections with encapsulated bacteria (*Neisseria meningitidis* types A, C, W, B, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B).
- Enrolling in clinical trials
- Newer drugs will help make this disease more manageable and practice changing

In summary, there will be choices for therapies to discuss with your patients. And I think that's one of the important takeaways I want to say, this is an exciting time in PNH. We have terminal complement inhibitors, which have revolutionized our treatment outcomes for our patients with PNH, where supportive care was the only thing we had prior to their approval. And with terminal complement inhibitors, we've decreased the risk of morbidity and mortality and the risk of thrombosis. And now we have also proximal complement inhibitors which are FDA-approved. So, when we talk about the terminal complement inhibitors, we have eculizumab, ravulizumab, which are C5 inhibitors and we have the proximal inhibitors, pegcetacoplan, which is C3 inhibitor, and iptacopan, which is recently approved, which is an oral factor B inhibitor. I think we're in an exciting time where we can personalize therapy for our patients based on the data that Dr. DeCastro will be discussing. We're in an era where we have newer agents, where data is very exciting and safe for our patients to be initiated on therapies which meet their lifestyle, which is most appropriate clinically for them and available to them.

Prior to initiation of all of these therapies, it's important to make sure you're following the immunization guidelines. And also, if you have an opportunity to enroll patients on clinical trials, it's great, because the thing is that that's how we learn more about these drugs and how we can improve the care for our patients with PNH.

Keep in mind, newer drugs will make this disease more manageable and it's going to be practice changing for them and as we know, from where we started with one drug approval, we're up to four, and I think there's more new exciting therapies to come. Thank you.

Evolving Strategies in PNH: The Current and Future Impact of Emerging Novel Agents in PNH

Harnessing the Power of the Complement Pathway

Dr. de Castro: Thank you, Dr. Patel. That was wonderful. I'm going to now cover the newer agents that are coming out in treatment of PNH, which has really changed the field and made things very exciting.

PNH Historical Treatments

- Prior to complement inhibition, treatment was primarily supportive in nature
- For hemolysis
  - Transfusion support if needed
  - Steroids (chronic therapy controversial)
- For bone marrow failure
  - Immunosuppressive therapy
  - Bone marrow transplant
- For thrombosis
  - Anticoagulation
  - Bone marrow transplant

Prior to the era of complement inhibition, treatment was primarily supportive in nature.

For hemolytic episodes, we used to use transfusion support if needed.

And while controversial, we did use steroids to shorten the hemolytic episodes, but chronic therapy with steroids obviously has long-term side effects.

For patients who had bone marrow failure, if it was severe enough, we would try immunosuppressive therapy, much similar to what we do for aplastic anemia.

And in those cases that failed that and still had severe cytopenias, we could consider bone marrow transplant.

For patients who had thrombotic episodes, we would obviously put them on anticoagulants. The problem with that is these patients still tend to have future thrombotic episodes.

And so, this was prior to the area of complement inhibition, an indication for bone marrow transplantation, although this was always difficult.

PNH: Emerging Therapies

- **Complement inhibition FDA Approved**
  - Eculizumab or ravulizumab
  - Pegcetacoplan
  - Iptacopan
- **In clinical trials**
  - Crovalimab
  - Pozelimab + cemdisiran
  - Zilucoplan
  - Danicopan (+ C5 inhibitor)
  - Vermicopan
  - OMS906
  - KP104
- **Supportive care remains important**
- **Role of prophylactic anticoagulation very unclear**
- **Allogeneic HCT has a very limited role**
- **Treatment goals**
  - Correct anemia[b]
  - Reduce fatigue[a]
  - Reduce risk of thrombosis, pulmonary hypertension, renal damage[c,d]

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

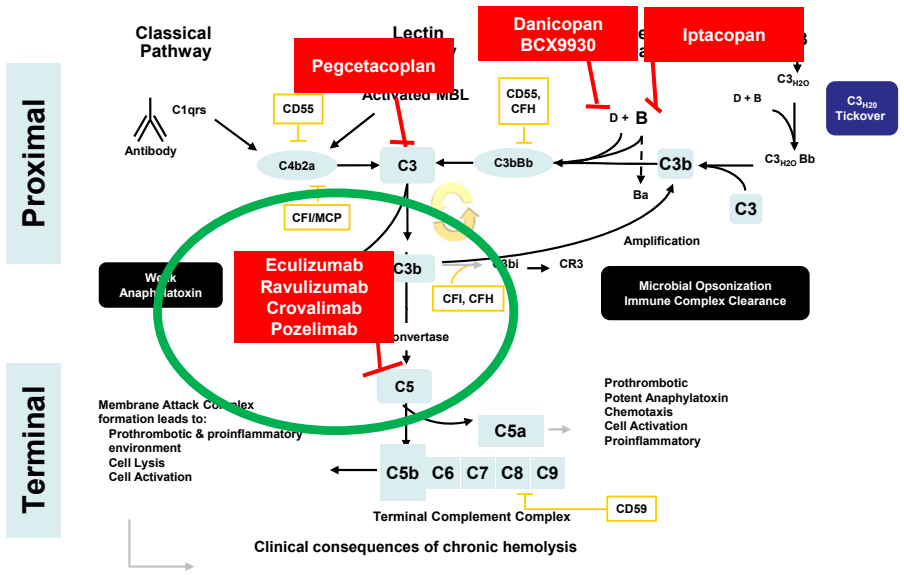
Bhumika already covered that we have four drugs now approved, FDA approved for the treatment of PNH and there are a bunch, as I've listed here, that are in clinical trials, some of which may get approval in the near future.

Supportive care is always an important part of everything we do, including transfusion support.

The role of using prophylactic anticoagulants is still very unclear. If you do have a thrombotic episode though, we do recommend putting patients on anticoagulants.

And allogeneic hematopoietic stem cell transplant has a very limited role in the age of these new complement inhibitors.

Complement Activation: Current and Emerging Targets



Figueroa 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

So, Bhumika covered the complement pathway, and there are multiple points that we can attack the complement pathway now.

C5 was the initial point that was picked, in part because it was felt that this would be the safest point to inhibit complement, as kids that are congenitally deficient in C5 only get meningococcal infections. Kids who are deficient in the proximal pathway, are much more immunocompromised and get all sorts of infections, especially encapsulated organisms.

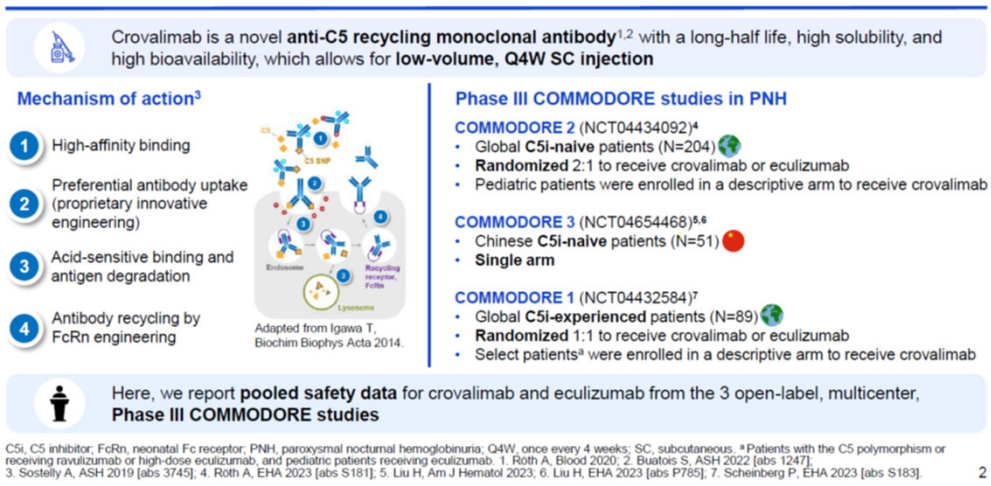
Newer C5 Inhibitors

- Crovalimab
- Pozelimab + cedisiran
- Zilucoplan
- KP104

We have some newer C5 inhibitors that are in clinical trials. These include drugs such as crovalimab, pozelimab plus cedisiran, which is a silencing RNA molecule, and zilucoplan. There's also an antibody called KP104, which is dual function in that it has a factor H portion on the terminal portion of the antibody. And by linking these two, we get inhibition both of the proximal and terminal components of complement.

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.



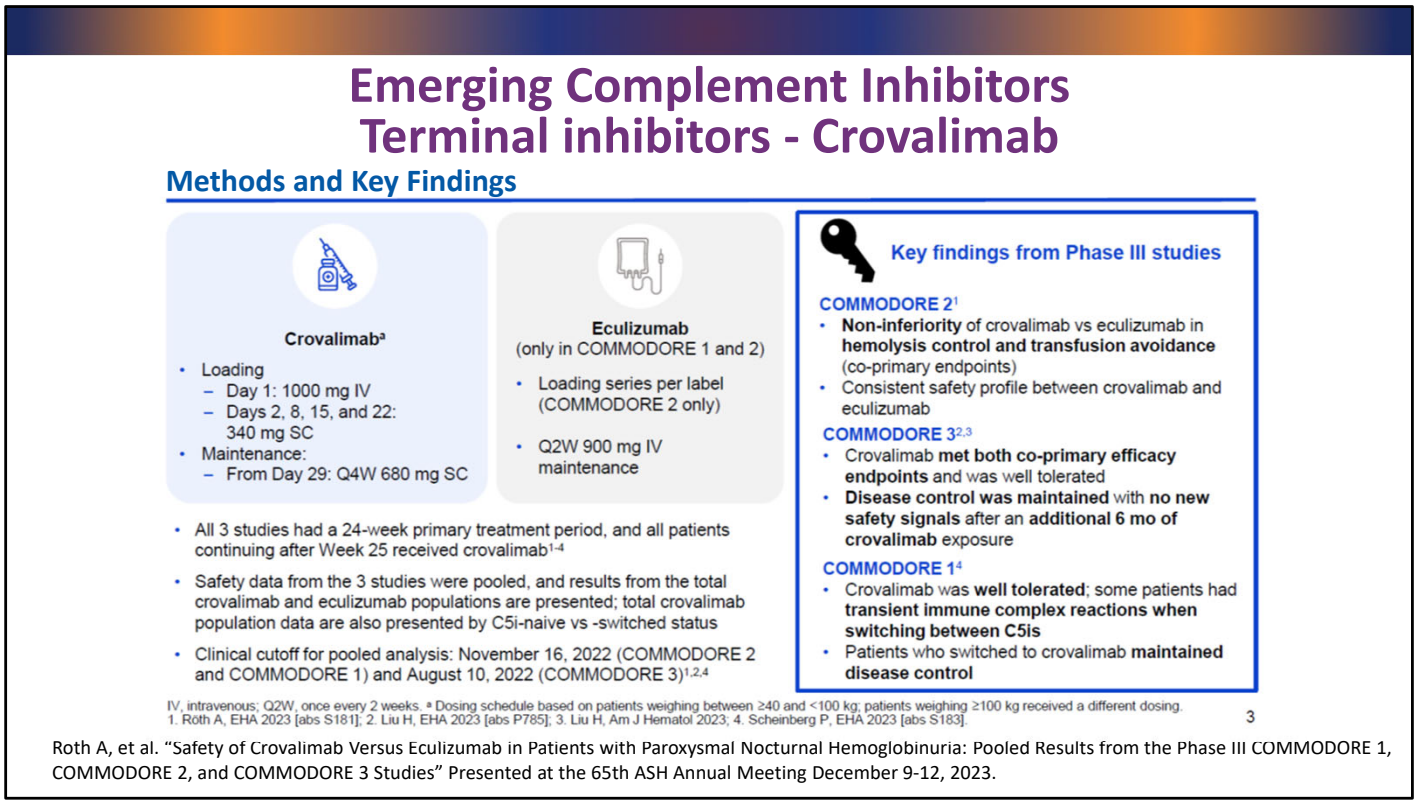
Roth, et al. “Safety of Crovalimab Versus Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria: Pooled Results from the Phase III COMMODORE 1, COMMODORE 2, and COMMODORE 3 Studies” Presented at the 65th ASH Annual Meeting December 9-12, 2023.

I'll cover these just briefly as a lot of data was presented at the recent ASH meeting. Crovalimab is an engineered antibody that was using the SMART technology.

Using this, it is in the circulation and recirculates, so it has a much longer half-life, and you can give low doses or low volumes subcutaneously at home. So, the current recommendation for this drug is to give it subcutaneously every four weeks.

It is a high-affinity binding antibody. It has preferential uptake, antibody uptake, which is innovative, and it is an acid-sensitive binding and antigen degradation. So, once it is in the circulation, it recirculates through the system.

Three phase three studies have been done using this antibody, and they're shown here. Two of them are in C5 inhibitor-naive patients, and one of them is a randomized study comparing it to eculizumab in patients who have a suboptimal response.



Roth A, et al. "Safety of Crovalimab Versus Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria: Pooled Results from the Phase III COMMODORE 1, COMMODORE 2, and COMMODORE 3 Studies" Presented at the 65th ASH Annual Meeting December 9-12, 2023.

You see here the loading doses that were given in the studies and the key findings were that this antibody is clearly non-inferior to eculizumab and controls hemolysis very well and also leads to transfusion avoidance in these patients. It is also very effective in complement-naive patients.

Emerging Complement Inhibitors
Terminal inhibitors - Crovalimab

Efficacy Across Phase III COMMODORE Studies

	C5i naive			Switched from a C5i to crovalimab	
	COMMODORE 2[1]		COMMODORE 3[2]	COMMODORE 1[3]	
	Crovalimab (n=134)	Eculizumab (n=69)	Crovalimab (n=51)	Crovalimab (n=39)	Eculizumab (n=37)
Hemolysis control (central LDH ≤1.5×ULN), mean	**79.3%**	**79.0%**	**78.7%**	**92.9%**	**93.7%**
Odds ratio[a] (95% CI)	1.0 (0.6, 1.8); **non-inferior**		NA	0.9 (0.3, 2.8)	
Transfusion avoidance	**65.7%**	**68.1%**	**51.0%**	**79.5%**	**78.4%**
Difference in proportion (95% CI)	−2.8 (−15.7, 11.1); **non-inferior**		51.0 (34.3, 65.1)[b]	1.8 (−16.7, 19.9)	
Patients with breakthrough hemolysis	**10.4%**	**14.5%**	**3.9%**	**10.3%**	**13.5%**
Difference in proportion (95% CI)	−3.9 (−14.8, 5.3); **non-inferior**		NA	−3.5 (−19.2, 11.7)	
Patients with hemoglobin stabilization	**63.4%**	**60.9%**	**51.0%**	**59.0%**	**70.3%**
Difference in proportion (95% CI)	2.2 (−11.4, 16.3); **non-inferior**		NA	−10.8 (−30.8, 10.4)[c]	
Mean change from baseline in FACIT-Fatigue	n=128 7.8[d]	n=66 5.2[d]	n=48 8.8[e]	n=38 1.1[d]	n=32 −2.6[d]
Difference in adjusted means (95% CI)	2.6 (0.7, 4.6); **descriptive**		NA	3.7 (0.1, 7.4)	

[a] Odds ratio >1 favors crovalimab. [b] Based on intrapatient comparison of transfusion avoidance between prescreening vs primary treatment period. [c] Driven by a difference of only 3 patients between arms. [d] From baseline through Week 25. [e] From baseline through Week 17; 95% CI: 6.0, 11.6.
1. Roth A, EHA 2023 [abs S181]; 2. Liu H, Am J Hematol 2023; 3. Scheinberg P, EHA 2023 [abs S183].

6

Roth A, et al. "Safety of Crovalimab Versus Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria: Pooled Results from the Phase III COMMODORE 1, COMMODORE 2, and COMMODORE 3 Studies" Presented at the 65th ASH Annual Meeting December 9-12, 2023.

You see here from this presentation at ASH, the efficacy amongst the phase three studies are shown here.

Hemolysis control was very comparable to eculizumab and ranged anywhere from 75 to 92%.

There was a high incidence of transfusion avoidance in these patients.

There was still an instance of breakthrough hemolysis in these patients. So, any complement after any event can lead to a breakthrough hemolytic episode.

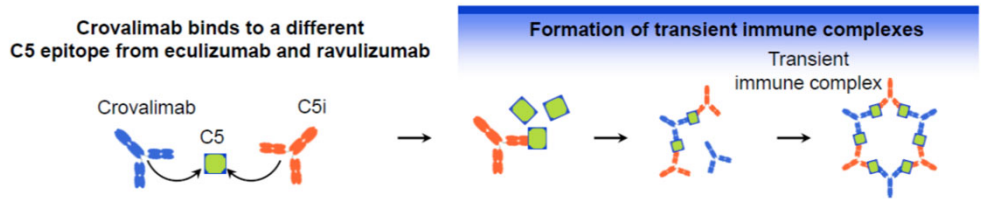
A good number of these patients had what's called hemoglobin stabilization, that is they didn't fall and didn't need transfusions.

And fatigue scores improved markedly in patients on this antibody. So, it will likely be taken up by the FDA in the near future for possible approval.

Emerging Complement Inhibitors
Terminal inhibitors - Crovalimab

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[1]
- 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 resolved transient immune complex reactions was 1.9 weeks (0.4–34.1)[2,3]; some clinical symptoms were ongoing at clinical cutoff

1. Nishimura J, Clin Pharmacol Ther 2023; 2. Roth A, EHA 2023 [abs S181]; 3. Scheinberg P, EHA 2023 [abs S183].

Roth A, et al. "Safety of Crovalimab Versus Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria: Pooled Results from the Phase III COMMODORE 1, COMMODORE 2, and COMMODORE 3 Studies" Presented at the 65th ASH Annual Meeting December 9-12, 2023.

One thing we did learn from using crovalimab is that these patients were already on a C5 inhibitor such as eculizumab. And by giving an antibody that binds to a different epitope on C5, you can lead to this formation of multimers, also known as transient immune complexes. And these can lead to a transient immune complex reaction, as we call it. It is usually self-limited and goes away in around two weeks. And the primary clinical presentation of this was more rash than anything else. There did not appear to be any anaphylaxis or any sort of kidney damage caused by these transient immune complexes.

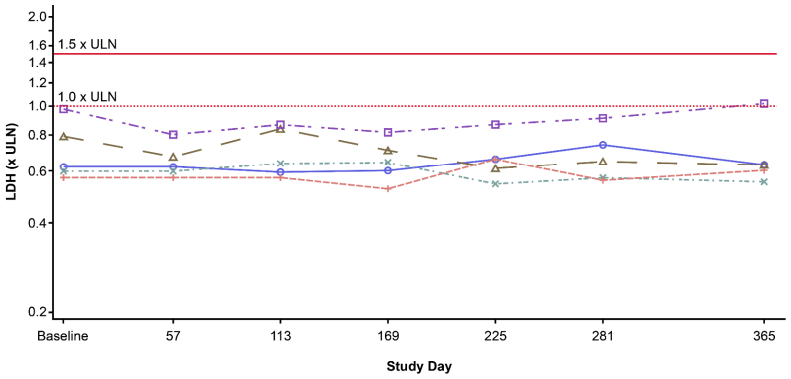
Emerging Complement Inhibitors Terminal Inhibitors: Pozelimab + Cemdisiran

- Pozelimab is an anti-C5 monoclonal antibody
- Cemdisiran is an N-acetylgalactosamine-conjugated small interfering RNA that suppresses liver production of C5
- Combination of pozelimab + cemdisiran is in Phase II and Phase III trials

2716 52-Week Open-Label Extension Data from a Phase 2 Study Evaluating the Safety and Efficacy of Pozelimab and Cemdisiran Combination Therapy in Patients with Paroxysmal Nocturnal Hemoglobinuria Who Switched from Eculizumab

- **N=5**
- **1 of the 5 experienced BTH during a CAC**

Figure 1. Spaghetti plot of LDH values (x ULN) by visit from the OLEP baseline to Day 365 in the OLEP[a]



[a]Study days for the OLEP have been renumbered starting with Day 1 at the time of the OLEP start.
LDH results were based on central laboratory values assessed at scheduled time points.
LDH, lactate dehydrogenase; OLEP, open-label extension period; ULN, upper limit of normal.

Kelly R, et al. Poster presentation at ASH, December 2023. San DIego, CA.

I will mention now pozelimab plus cemdisiran.

Pozelimab, again, is another anti-C5 monoclonal antibody with a different epitope.

And cemdisiran is this small interfering RNA that suppresses liver production of C5. And the hope is by having less production of C5, along with the antibody there, is that you will have less episodes of breakthrough hemolysis.

This combination is now in phase two and phase three trials.

And I show you here just the presentation of the phase two data at the ASH meeting in December where patients received this drug.

Now, you'll note this is a small study. The N is only five. And despite our hope of seeing less breakthrough hemolysis, they've already had one episode during a complemented activating event.

So, we will have to see if this combination of drugs really does work better in terms of preventing breakthrough hemolysis.

Emerging Complement Inhibitors
Terminal Inhibitors - Zilucoplan

- Zilucoplan is a cyclic peptide that binds to C5 and inhibits its cleavage
- Administered subcutaneously once a day
- FDA approved for the treatment of myasthenia gravis
- Early trials in PNH looked promising

I will just briefly mention zilucoplan. Zilucoplan is a cyclic peptide that binds C5 and inhibits its cleavage. It is given subcutaneously once a day. It is now FDA approved for the treatment of myasthenia gravis.

There were some early trials in PNH which looked promising, but I think the company's decided not to take this further in terms of PNH.

Limits of Terminal (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

[a]Subías Hidalgo M, et al. *Immunobiology*. 2017;222:363-371; [b]Hill A, et al. *Haematologica*. 2010;95:567-573.

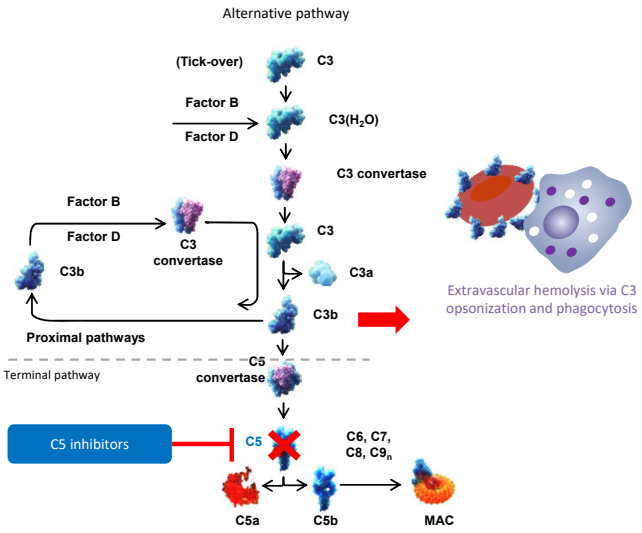
Now, as was mentioned, there are some limits to C5 targeting therapy that we learned about as we did these studies and followed these patients more long-term. The big issue is that the responses are somewhat heterogeneous in that almost all the patients have coding of the red cells with C3 fragments, as was mentioned and almost, a lot of patients are now showing low levels of continued hemolysis.

Some of these can be quite marked, and about 25 to 35% of patients may still require red cell transfusions.

So, we call these patients suboptimal responders. Anybody who is still markedly anemic and fatigued, or anybody who still needs transfusion, is a suboptimal responder to a C5 therapy. And we think that the majority of these cases are caused, again, by this extravascular hemolysis.

So, as these C3 fragments are on the surface of the PNH red cells, they are taken up by the reticulo-endothelial system and this leads to extravascular hemolysis. And the degrees of this are different in different patients.

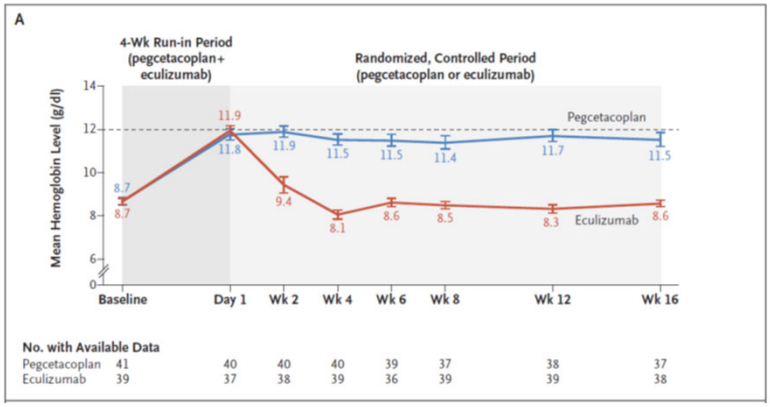
Proximal Complement Inhibitors



So, this led to a look at proximal complement inhibition. Again, the proximal complement inhibitors are there to block C3 and earlier parts of the complement cascade, as shown in this cartoon. And by doing that, we hope that we will not see this extravascular hemolysis from the C3 coding on PNH red cells. And we've targeted initially C3, factor B, and factor D.

Proximal Complement Inhibitors
Pegcetacoplan

- Pegcetacoplan is a pegylated pentadecapeptide that targets C3; administered by SQ pump twice a week
- Recently an OBI was approved
- 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
- FDA approved May 2021



Hillmen P, et al. Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria. *N Engl J Med*. 2021;384:1028-1037.

The first of these was the C3 inhibitor called pegcetacoplan, which is a pegylated pentadecapeptide. It is given subcutaneously by a pump twice a week. There is now an on-body injector that was approved that makes it a little easier for patients in that they just pop this right onto their skin and it gives it automatically. The PEGASUS trial was the phase three randomized multi-center trial. That was the registry trial, and it compared pegcetacoplan to eculizumab in PNH patients that had a hemoglobin less than 10.5, that is probably suboptimal responders. The primary endpoint was the change in hemoglobin at week 16. And you see in this bar graph on the right here that we gave the patients both drugs for four weeks so there wouldn't be any hemolytic episodes during the time that we were transitioning patients from one drug to the other. And then they were randomized to either pegcetacoplan alone or eculizumab alone. And pegcetacoplan was clearly superior in raising the hemoglobin levels by week 16. Other outcomes that were looked at were all non-inferior outcomes. Again, pegcetacoplan looked better in almost all of these in terms of the clinical outcomes.

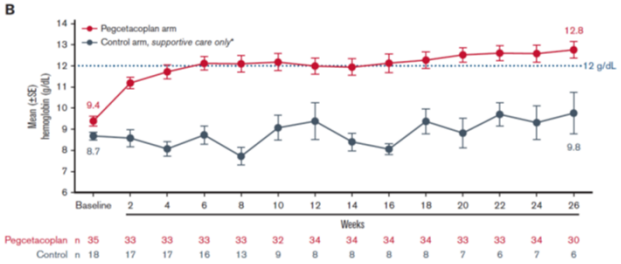
The side effects from pegcetacoplan are fairly mild and tolerable. These include injection reactions at the site of injection, since it is a sub-Q drug, diarrhea, which was usually mild and self-limited, and there were some cases of breakthrough hemolysis.

Now the concern is, as we treated patients with these C3 inhibitors, we blocked both intravascular and extravascular hemolysis. And by doing so, there was a larger proportion of PNH red cells in the circulation. And if a complement activating event came along that increased the levels of C3, you could overwhelm this drug. And the real concern, which has really never been proven is that these episodes of hemolysis would be more brisk and more severe.

A

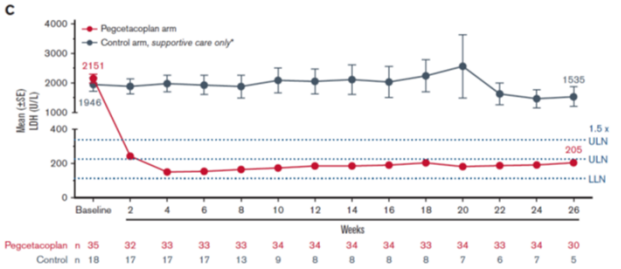
Coprimary end points	Pegcetacoplan arm (n = 35)	Control arm *supportive care only** (n = 18)	Difference 95% CI	*P* value
Hemoglobin stabilization, n (%)†	30 (85.7)	0 (0)	73.1 (57.2, 89.0)	<.0001
CFB in LDH levels, LS mean (SE), U/L‡	−1870.5 (101.0)	−400.1 (313.0)	−1470.4 (−2113.4, −827.3)	<.0001

B



Pegcetacoplan n	35	33	33	33	33	32	34	34	34	34	33	33	34	30
Control n	18	17	17	16	13	9	8	8	8	8	7	6	7	6

C



Pegcetacoplan n	35	32	33	33	33	34	34	34	34	33	34	33	34	30
Control n	18	17	17	17	13	9	8	8	8	8	7	6	7	5

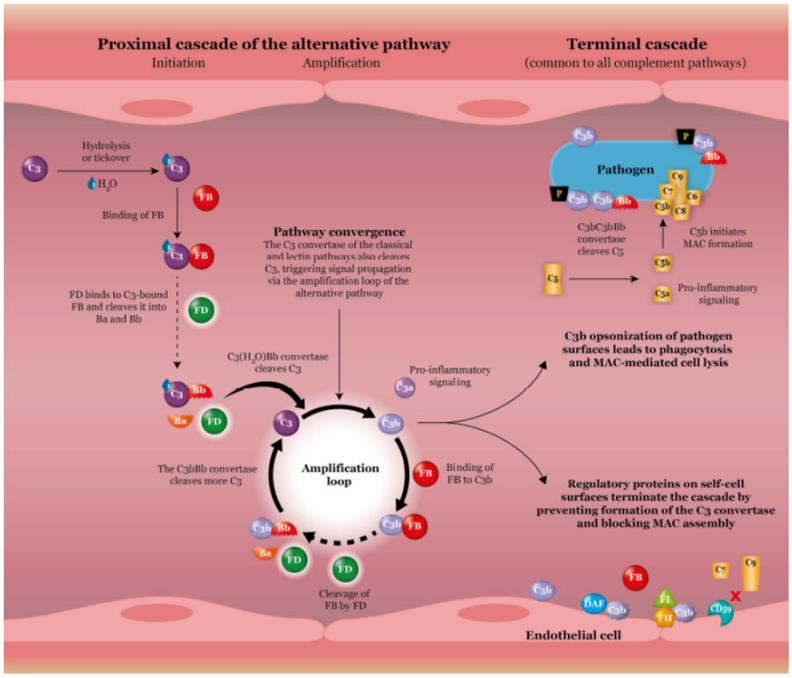
Proximal Complement Inhibitors Pegcetacoplan – PRINCE Trial

- Pegcetacoplan controls hemolysis in complement inhibitor-naïve patients with paroxysmal nocturnal hemoglobinuria

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

The PRINCE trial looked at pegcetacoplan in complement inhibitor-naive patients. This was done outside of the US. And again, you see the same rise in hemoglobin as compared to standard of care in patients with PNH. So, the FDA approved this drug for both naive patients and for patients if they wanted to switch from a C5 inhibitor.

Factors B and D as Targets

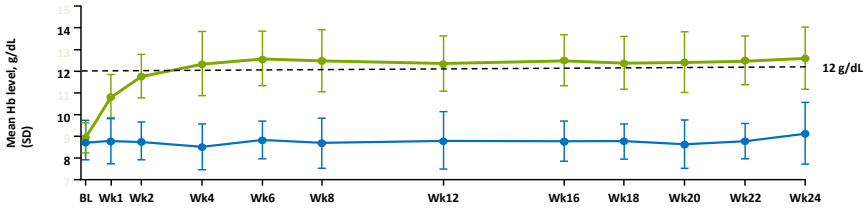


Barratt J, Weitz I. "Complement Factor D as a Strategic Target for Regulating the Alternative Complement Pathway" *Frontiers Immunol. 2021;*1-15.

I'll change gears now to factor B and factor D as targets. Factor B and factor D are cofactors for the C3 convertase and are necessary for C3 activation and then leading to further activation of the complement system. So, if we inhibit either factor B or factor D, you can get blockage again of that amplification loop and of C3 convertase.

Proximal Complement Inhibitors - Iptacopan

- Iptacopan is a first-in-class, oral, selective factor B inhibitor
- 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 ≥2 g/dL in the absence of RBC transfusions and hematological response defined as Hb ≥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 ≥12 g/dL, associated with a higher rate of transfusion independence and reduced patient-reported fatigue, compared with SoC
- Approved by FDA Dec 2023



Mean Hb (SD) over time during the 24-week randomized treatment period‡

de Latour RP, et al. Presented as an oral abstract at the 64th ASH annual meeting, New Orleans, Dec 2022.

Iptacopan is the first in class oral. It is given orally, as the others have all been IV or sub-Q, and it is a factor B inhibitor.

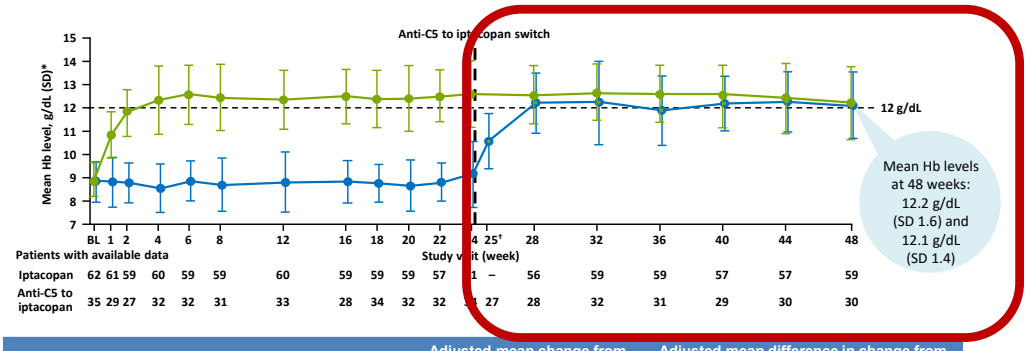
There were two trials that looked at this, the APPLY trial and the APPOINT trial. APPLY is the open all-randomized multi-center phase three trial in patients with residual anemia, despite usually a C5 inhibitor.

There were two primary endpoints, again, looking at the hematological response as described as an increase from baseline to greater than two grams per deciliter without red cell transfusions or as a response defined as a hemoglobin rising above 12 grams per deciliter in the absence of transfusions.

And when we looked at these, the APPLY trial, oral iptacopan monotherapy had significant improvement in achieving a meaningful hemoglobin increase in these patients without any transfusions. And there was a reduction in fatigue compared to a standard of care.

And as we mentioned, this drug was just approved in December of 2023. It is oral, which is very attractive to patients. One of the concerns is what happens if the patient is non-compliant, as it does have a short half-life and has to be given twice a day, and that concern still exists. So, we would not recommend this in a patient that you know will have issues with non-compliance.

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



	Treatment arm	Adjusted mean change from baseline at Week 48 (95% CI)	Adjusted mean difference in change from baseline (95% CI): Week 48 vs Week 24
Change from baseline‡ in Hb level (g/dL)§	Iptacopan	**+3.35** (3.04,‖ 3.67‖)	**−0.41** (−0.80, −0.01)
	Anti-C5 to iptacopan	**+3.36** (2.94,‖ 3.79)	**+3.02** (2.49,‖ 3.56)

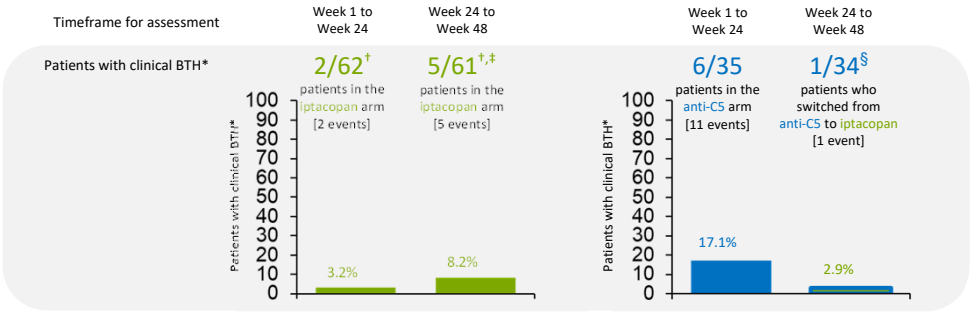
*Includes post-transfusion data; †At Week 25, Hb data were only available for one patient in the iptacopan arm (Hb level: 13.9 g/dL); this was not a scheduled visit in the protocol for the iptacopan arm but was for the anti-C5-to-iptacopan arm. The value in the iptacopan arm is not plotted on the graph as one patient cannot be representative of the whole treatment group; ‡Change from baseline was analyzed using a mixed model of repeated measures that adjusted for covariates, including baseline Hb; §Analysis includes all central laboratory Hb data, including post-transfusion data; ‖The data in this presentation are derived from the final APPLY-PNH dataset at trial completion. Following the submission of this ASH 2023 abstract, it was confirmed that another RBC transfusion was administered to a patient in the iptacopan arm during the 24-week randomized treatment period; therefore, there are minor numerical differences between this presentation and its published abstract. BL, baseline; CI, confidence interval

Oral presentation at the 65th ASH Annual Meeting, San Diego, CA and virtually on 9-12 December 2023.

You see here the presentation from the ASH meeting where the patients who were on the iptacopan arm and those that were on the eculizumab arm who were allowed then to cross over and get iptacopan after 24 weeks.

And all of them had this rise in hemoglobin to above 12, which was very impressive or close to all of them had this rise in hemoglobin to above 12.

Clinical BTH Events Were Infrequent With Iptacopan



- 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[1]

*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;
†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; ‡Of 62 patients in the iptacopan arm, 61 entered the extension period; §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. Peffault de Latour R *et al. Blood* 2023;142:suppl1:1338 (ASH 2023 poster presentation on Saturday 9 December at 17:30–19:30 PST [session 508, bone marrow failure: acquired])

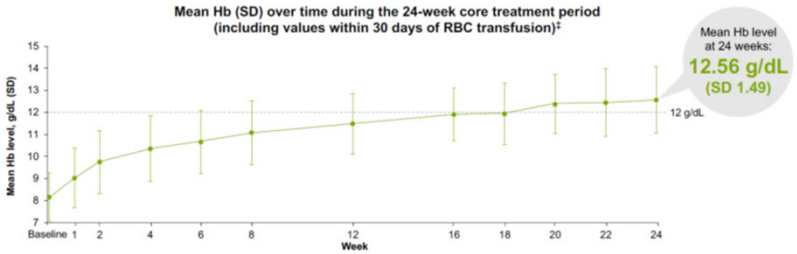
Oral presentation at the 65th ASH Annual Meeting, San Diego, CA and virtually on 9-12 December 2023.

There were still some breakthrough events that occurred with iptacopan. So, we still haven't found the perfect drug that's going to prevent breakthrough hemolysis if there is a complement-activating event. We're still looking for that and that may be future drugs, but we are still hoping that these drugs are clearly reducing this incidence of breakthrough hemolysis.

The incidence of estimated incidence of breakthrough hemolysis with iptacopan is about 0.11.

Iptacopan (LNP023): Oral Factor B Inhibitor

- APPOINT 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



49th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT), 2023.

The APPOINT study was a phase three multi-center study done again outside of the US in patients who were treatment-naive.

And again, you see that same rise in hemoglobin level in patients who have never seen a complement inhibitor.

So, this drug is very effective whether you've been on a C5 inhibitor or you've not been on one. And at least in this multi-center study, there were no episodes of breakthrough hemolysis.

Proximal Complement Inhibitors - Danicopan

- Danicopan is a first-in-class oral Factor D inhibitor
- ALPHA is a phase 3 randomized, multicenter trial comparing danicopan versus placebo as an add on to standard of care C5 inhibitor (eculizumab or ravulizumab) in PNH patients with evidence of EVH on C5 inhibitor therapy
- Primary endpoint was the change in hemoglobin from baseline to week 12
- All key secondary endpoints (Hgb>12, LDH, Facit-Fatigue) showed danicopan to be superior as an add on compared to placebo

So, we'll talk briefly about danicopan. Danicopan is an oral factor D inhibitor. So again, one of the cofactors for activating C3.

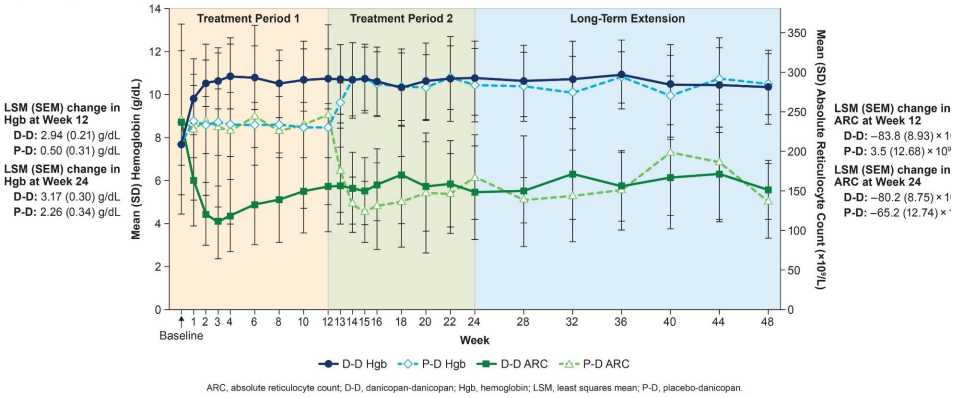
It is being tried in patients compared to eculizumab, but it's being given in combination with eculizumab or ravulizumab in PNH patients who have extravascular hemolysis ongoing.

The primary endpoint of this study was a change in hemoglobin from baseline to week 12 and all key secondary endpoints were found to be improved, including a hemoglobin greater than 12, LDH, fast fatigue scores. So, this drug again looks very promising, but again, it has to be given in combination with a C5 inhibitor, so that even though it's oral, patients will still need to get either IV or sub-Q C5 therapy.

Proximal Complement Inhibitors - Danicopan

- Danicopan as add-on to Rav or Ecu significantly improves Hgb and ARC levels and reduces the need for transfusion by addressing cs-EVH while maintaining control of IVH through 48 wks of treatment
- Danicopan demonstrated a favorable benefit-risk profile with no deaths, meningococcal infections, or discontinuations due to hemolysis

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



ARC, absolute reticulocyte count; D-D, danicopan-danicopan; Hgb, hemoglobin; LSM, least squares mean; P-D, placebo-danicopan.

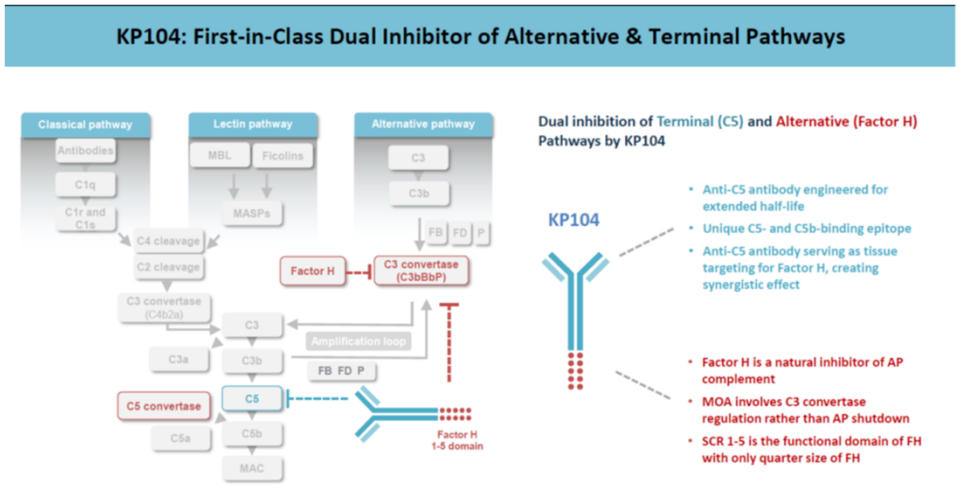
Kulasekararaj A, et al. "Danicopan As Add-on Therapy to Ravulizumab or Eculizumab Versus Placebo in Patients with Paroxysmal Nocturnal Hemoglobinuria and Clinically Significant Extravascular Hemolysis: Phase 3 Long-Term Data" Oral Presentation at the 65th ASH Annual Meeting, San Diego, CA and virtually on 9-12 December, 2023.

You see here again from the ASH presentation, this now following patients out for 48 weeks, that even on the long-term extension study this response in terms of hemoglobin levels was maintained for 48 weeks on patients with danicopan and a C5 inhibitor.

There were no deaths, there were no meningococcal infections, there were no discontinuations due to hemolysis. Again, there were, unfortunately, some breakthrough events even on these drugs, even though we're blocking both C, the proximal and terminal portions of complement.

Additional Complement Inhibitors Under Investigation

- KP104
  - Anti-C5 antibody linked to a portion of Factor H
  - Inhibits both proximal and terminal complement



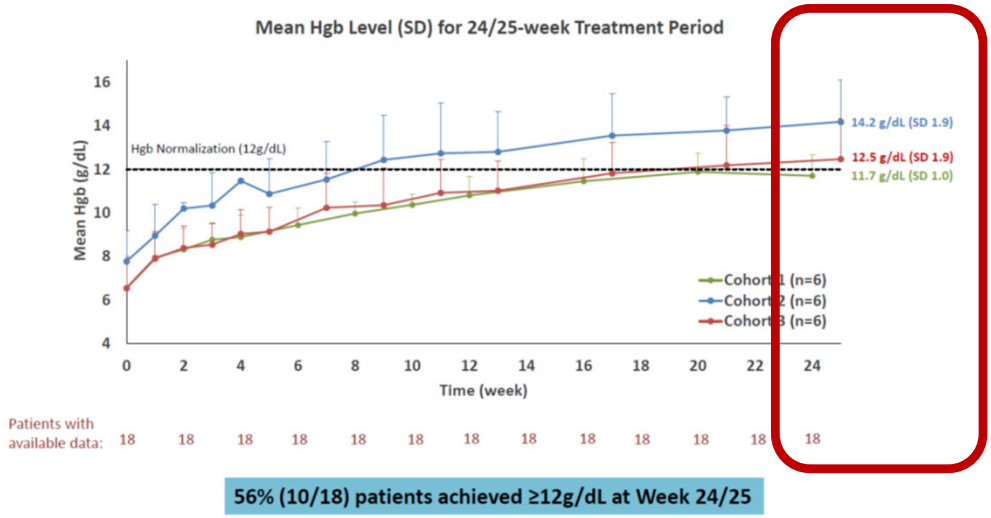
Zhang F, et al. "KP104, a bifunctional C5 antibody / Factor H fusion protein, effectively controls both intravascular and extravascular hemolysis: 24/25-week results from an ongoing Phase 2 study in Complement-inhibitor naïve patients with PNH" Oral Presentation at the 65th ASH Annual Meeting, San Diego, CA and virtually on 9-12 December, 2023.

I'll briefly mention two drugs that are under investigation, although there are probably others that are also under investigation.

KP104, as I mentioned, is this anti-C5 antibody which they've engineered to link a portion of factor H, which is an inhibitor of the proximal pathway.

And so, this drug blocks both proximal and terminal complement pathways, and it will be a single drug given intravenously. And this was presented again at the ASH meeting.

Additional Complement Inhibitors Under Investigation



56% (10/18) patients achieved ≥12g/dL at Week 24/25

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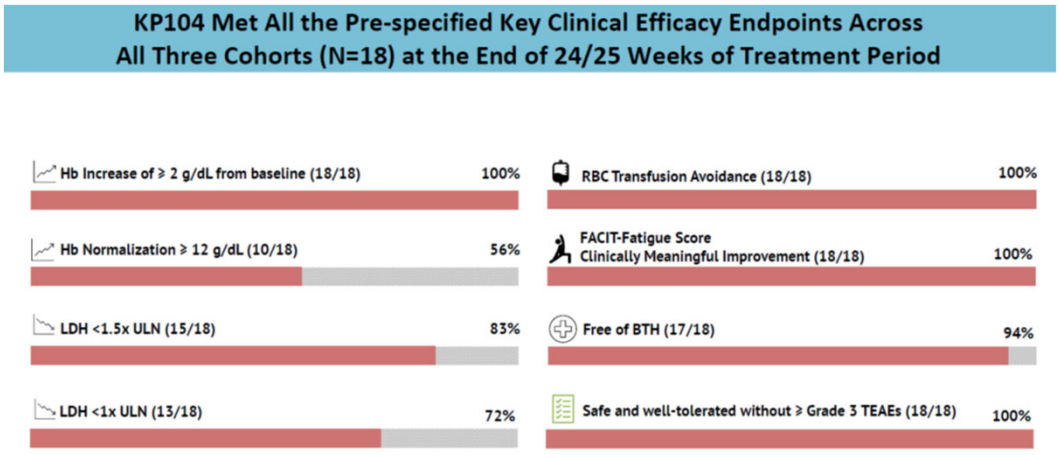
And you see here the hemoglobin levels when they got to the middle cohort showed hemoglobin levels above 14 by week 24. So, maybe we're seeing even more improvement in terms of raising the hemoglobin to near normal levels.

Additional Complement Inhibitors Under Investigation



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All the other key clinical endpoints looking at this drug from hemoglobin increases in red cell transfusion avoidance was 100%.

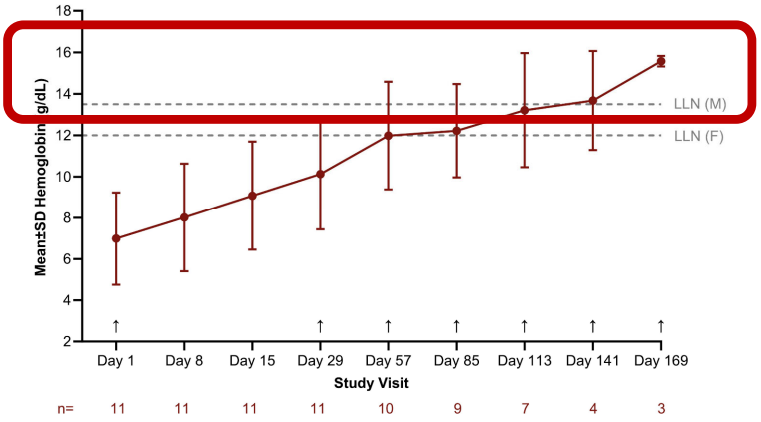
So, LDH levels fell in the vast majority of these patients to less than 1.5 the normal and in some even to less than one times the normal level.

94% avoided breakthrough hemolysis.

Additional Complement Inhibitors Under Investigation

- OMS906
  - Monoclonal antibody targeting MASP-3 which is an activator of the Factor D (alternative pathway)

Figure 1. Mean (±SD) Hemoglobin by Study Visit in Patients Receiving Low-Dose SC OMS906



Black arrows indicate OMS906 administration following laboratory marker collection. F, female; LLN, lower limit of normal; M, male; SC, subcutaneous; SD, standard deviation.

Karnabeda O, "OMS906, a Novel Alternative Pathway MASP-3 Inhibitor, Normalizes Hemoglobin Levels and Increases Clone Size in Treatment-Naïve PNH Patients" Oral Presentation at the 65th ASH Annual Meeting, San Diego, CA and virtually on 9-12 December, 2023.

The other agent I'll just mention is this OMS906 agent, again presented at the ASH meeting. This is a monoclonal antibody targeting the MASP-3, which is part of the lectin binding protein activation, which we never thought of would have been involved in PNH, but it turns out that MASP-3 is an activator converting pro-factor D into the factor form of factor D. And by doing, inhibiting MASP-3, there is no increase in MASP-3 as part of any sort of inflammatory pathway. And so, you can get complete blockage of factor D by blocking at MASP-3.

And you see here in this early study that was done, again, hemoglobin levels rising above 14 to 16 in patients on this agent. So, perhaps this will be a promising agent also.

Complement Inhibition for PNH: Which One Should We Use?

- Now have 4 FDA approved complement inhibitors for PNH, more on the way
- Some target terminal pathway, others the proximal pathway
- One is oral, others given IV or subQ at various intervals
- Some may be better at achieving a higher hemoglobin level
- Breakthrough hemolysis is still an issue
- Other considerations: side effects, rate of thrombosis, cost and insurance coverage, compliance

So, we have complement inhibition for PNH, and now we have four FDA-approved agents. Which one should we use? And there are probably going to be more agents on the way. Some target the terminal pathway, others are targeting the proximal pathway. Some are actually going to target both of the pathways. At least one of the FDA-approved drugs is oral. Others are given intravenously and sub-Q at various intervals. Some, as I just showed you, may be better at achieving a higher hemoglobin level.

Breakthrough hemolysis is still an issue; as you get better and better, you have a higher percentage of circulating PNH cells that are susceptible to any complement activation.

And we have to consider all the side effects and all the other problems listed here in terms of which patients should get which drug. There's going to be a patient preference issue. Patients may want to be on an oral drug. Others may say, no, I want the IV drug given every eight weeks, so that'll be interesting to see how that plays out.

And there's going to be insurance issues in terms of cost and which ones the insurance companies prefer as time goes on. So, we're still in an era of trying to figure out which ones are going to be best and which ones should be used. And it should probably be tailored to each individual patient with a discussion of the side effects and risks of each drug.

PNH:
Emerging Therapies 2024

Case Study

At this point, I'd like to stop and just present a case study.

Patient Case

- Patient C is a 41-year-old female who presented in Jan 1998 with shortness of breath and heavy menstrual periods. She was found to be pancytopenic
- 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

This patient is a 41-year-old female who presented in January of 1998 with shortness of breath and heavy menstrual periods. She was found to be quite pancytopenic.

A workup including all sorts of studies with a bone marrow biopsy showed aplastic anemia. And she was treated with ATG and cyclosporine, which was the standard at the time, and had complete count recovery.

She even had a bone marrow biopsy a year later that was normal cellular.

Patient Case

- She did well until 2013 when she noticed fatigue
- Labs 8/22/13 showed WBC 3.4, Hgb 5.7, HCT 17.5, plt 142 K
- 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 9/12/2013

She did well for many, many years until 2013 when she noticed increasing fatigue.

And when she went to her PCP, she had a hemoglobin of 5.7 with a platelet count and a white cell count that were just slightly low.

She had a bone marrow biopsy done, which was normal cellular, and she had erythroid hyperplasia.

She had a normal FISH and normal cytogenetics.

And the physician there was smart enough to run a test for PNH, and her peripheral blood flow cytometry test was positive.

She was started on eculizumab in 2013, because it was the only drug available at that time.

Patient Case

- CBC 1/13/2014 showed WBC 3.8, Hgb 9.4, HCT 28, plt 188K. LDH 268
- Evaluated for bone marrow transplant, not felt to be a candidate
- Still didn't feel great, required transfusions q 3 months despite increasing dose of eculizumab to 1200 mg q 2 weeks
- June 2017: WBC 5.8, Hgb 7.6, HCT 23, plt 247K. LDH 263. T bili 7.1, normal transaminases. Retic 20.60%, DAT weekly positive for complement

By January of 2014, she had a white count of 3.8, a hemoglobin of 9.4, platelet count of 188, and an LDH that was lower but not quite normal at 268.

She was referred for a possible bone marrow transplant but not felt to be a candidate.

And then she continued to go on not feeling very well and requiring transfusion of the average about every three months, despite increasing the dose of eculizumab up to 1200 milligrams every two weeks.

In 2017, she was referred to me. You see her hemoglobin was 7.6 with normal white cells and platelets. Her LDH still was in the slightly elevated range at 263. She had a high bilirubin, normal transaminases, a very high reticulocyte percentage. Her Coombs test was weekly positive for complement.

So, I'm going to ask Dr. Patel to comment on her labs and what she would like to see if this patient really is not responding well to her therapy.

Dr. Patel: Thank you, Dr. DeCastro. I think this is a great case that we commonly see in clinical practice. I think, number one, you stressed an important point, the importance of monitoring for a PNH clone, especially in aplastic anemia, and the evolution of it in how you continue to monitor aplastics with a PNH clone and making sure they don't have evolution of it and making sure they're managed properly.

Some of the highlights here for me as a clinician that I would, that I'm a little bit worried about is this despite optimal C5 therapy, she has ongoing anemia, right? And she's still requiring transfusions. So, some of these were the flags that as you were discussing the case that stood out to me. Her white blood cells and platelets look good, but definitely she still has a degree of ongoing hemolysis, intravascular hemolysis, but her weekly positive data shows that she has some with optimal C5 therapy, she has extravascular hemolysis.

So, she would be a candidate that I would think about using a proximal inhibitor to try to get her some better improvement in her anemia, so that way she can have improvement in her symptoms and her transfusion requirements. And I think that's what I would think about C3 inhibitors or potentially consider oral factor B inhibitor, depending on her clinical situation, I would consider that.

Patient Case

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- June 2017: WBC 5.8, Hgb 7.6, HCT 23, plt 247K. LDH 263. T bili 7.1, normal transaminases. Retic 20.60%, DAT weekly positive for complement
- Felt to be sub-optimal responder, likely due to C3 coating of her red cells and extravascular hemolysis

Dr. de Castro: Thank you. Yes, that's exactly what we thought at the time. We thought she was a suboptimal responder due to C3 coding of her red cells and this extravascular hemolysis that was ongoing in her.

Patient Case

- Entered onto the PEGASUS clinical trial using APL-2 (pegcetacoplan) on 4/10/2019
- Patient C continues to be followed on pegcetacoplan
- Absolutely no complaints
- WBC 5.3, Hgb 14.6, Hct 42, platelet 200. LDH 156, T bili 1.9. Normal reticulocyte count
- PNH screen shows granulocytes clone size 97%, red cells 95% clone size
- She has been on commercial product since April 2020 and continues to do very well

So, she was entered onto the PEGASUS clinical trial using APL-2, which is now known as pegcetacoplan in 2019.

She did absolutely wonderful. She was, continues to be followed on pegcetacoplan. She has no complaints. You see her hemoglobin rose to 14.6. Her LDH is normal. She has normal reticulocyte count.

And her PNH screen now shows that her red cell clone size is approximating her white cell clone size. That is the PNH cells are 95 to 97 percent.

She's been converted over to commercial products since 2020 and continues to do very well. So, this is an example of using a C3 inhibitor in somebody who's had a suboptimal response to C5 inhibition due to extravascular hemolysis.

Dr. Patel: I would agree. She seems like she's doing really well, so I think this was a great plan for her moving forward. And especially with the new infusion devices, this patient's going to do well as she moves forward.

Conclusion

- PNH is a rare and very unique, acquired disease characterized by hemolysis, cytopenias and thrombosis
- Inhibition of the complement pathway has led to marked improvements in hemolysis, quality of life and survival
- Multiple options for targeting the complement pathway at different points are now available or will be in the near future

So, in conclusion, PNH is a very rare and unique disease. It's acquired, you're not born with this. It's characterized by hemolysis, cytopenias, and thrombotic episodes.

Inhibition of the complement pathway has led to marked improvements in hemolysis, quality of life, and in data that I haven't shown you survival.

And we now have multiple options for targeting the complement pathway at different points, which are either FDA-approved or will become available hopefully in the near future.

This concludes our discussion of the evolving products and treatments available for PNH patients. Please don't forget to log in and complete your evaluation for continuing education credit. And thank you so much for your participation.