

Allegheny Health Network



**West Penn**  
Hospital

# **THE LATEST IN PNH: NEW TREATMENT OPTIONS AND DEALING WITH SIDE EFFECTS**

**Anna Koget, D.O.**

**Allegheny Health Network**

# WHAT IS PNH?

- Paroxysmal Nocturnal Hemoglobinuria
- **Acquired** disorder of stem cells
- Rare, potentially life threatening
- Spontaneous genetic mutation that causes red blood cells to be deficient in a protein, leaving them fragile
- A delayed or missed diagnosis prevents patients from receiving appropriate treatment and impacts survival



# CLINICAL PRESENTATION

- Destruction of RBC ( hemolysis)
- Blood clots ( thrombosis)
- Impaired bone marrow function
- Risk of developing other hematological malignancies such as AML ( acute myeloid leukemia)



# HISTORICAL PROSPECTIVE

- First recognized in the second half of the nineteenth century
- Paul Strübing differentiated PNH from other disorders
- He theorized that PNH red blood cells were especially sensitive to sleep-induced acidosis
- The name, paroxysmal nocturnal hemoglobinuria, was given to this disease by a Dutch physician, Ennekin, in 1928.



# EPIDEMIOLOGY

- Rare
- 1 to 10 cases per million population
- Mostly a disease of adults, although childhood cases have been reported ( median age of onset in 30's)
- The condition affects males and females alike
- PNH has been reported from almost every country in the world; there is no known ethnic or geographic distribution
- 10 year survival 65-76%



# SO, WHAT HAPPENS IN PNH?

## Red Cell Breakdown



## Who is involved?

- Good guys – CD 55, CD 59 – protect cells from the breakdown
- Bad guys – MAC (membrane attack complex) – causes cells to breakdown
- PNH cells lose an anchor that typically keeps CD 55 and CD 59 on the cell, thus losing ability to protect cells from destruction



# WHAT HAPPENS NEXT?

- The red cells leak hemoglobin into the blood
- Products from red cell breakdown filter through the kidney
- When urine is concentrated overnight during sleep, the morning urine becomes dark – “cola colored”



# WHAT ARE THE SYMPTOMS OF PNH?

- Variable 23 percent had been hospitalized and 17 percent were unable to work
- International PNH Registry that included 1610 patients; over 93 percent were symptomatic
- Fatigue – 80 percent
- Shortness of breath – 64 percent
- **Dark urine** (hemoglobin in the urine) – 62 percent
- Abdominal pain – 44 percent
- Bone marrow suppression – 44 percent
- Erectile dysfunction – 38 percent
- Chest pain – 33 percent
- **Blood clots** – 16 percent
- Kidney problems – 14 percent



## Signs and symptoms of PNH may include:

Extreme tiredness<sup>8</sup>

Low healthy red blood cell count<sup>9</sup>

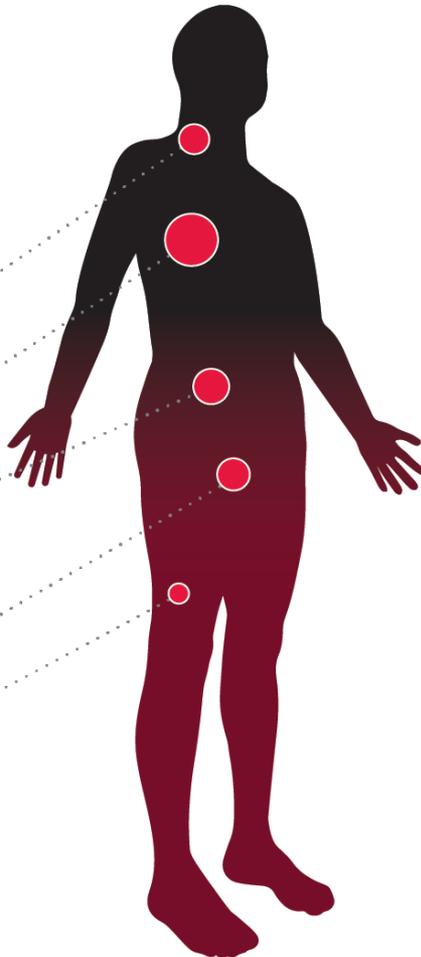
Difficulty swallowing<sup>10</sup>

Shortness of breath<sup>8</sup>

Abdominal pain<sup>8</sup>

Erectile dysfunction<sup>\*,8</sup>

Hemoglobinuria<sup>8</sup>



PNH deaths can be caused by blood clots in the veins and arteries<sup>6,7</sup>

PNH deaths can be caused by kidney failure<sup>6</sup>

Patients with PNH may suffer from pulmonary hypertension, a type of high blood pressure that can affect the arteries of the lung<sup>11</sup>

Adapted from:

Schrezenmeier H, et al. 2014. An analysis of baseline characteristics and disease burden in 856 patients enrolled in the International PNH Registry, as of June 30, 2012, and completed baseline patients' questionnaires relating to symptoms of PNH, QoL, and work.

Nishimura J, et al. 2004. An epidemiologic analysis on 385 patients with PNH from the US and Japan.

Weitz I, et al. 2013. A cross-sectional validation study of self-reported outcomes in 29 patients with PNH.



# QUALITY OF LIFE IMPAIRMENT

- Pain reported by 50% of patients
- Abdominal pain reported by 47% of patients
- Fatigue reported by 76% of patients – described as severe or debilitating
- Clinical symptoms of pulmonary hypertension were prominent ( 48%) – shortness of breath 37%, chest pain 13%



# COMPLICATIONS OF PNH

- Clotting
- Low blood counts
- Association with other hematological disorders such as aplastic anemia and myelodysplastic syndrome
- Progression to acute leukemia



# CLOTTING IN PNH

- Most common cause of death in PNH
- Relatively rare as a presenting feature ( 5%) but eventually occurs in up to 40% of patients with PNH
- Typically involve the venous ( deep veins in the legs, lung) rather than the arterial system ( heart attack, stroke) , but both venous and arterial events have been reported
- Can also have thrombosis in atypical locations



# ATYPICAL CLOTTING LOCATION

- Budd-Chiari syndrome ( liver vein clotting)
- Intraabdominal vessels including the inferior vena cava, portal vein, or splenic vein
- Skin veins
- Brain ( cerebral) veins



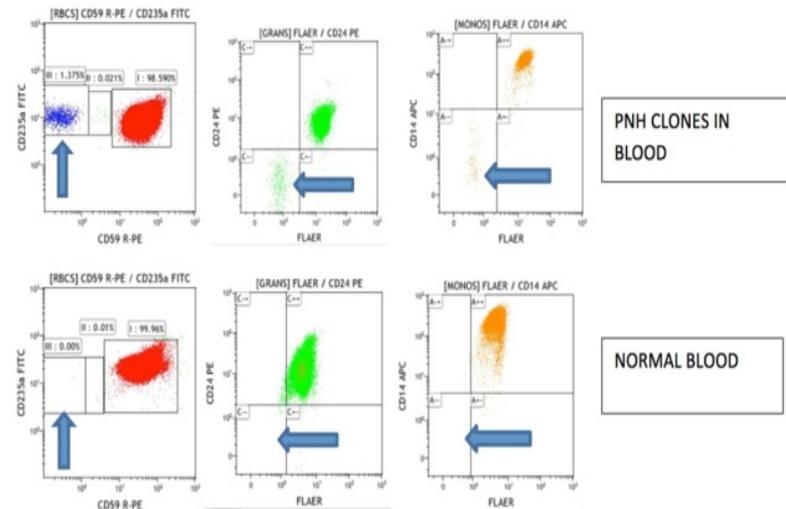
# HOW DO WE DIAGNOSE PNH?

- **Complete blood count with differential**
- **Reticulocyte count**
- **LDH**
- **D-dimer**
- **Liver function test**
- **Kidney function test**
- **Iron panel**
- **Bone marrow aspirate, biopsy, iron stain, and cytogenetics**
- **Imaging studies**
- **Flow cytometry**



# FLOW CYTOMETRY

- Most useful and accepted method to confirm the diagnosis of PNH
- Performed by incubating the patient's blood cells with fluorescently-labeled monoclonal antibodies that bind to proteins, which are reduced or absent on blood cells in PNH
- Both erythrocytes ( red cells) and granulocytes( white cells) should be tested



# PNH CLASSIFICATION

- **Classic PNH** – PNH with clinical evidence of cell breakdown, without another bone marrow abnormality.
- **PNH in the context of another bone marrow disorder** – Red cell breakdown as well as another primary bone marrow abnormality such as aplastic anemia , a myelodysplastic syndrome , or primary myelofibrosis
- **Subclinical PNH** – A small population of PNH cells without red cell breakdown. This is more commonly detected in patients with another bone marrow disorder



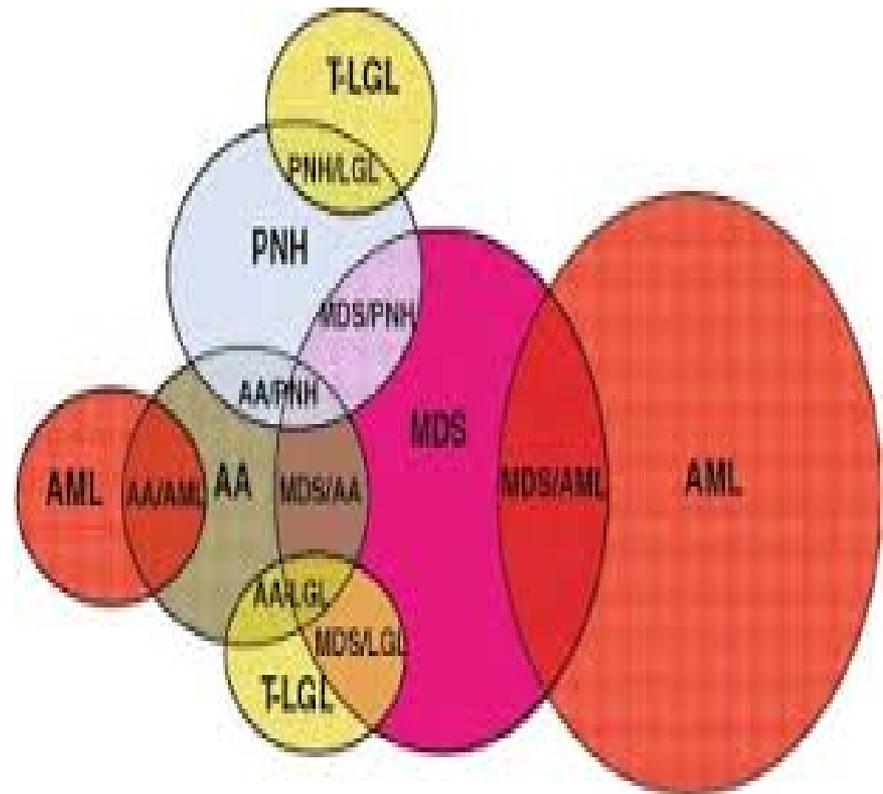
# WHO SHOULD BE TESTED FOR PNH?

- Patients with unexplained hemolytic anemia
- Patients with bone marrow failure, including aplastic anemia and MDS
- Patients with hemoglobinuria
- Patients with unusual/repetitive thrombosis, and arterial thrombosis otherwise unexplained.
- Patients with episodic swallowing problems or abdominal pain of unclear etiology with associated hemolysis



# PNH WITH APLASTIC ANEMIA

- The incidence of PNH is significantly increased in patients with acquired (but not inherited) aplastic anemia
- PNH clones in up to 60 percent of patients
- Presence of PNH clone predicts response to immunosuppression in AA and MDS



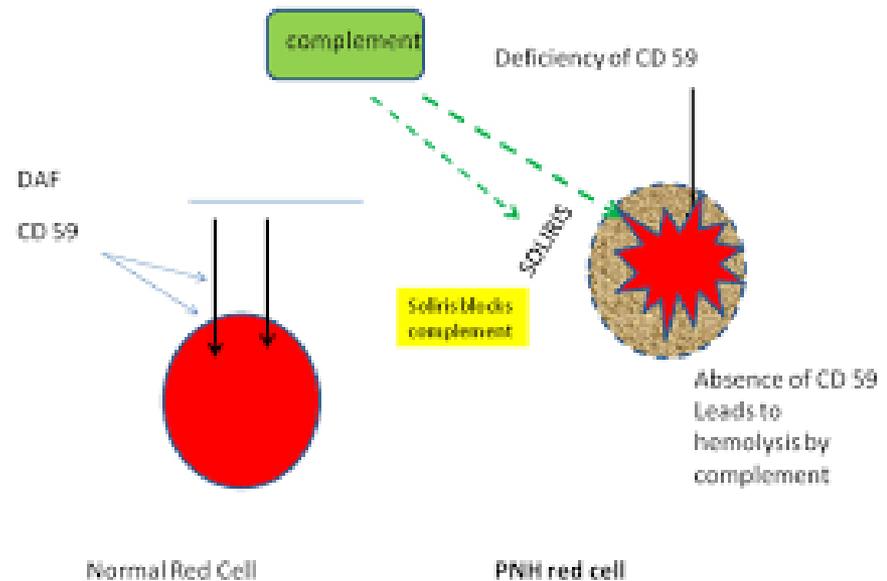
# PNH TREATMENT OVERVIEW

- For patients with hemolytic (classical) PNH, stem cell transplant and Eculizumab are the only established therapies
- Patients with symptoms of thrombosis should be evaluated promptly and treated with therapeutic anticoagulation as well as Eculizumab
- Supplemental iron should be administered to patients who are iron deficient. Supplemental folic acid ( 1-2 mg daily) can be used for chronic hemolysis. Transfusion support can be used if symptomatic
- For asymptomatic patients or those with mild symptoms, active “watch and wait” approach is appropriate



# ECULIZUMAB

- humanized monoclonal antibody that dramatically reduces complement-mediated red cell breakdown in patients with PNH.



# ECULIZUMAB ADMINISTRATION

- 600 mg intravenously once per week for the first four
- 900 mg intravenously one week later
- 900 mg intravenously once every two weeks thereafter.
- Administration is continued **indefinitely**

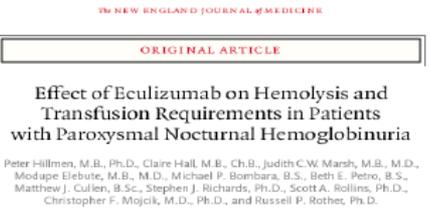


**SOLIRIS**<sup>®</sup>  
(eculizumab)  
Injection for Intravenous Use  
300 mg/30 mL vial



# SOLIRIS® PNH Clinical Studies

**Pilot Study – NEJM. 2004**  
N = 11



**TRIUMPH – NEJM. 2006**  
Pivotal Phase III, Double-Blind, Placebo-Controlled Trial, N = 87



**SHEPHERD – Blood. 2008**  
Broader patient population, including those receiving minimal transfusions or with thrombocytopenia, N = 97



**Long-Term Extension Trial**  
**Hillmen Blood. 2007**  
Evaluated long-term safety, efficacy and effect on thrombosis; Placebo patients switched to SOLIRIS®  
N = 187

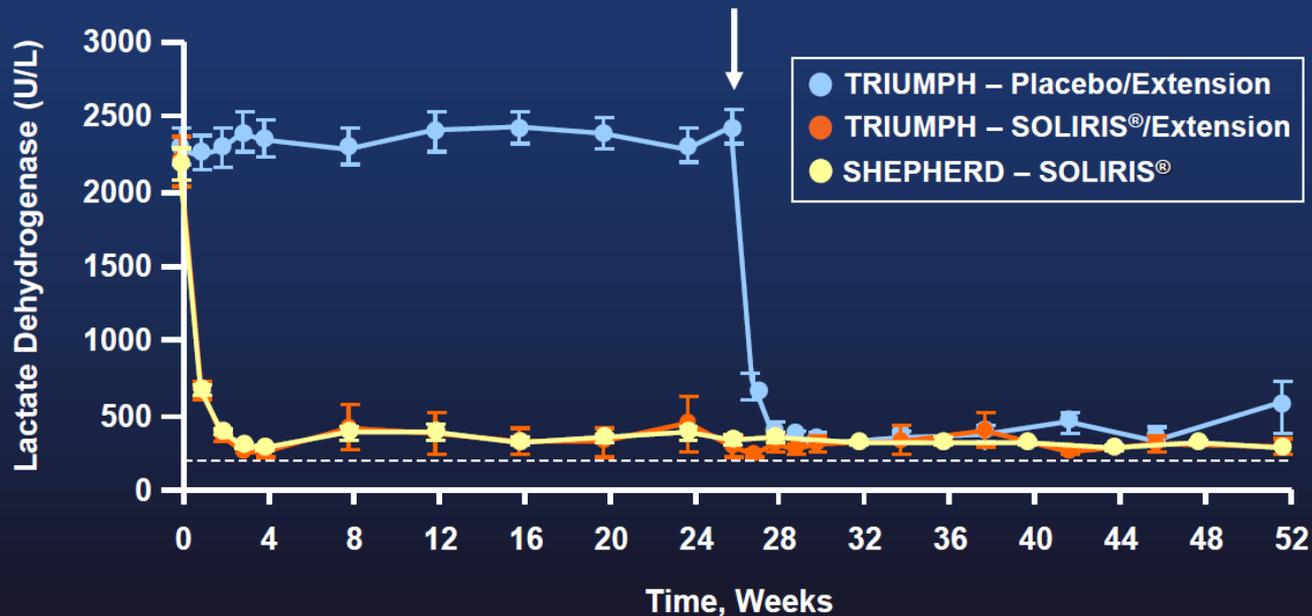
Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria

Peter Hillmen,<sup>1</sup> Petra Muus,<sup>2</sup> Ulrich Döhrsen,<sup>3</sup> Antonio M. Ristano,<sup>4</sup> Jörg Schubert,<sup>5</sup> Lucio Luzzatto,<sup>6</sup> Hubert Schrezenmeier,<sup>7</sup> Jeffrey Szer,<sup>8</sup> Robert A. Brodsky,<sup>9</sup> Anita Hill,<sup>1</sup> Gerard Socié,<sup>10</sup> Monica Bessler,<sup>11</sup> Scott A. Rollins,<sup>12</sup> Leonard Ball,<sup>13</sup> Russell P. Rother,<sup>12</sup> and Neal S. Young<sup>13</sup>

<sup>1</sup>Leeds General Infirmary, Leeds, United Kingdom; <sup>2</sup>Radboud University Medical Center, Nijmegen, The Netherlands; <sup>3</sup>University Essen, Essen, Germany; <sup>4</sup>Federico II University, Naples, Italy; <sup>5</sup>Saarland University Medical School, Homburg-Saarland, Germany; <sup>6</sup>Hofuko Teseano Turron, Florence, Italy; <sup>7</sup>Institute of Transfusion Medicine, University Hospital, Ulm, Germany; <sup>8</sup>Royal Melbourne Hospital, Melbourne, Australia; <sup>9</sup>Johns Hopkins School of Medicine, Baltimore, MD; <sup>10</sup>Hôpital Saint-Louis and Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France; <sup>11</sup>Washington University, St Louis, MO; <sup>12</sup>Alexion Pharmaceuticals, Cheshire, CT and <sup>13</sup>National Heart, Lung, and Blood Institute, Bethesda, MD

# ECULIZUMAB: REDUCTION IN RBC DESTRUCTION

## TRIUMPH and SHEPHERD: 86% Reduction in LDH



→ TRIUMPH placebo patients switched to SOLIRIS® after week 26.  
All TRIUMPH patients entered the long-term extension study.

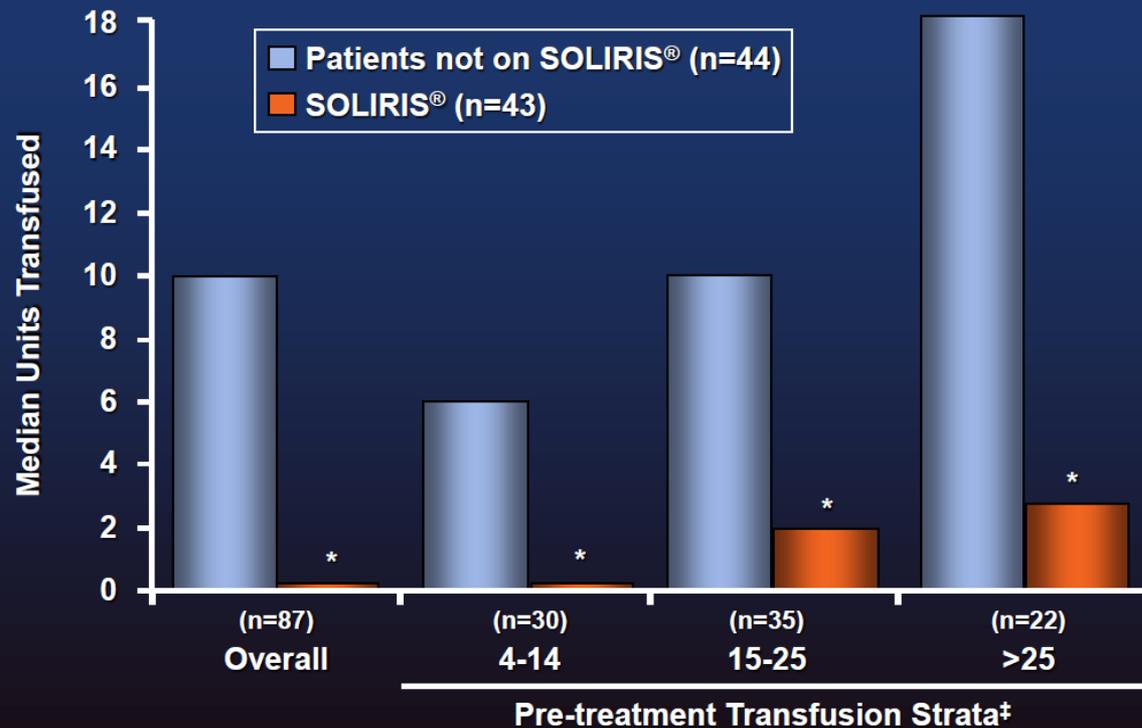
$P < 0.001$  at all measured time points.

Hillmen P et al. *Blood*. 2007;110(12):4123-8.



# ECULIZUMAB: REDUCTION IN BLOOD TRANSFUSION NEED

## 73% Reduction in Mean Units Transfused Across all Subgroups<sup>1</sup>



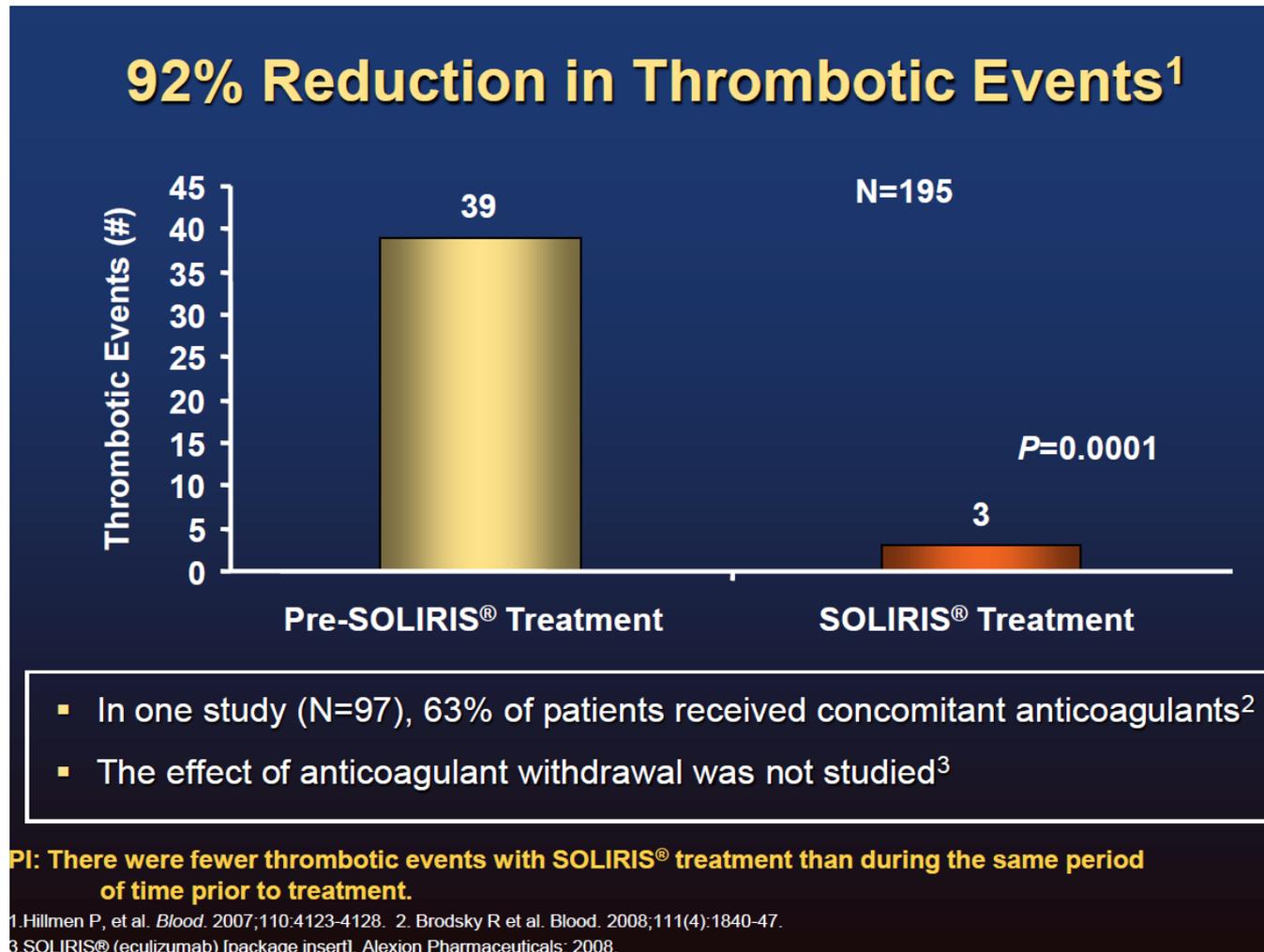
\* $P < 0.001$ .

<sup>‡</sup>Transfusion data obtained during 12 months before treatment; values were normalized for a 6-month period

1. Hillmen P et al. *N Engl J Med*. 2006;355:1233-1243. 2. Schubert J. *Br. J Haematol*. 2008;142(2):263-72.



# ECULIZUMAB: REDUCTION IN THROMBOSIS ( CLOTTING)



# ECULIZUMAB: ADVERSE EVENTS

## Adverse Reactions Reported in $\geq 5\%$ of SOLIRIS<sup>®</sup> Treated Patients in TRIUMPH

Reaction	Patients, n (%)	
	SOLIRIS <sup>®</sup> (n = 43)	Placebo (n = 44)
Headache	19 (44)	12 (27)
Nasopharyngitis	10 (23)	8 (18)
Back pain	8 (19)	4 (9)
Nausea	7 (16)	5 (11)
Fatigue	5 (12)	1 (2)
Cough	5 (12)	4 (9)
Herpes simplex virus infections	3 (7)	0
Sinusitis	3 (7)	0
Respiratory tract infection	3 (7)	1 (2)
Constipation	3 (7)	2 (5)
Myalgia	3 (7)	1 (2)
Pain in extremity	3 (7)	1 (2)
Influenza-like illness	2 (5)	1 (2)



## ECULIZUMAB: SUMMARY OF EFFICACY

- Eculizumab treatment was associated with the following improved outcomes compared with placebo:
- Reduction of anemia /stable hemoglobin(49 %versus 0 %)
- Fewer transfusions (median number of units 0 versus 10; transfusion independence in 51 versus 0 %)
- Improved measures of hemolysis ( RBC breakdown)
- Improved quality of life
- There were no deaths or serious adverse events related to therapy



## ECULIZUMAB: LONG TERM UPDATE

- An open-label extension study evaluated long-term outcomes in 187 of the initial 195 patients from TRIUMPH, SHEPHERD, and an earlier pilot study
- Improvements in transfusion requirements and reductions in hemolysis were sustained during 5.5 years of observation.
- Fewer patients experienced clotting while receiving Eculizumab than prior to the drug ( 4% vs 32%)
- Kidney function improved or stabilized in 93 %
- There were four deaths, all unrelated to therapy (three-year survival estimate 98%).



# WHAT PREDICTS GOOD RESPONSE TO ECULIZUMAB?

- Predictors of a response to Eculizumab are under investigation.
- Studies indicate greater response correlates with:
  - Larger PNH clone size
  - Adequate bone marrow function
  - Absence of inflammatory condition



# BLACK BOX WARNING

- **WARNING: SERIOUS MENINGOCOCCAL INFECTION**
- increases the risk of meningococcal infections
- Vaccinate patients with a meningococcal vaccine at least 2 weeks prior to receiving the first dose
- Monitor patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary



# PREVENTION OF MENINGITIS

- Associated with a 1000-fold to 2000-fold increased incidence of meningococcal disease
- Life-threatening and fatal meningococcal infections have occurred in patients treated with these drugs
- Antibiotics for prevention of meningococcal infection (in addition to vaccination) penicillin 500 mg orally twice daily)
- In the presence of penicillin allergy, a macrolide can be substituted



# ECULIZUMAB: IS THERE A CATCH?

- Cost is major barrier to the use
- 400000\$ per year
- Continuous indefinite treatment is recommended which further increases the cost



# UNMET CLINICAL NEEDS IN ANTI-COMPLEMENT THERAPY

- **Rare intrinsic (genetic) resistance**
- **Suboptimal hematological benefit**
- **Underlying bone marrow failure**
- **Breakthrough RBC breakdown**
- **• C3-mediated extravascular hemolysis**
- **Patient perspective: i.v. therapy, bi-monthly infusion**
- **Limited access (worldwide) and costs**



# PNH: WHATS NEW?

- Ravulizumab (ALXN 1210)

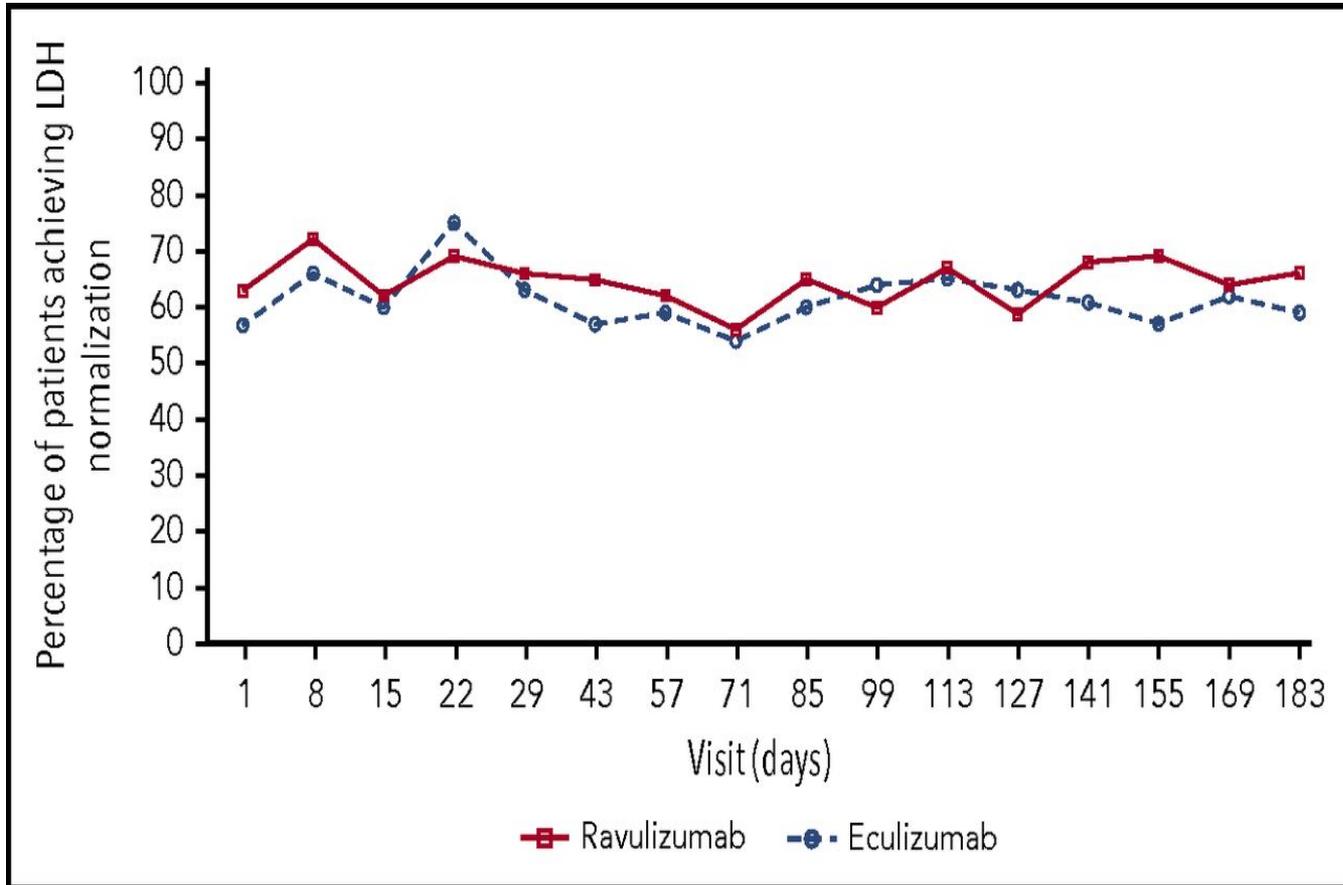


# RAVULIZUMAB

- Monoclonal antibody that is virtually identical to Eculizumab
- Longer half life that permits maintenance therapy every 8 weeks
- Used for treatment of PNH for patients  $\geq 18$  years old
- Consists of a loading dose followed by maintenance dosing, administered by intravenous infusion
- Maintenance doses are administered every eight weeks, beginning two weeks after the loading dose



# RAVULIZUMAB VS ECULIZUMAB



# RAVULIZUMAB CONCLUSIONS

- Ravulizumab every 8 weeks is noninferior to eculizumab every 2 weeks across all efficacy end points in eculizumab-experienced PNH patients.
- Patients with PNH may be safely and effectively switched from labeled-dose eculizumab every 2 weeks to ravulizumab every 8 weeks.



# STEM CELL TRANSPLANTATION ROLE

- PNH complications unresponsive to Eculizumab ( or if Eculizumab not available)
- Only curative therapy for PNH
- Limited to the most severely affected patients because of potential life threatening complications ( graft vs host disease, transplant related mortality, lack of donor)
- Overall survival rate in the range of 50-70%



## PNH: SPECIAL POPULATIONS

- Children – rare, management similar to adults
- Pregnancy – increased maternal and fetal morbidity and mortality, high risk for clotting – may need to use prophylactic anticoagulation starting in third trimester and continue 6-12 weeks postpartum.
- Eculizumab can be continued during pregnancy and breastfeeding
- Patients with PNH should avoid hormonal methods of contraception due to higher risk of clotting
- Surgery can precipitate hemolysis



# CONTACT INFORMATION

- Anna Koget
- 412 578 4484
- [Anna.Koget@ahn.org](mailto:Anna.Koget@ahn.org)



# THANK YOU!

- Questions?

