Clinical Manifestations of PNH

I. Hemoglobinuria
II. Bone Marrow Failure
III. Blood Clots

Case Study:
31 year old woman with AA/PNH

Blood Clot

Hemoglobinuria

Packs of red blood cells

Red cell transfusions

Blood transfusions

Eculizumab

Aplastic Anemia

Lactate dehydrogenase

Normal range

Hemoglobin (G/D/H)

Clinical Manifestations of PNH
Age Distribution of Patients with PNH

Hemoglobinuria in PNH
Hemoglobinuria ≠ Blood in urine

Hemoglobin in urine
Hemoglobinuria
PNH !

Blood in urine
Hematuria
Not PNH !

centrifugation

microscopic examination

GPI-linked Proteins Deficient on PNH Blood Cells

Hematopoietic Stem Cell

CD59, CD109

CD55, CD59 (Cromer Ag)

CD58, PrPc (Cartwright Ag)

CDw108 (John Milton Hagen Ag)

Dombroch residue

Holley Gregory AG

Bessler 2003

Complement Activation

Classical Lectin

Alternative

CD55

C3b C5

C6 C7 C8 C9

CD59

MAC C5b 9
Complement activation leads to complement lysis. CD55 and CD59 protect red blood cells from complement lysis. In PNH, lack of CD55 and CD59 causes complement lysis of red blood cells.

Complement Mediated Lysis in PNH:
Activation → Deposition on the surface → Intravascular Hemolysis.

Complement Attack on PNH Red Blood Cells

Diagnosis of PNH by the Ham Test

Diagnosis of PNH Today
Deficiency of GPI-Linked Proteins on PNH-Granulocytes
Flow cytometry on peripheral white blood cells:

% of Granulocytes deficient for CD59 or FLAER

= Size of the PNH Clone

PNH Testing

PNH Red Blood Cells

PNH Type I  Type II  Type III

CD59

Normal  Intermediate  No expression of CD59

Flow Cytometric Analysis of Red Blood Cells

PNH I  PNH I + III  PNH II  PNH I + II + III

Counts

CD59

Normal  PNH  PNH  PNH
Bone Marrow Failure

Normal bone marrow

Bone Marrow Failure (BMF)
Aplastic Anemia (AA)

The Bone Marrow is the Site of Blood Cell Production

Bone Marrow

Red Blood Cells

Lymphocytes

Granulocytes

Eye leukocytes

Neutrophils

White Blood Cells

Platelets

Bone Marrow Biopsy

Iliac Crest

Bone Marrow
Bone Marrow Examination

Bone marrow aspirate

Bone marrow biopsy

Bone Marrow in PNH

Giemsa, Wright
Courtesy of J Choi CHOP

Bone Marrow in PNH

H&E
Courtesy of J Choi CHOP
Case Study: 31 year old woman with AA/PNH

Red cell transfusions

Blood Clot

Hemolysis (LDH)

Packs of red blood cells

Aplastic Anemia

Lactate dehydrogenase

Blood Clot

AA

PNH

Relationship of PNH with Aplastic Anemia (AA)

Peripheral blood cell count

Normal

PNH

Normal PNH

Normal AA/PNH

Cytopenia

Hemolytic / Classical PNH

AA/ PNH

Adapted from Rotoli & Luzzatto 1989

Relationship of PNH with Myelodysplastic Syndrome (MDS)

MDS within PNH

PNH and MDS

PNH within MDS

% Blood Cells

PNH clone MDS

% Blood Cells

MDS

% Blood Cells

PNH clone

MDS

PNH clone

MDS within PNH

PNH and MDS

PNH within MDS
Blood Clots in PNH

Healthy blood flow  Obstructed blood flow

Platelet
Red blood cell
Blood clot
Thrombus

Blood Clot in the Liver and Brain
in a Patient with PNH

Blood clot in the liver vein
Blood Clot in the brain
with a small stroke

The bigger the PNH Clone
The more likely a Blood Clot

Courtesy of University of Wisconsin Medical School, Madison, WI.
Blood Clots are more Frequent in Patients With a Large PNH Clone

Blood Clots in Patients with PNH

- Blood clots in the veins: ~ 32-40%
  - Belly: ~ 1/3
  - Head: ~ 6%
  - Legs / Embolus: ~ 1/3
  - Other: ~ 1/3
  - Stroke: ~ 14%

The Mechanisms of Disease in PNH

- Bone Marrow Failure
- Occurrence of PNH blood cells
- Extravascular Hemolysis
- Inappropriate complement activation
- Intravascular Hemolysis
- Blood Clot
- Abdominal pain
- Bloating
- Back pain
- Headache
- Erectile dysfunction
- Esophagospasm
- Fatigue
- Anemia
- Hemoglobinuria
- Kidney failure
- Infections
- Bleeding
- Gallstones
- Low blood cell counts
Treatment for PNH
Personalized Treatment Plan

Cure
- Stem Cell Transplant
- Spontaneous remission

Supportive
- Anticoagulation (blood thinner)
- Red cell transfusion
- Iron (only in non-transfused patients)
- Folate 5mg daily
- Erythropoietin (with Soliris)
- Pain management

Disease Modifying
- Immunosuppression
- Complement inhibitors (Eculizumab, Soliris™)

Treatment of PNH:
- Hematopoietic Stem Cell Transplant

Bone Marrow Failure
- Occurrence of PNH blood cells
- Extravascular Hemolysis
- Gallstones
- Inappropriate complement activation
- Anemia
- Hemoglobinuria
- Blood Clot
- Abdominal pain
- Bloating
- Back pain
- Headache
- Erectile dysfunction
- Esophagospasm
- Fatigue
- Infections
- Bleeding
- Kidney failure

Treatment of Bone Marrow Failure in PNH:
- ATG, Cyclosporine, Growth Factors

Bone Marrow Failure
- Occurrence of PNH blood cells
- Extravascular Hemolysis
- Gallstones
- Inappropriate complement activation
- Anemia
- Hemoglobinuria
- Blood Clot
- Abdominal pain
- Bloating
- Back pain
- Headache
- Erectile dysfunction
- Esophagospasm
- Fatigue
- Infections
- Bleeding
- Kidney failure
Eculizumab (humanized anti-C5 antibody)
Soliris

FDA/EMEA approval 2007

- 100 ml over 30 minutes
- Intravenous
- Initially every week (4x)
- then every other week

Soliris Blocks Complement Lysis
of PNH Red Blood Cells

CD55
CD59
Red Blood Cell

Case Study:
31 year old woman with AA/PNH

Blood Clot

Hemoglobin (g/dL)

Red cell transfusions

Packs of red blood cells

Aplastic Anemia

Eculizumab
Eculizumab Reduces the Frequency of Transfusions


Eculizumab Reduces the Risk of Blood Clots


Eculizumab Improves but does not Normalize Hemoglobin Levels

Intravascular Hemolysis

Extravascular Hemolysis

→ Hemoglobinuria
→ High LDH

→ No Hemoglobinuria
→ Low LDH

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Intravascular Hemolysis

Activation → Deposition on the surface → Extravascular Hemolysis

Classical Lectin

Alternative

C3b

C5 C6 C7 C8 C9

CD55

CD59

Extravascular Hemolysis

Activation → Deposition on the surface → Extravascular Hemolysis

Classical Lectin

Alternative

C3b

C5 C6 C7 C8 C9

CD55

CD59

---
Blood Clot
Blocks intravascular hemolysis and associated symptoms

Anemia
Bone Marrow Failure
Low blood cell counts

Intravascular Hemolysis
Infections
Anemia
Hemoglobinuria
Kidney failure

Blood Clot
Abdominal pain
Bloating
Back pain
Headache
Erectile dysfunction
Esophagospasm
Fatigue

Meningococcal Bacterial Infection
• Fever >101
• Chills
• Altered mental status
• Headache
• See your doctor!
• Go to nearest emergency room!
• Start emergency antibiotics!
• Show your “Patient Safety Card”!
• Keep your vaccination up-to-date!

Meningococcal Vaccines
– Meningococcal quadrivalent conjugate vaccine (MCV4 or Menactra®) for adolescents and adults every 5 years for individuals 2-55 years.
– Meningococcal quadrivalent polysaccharide vaccine (MPSV4 or Menomune®) for individuals older than 55 years.
– Does not protect against all meningococcal strains!
– In some countries different strains are more abundant - > prophylactic antibiotics (Penicillin 250mg 2/day)

– prophylactic antibiotics (Penicillin 250mg 2/day)
Pregnancy in PNH

Risks of Pregnancy in PNH

Mother:
- Anemia
- Low platelets and bleeding
- Infection (urinary tract)
- Recurrence of aplastic anemia
- Blood clots during and after pregnancy

Child:
- Early and late fetal death
- PNH is not inherited

Management of Pregnancy in PNH

Discuss
Plan
Verify
Prevent
Monitor
Treat early

- Hematologist familiar with PNH
  - Obstetrician familiar with high risk pregnancy
  - Neonatologist
Alternatives to Pregnancy in PNH

• Adoption
• Surrogate pregnancy (legal contract)
  – Laws differ from state to state and country to country
  – Egg donation (gestational surrogacy)
    • Risk of bleeding during oocyte harvest
    • Risk of thrombosis (hyperstimulation syndrome)
  – In vitro fertilization (embryos may be stored)
  – Surrogate pregnancy
    • Gestational contracted motherhood

PNH Registry Overview

The PNH Registry is an ongoing global, observational, non-interventional study collecting safety, effectiveness, clinical characteristic and quality of life data on patients with PNH irrespective of clone size or treatment.

The PNH Registry has been established in order to describe the real world outcomes of PNH, capturing a wide range of patients from all over the world.
PNH Registry Objectives

- Enhance the understanding of PNH demographics and real world outcomes
- Provide real world data characterizing clinical and subject-reported outcomes associated with PNH treatment regimens
- Raise disease awareness in the medical community and PNH patient population

Global Presence

- The PNH Registry is the largest, most comprehensive database on PNH
  - First patient enrolled in January 2005
  - As of December 2010
    - 5 continents
    - 10 countries
    - 182 enrolling sites
    - 875 patients

Highlights from the 2010 American Society of Hematology Meeting:

**Paroxysmal Nocturnal Hemoglobinuria (PNH)**

**Longterm Eculizumab Results**

**639: Long Term Treatment with Eculizumab In Paroxysmal Nocturnal Hemoglobinuria (PNH): Sustained Efficacy and Improved Survival**


**4237: Long Term Safety and Efficacy of Sustained Eculizumab Treatment In Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)**

Robert A. Brodsky, M.D., Carlos de Castro III, M.D., Ph.D., Joerg Schubert, M.D., Jaroslaw P. Maciejewski, M.D., Ph.D., FACCP, Ulrich Duehrsen, M.D., Lucio Luzzatto, M.D., FRCP, FRCPath, Petra Muus, M.D., Ph.D., Jeffrey Szer, BMedSc, M.B.B.S., FRACP10, Gérard Socié, M.D., Ph.D., and Peter Hillmen, M.B.Ch.B., FRCP, FRCPath, Ph.D.
Long-term Treatment With Eculizumab in Paroxysmal Nocturnal Hemoglobinuria: Sustained Efficacy and Improved Survival

- 79 patients with PNH were treated with eculizumab during an 8-year study period
- 66% of the eculizumab-treated patients became transfusion independent
- 3 patients died during the 8-year study period from causes unrelated to PNH, suggesting that eculizumab yields survival similar to that of a normal age-matched and sex-matched population

<table>
<thead>
<tr>
<th>Prior to Eculizumab Therapy</th>
<th>With Eculizumab Therapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular Hemolysis (Mean LDH Level [Range])</td>
<td>2800 (587-10,300) IU/L</td>
<td>500 (177-1793) IU/L</td>
</tr>
<tr>
<td>Mean Annual Transfusions Required</td>
<td>24.6 units</td>
<td>14.6 units</td>
</tr>
<tr>
<td>Thrombotic Event Rate (Per 100 Patient Years)</td>
<td>5.60</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Kelly et al. ASH 2010; Abstract 639.

Highlights from the 2010 American Society of Hematology Meeting:
Paroxysmal Nocturnal Hemoglobinuria (PNH)

Extravascular Hemolysis

4240 Low Level Residual Extravascular Haemolysis Is Common Following Eculizumab Treatment In Paroxysmal Nocturnal Haemoglobinuria (PNH), but Does Not Affect Transfusion Requirement


New Therapeutics

638 TT30, a Novel Human Complement Inhibitor in Development for Paroxysmal Nocturnal Hemoglobinuria and Other Hemolytic Disorders, Demonstrates Red Blood Cell Surface Targeting and Retention in a Model of Complement Alternative Pathway-Mediated Hemolysis

Masha Fridkis-Hareli, Ph.D., Michael Storek, Ph.D., Antonio M. Ristano, M.D., Ph.D., Arte S. Lundberg, M.D., Christopher J Horvath, D.V.M., M.S., DACVP, and V. Michael Holers, M.D.

TT30 Blocks Complement Activation on PNH Red Blood Cells
Intravascular Hemolysis

Activation -> Deposition on the surface -> Intravascular Hemolysis

Classical Lectin

Alternative

C5b

C5a

C6 C7 C8 C9

CD55

CD59

TT30 Stops Complement Deposition & Hemolysis

Activation ->

Classical Lectin

Alternative

C5

C5a

C6 C7 C8 C9

MAC (C5b-9)

CD55

CD59

TT30 Inhibition of Complement Alternative Pathway

- Using an in vitro rabbit RBC model, TT30 was shown to selectively inhibit CAP activation and remain bound to RBCs for extended periods, supporting the in vivo retention mechanism observed in murine models.2

- TT30 was shown to be fully bioavailable after subcutaneous administration to monkeys.2

- TT30 appears to block both intravascular and extravascular hemolysis in patients with PNH and will be further evaluated in clinical trials.
We are always looking for study participants

For further information
Contact

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Thank You!

For Information Contact

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