Paroxysmal Nocturnal Hemoglobinuria: A Chronic, Systemic and Life-Threatening Disease

- Prevalence: 15.9 / million
- Diagnosed at all ages
  - Median age early 30's
- Progressive disease
  - Uncontrolled complement activation underlies the morbidities and mortality
- Despite best supportive care
  - 5 year mortality: 35%


Paroxysmal Nocturnal Hemoglobinuria

- It’s not paroxysmal
  - Even in the absence of symptoms, destructive progression of hemolysis is ongoing
- It’s not nocturnal
  - Hemolysis in PNH is subtle and constant, 24 hours a day
- Hemoglobinuria is a less commonly seen complication
  - ¾ patients present without hemoglobinuria

The Defect in PNH

PNH is an acquired hemolytic disorder characterized by the somatic mutation of the PIG-A gene which prevents GPI-anchored proteins from binding to the cell surface.

**CD59**
- Forms a defensive shield for RBCs
- Prevents formation and augments instability of the C3 convertase, attenuating the complement cascade
- Inhibits the assembly of the membrane attack complex

**CD55**
- Prevents formation and augments instability of the C5 convertase, attenuating the complement cascade

**GPI-anchor**
- Normal red blood cells are protected from complement lysis
- PNH red blood cells lack GPI-anchored proteins

**Normal red blood cells are protected from complement mediated lysis.**

**Without this protective shield, PNH red blood cells are destroyed.**

**Significant. Hematologic, Mortality.**

**Thrombosis**
- First thrombotic event can be fatal
- First TE increases risk for death 5 to 10-fold

**Chronic Kidney Disease**
- Accounts for 40-67% of deaths
- Is not adequately managed with anticoagulation

**All patients with PNH are at risk for thrombosis**

**Common Symptoms of PNH**
- Fatigue
- Nocturnal Dyspnea
- Dysphagia
- Hemoglobinuria
- Gastrointestinal bleeding

**Significant Impact on Morbidity.**

**Thrombosis in PNH**

- Is the leading cause of death
- Accounts for 40-67% of deaths
- First thrombotic event can be fatal
- First TE increases risk for death 5 to 10-fold
- Up to 44% of patients experience clinical thrombotic events
- Occurs in typical and atypical sites
- Is not adequately managed with anticoagulation
- All patients with PNH are at risk for thrombosis

**First TE increases risk for death 5 to 10-fold.**
Mechanisms for Thrombosis in PNH

Multifactorial pathogenesis of thrombosis in PNH:

- Hemolysis
  - Reduced nitric oxide
  - Platelet hyperreactivity
  - Hypercoagulability
  - Prothrombotic membranes
- Impaired fibrinolysis
- Excessive platelet activation from CD59 deficiency
- Complement C5a also contributes to increased thrombotic risk
- Tissue factor initiated coagulation


Thrombosis is Associated With Risk of Early Mortality

TE increases risk of death 7-15 fold over patients with no TE

- TE was a strong predictor of mortality (OR 6.99; 95% CI 3.2-15.2; P<0.0001) in a South Korean PNH registry
- 21% of TE patients presented with a TE prior to PNH diagnosis
- TE was an independent prognostic factor related to poor survival (HR 15.4; 95% CI 9.3-25.4; P<0.001) in a large cohort of French PNH patients


PNH Granulocyte Clone Size (%)

South Korean National Registry.

<table>
<thead>
<tr>
<th>% TE</th>
<th>&lt;20%</th>
<th>20-50</th>
<th>&gt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>19%</td>
<td>37%</td>
<td>44%</td>
<td>0%</td>
</tr>
<tr>
<td>10%</td>
<td>20%</td>
<td>30%</td>
<td>40%</td>
</tr>
<tr>
<td>&gt;50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Common Clinical Symptoms are Predictive of Thrombosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>0.6</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>0.5</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1.0</td>
</tr>
<tr>
<td>Hemoglobinuria</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Thrombosis in PNH Conclusions

- 40-67% mortality in PNH results from thrombosis¹
- Thrombosis is the leading cause of death in PNH²
- First TE increases risk for death 5 to 10-fold¹
- DVT or PE most common clinical presentation¹
- Arterial thromboses are also common³
- Anticoagulant therapy may not be adequate to control thrombosis in PNH¹
- Anticoagulant therapy also associated with higher risk of fatal hemorrhage in IPNH³
- Clinical thrombosis evident in PNH patients:¹
  - Minimal hemolysis
  - No transfusion history
  - Smaller clone size³

Kidney Pathology in PNH

- Chronic hemolysis and cell-free plasma hemoglobin lead to chronic kidney disease in PNH¹⁻⁴
- Repetitive exposure of tissue to cell-free hemoglobin may lead to renal damage in PNH¹⁻⁴
- 80% of PNH patients (median age of 31.5 years) had MRI evidence of significant renal hemosiderosis¹,⁵
  - Marked hemosiderin deposits in the proximal renal tubule are a common feature in all autopsy and biopsy reports dealing with PNH
  - Demonstrable by MRI even when no overt hemoglobinuria is seen
- Autopsy and biopsy often show interstitial nephritis and fibrosis³,⁴


Chronic Kidney Disease

Common Symptoms of PNH

Thrombosis

Thrombosis in PNH Conclusions

- 40-67% mortality in PNH results from thrombosis¹
- Thrombosis is the leading cause of death in PNH²
- First TE increases risk for death 5 to 10-fold¹
- DVT or PE most common clinical presentation¹
- Arterial thromboses are also common³
- Anticoagulant therapy may not be adequate to control thrombosis in PNH¹
- Anticoagulant therapy also associated with higher risk of fatal hemorrhage in IPNH³
- Clinical thrombosis evident in PNH patients:¹
  - Minimal hemolysis
  - No transfusion history
  - Smaller clone size³

Kidney Pathology in PNH

- Chronic hemolysis and cell-free plasma hemoglobin lead to chronic kidney disease in PNH¹⁻⁴
- Repetitive exposure of tissue to cell-free hemoglobin may lead to renal damage in PNH¹⁻⁴
- 80% of PNH patients (median age of 31.5 years) had MRI evidence of significant renal hemosiderosis¹,⁵
  - Marked hemosiderin deposits in the proximal renal tubule are a common feature in all autopsy and biopsy reports dealing with PNH
  - Demonstrable by MRI even when no overt hemoglobinuria is seen
- Autopsy and biopsy often show interstitial nephritis and fibrosis³,⁴

Kidney failure is the cause of 8-18% of PNH-related deaths\(^1\)
- Kidney failure in PNH is caused by hemolysis\(^2\)
- 64% of patients with PNH exhibit chronic kidney disease at any one time\(^3\)
- Late stage renal impairment in PNH is predictive of mortality\(^4\)

Kidney disease is underappreciated in PNH\(^3\)

Common Symptoms Have a Significant Impact on Quality of Life

- 57% reported abdominal pain
- 66% reported shortness of breath
- 41% reported dysphagia
- 47% reported erectile dysfunction
- 96% reported fatigue

~75% of Patients Reported Symptoms as Moderate to Very Severe

59% patients were transfusion-free for at least 12 months or had never been transfused
76% were forced to modify their daily activities to manage their PNH
17% were unemployed due to PNH

Soliris® (eculizumab)
Soliris is the First and Only Approved Therapy for PNH

Soliris is a Complement Inhibitor Indicated for the Treatment of Patients With PNH to Reduce Hemolysis

Soliris Humanized
First in Class Anti - C5 Antibody

- Human IgG2 Heavy Chain
- Constant Region 1 and Hinge (Eliminates Fc receptor binding)
- Human IgG2 Heavy Chain Constant Region 2 and Hinge (Eliminates complement activation)

Complement Cascade

Proximal
- C3b
- C3a

Terminal
- C5b
- C5b-9

Soliris Blocks Terminal Complement

- Soliris binds with high affinity to C5-2
- Terminal complement - C5a and C5b-9 activity blocked
- Proximal functions of complement remain intact
- Weak anaphylatoxin
- Immune complex clearance
- Microbial opsonization

Soliris Experience in PNH Clinical Trials

- TRIUMPH - Hillmen et al., NEJM, 2004
- Pilot Phase II Double-Blind, Placebo-Controlled Trial, N = 87

- SHEPHERD - Brodsky et al., Blood, 2006
- Broader patient population, including those receiving minimal transfusions or with thrombocytopenia, N = 97

- Long-Term Extension Trial - Hillmen/Peer, 2007
- Evaluated long-term safety, efficacy and effect on thrombosis; Placebo patients switched to Soliris, N = 152

195 Patients With >250 Patient Years of Soliris Exposure
86% Reduction in LDH: TRIUMPH and SHEPHERD

<table>
<thead>
<tr>
<th>Time, Weeks</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>36</th>
<th>40</th>
<th>44</th>
<th>48</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIUMPH – Placebo/Extension</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>TRIUMPH – Soliris/Extension</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>SHEPHERD – Soliris</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

100% response after the first dose

TRIUMPH placebo patients switched to Soliris after Week 26
All TRIUMPH patients entered the long-term extension study

92% Reduction in Thrombotic Events

<table>
<thead>
<tr>
<th>Thrombotic Events (#)</th>
<th>Pre-Soliris Treatment</th>
<th>Soliris Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=195</td>
<td></td>
<td>P=0.0001</td>
</tr>
</tbody>
</table>

- 63% of patients received concomitant anticoagulants
- The effect of anticoagulant withdrawal was not studied
- Events observed in both venous and arterial sites
- There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment

5. Dyspnea* (P=0.002)
6. EORTC Fatigue* (P<0.001)
7. Pain (P<0.001)

Soliris Treatment Results in Large and Clinically Meaningful Improvements in Patient-Reported Outcomes

<table>
<thead>
<tr>
<th>Patient-Reported Outcomes</th>
<th>Standard Effect Size (SES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>1.20</td>
</tr>
<tr>
<td>EORTC Fatigue</td>
<td>1.42</td>
</tr>
<tr>
<td>Pain</td>
<td>1.13</td>
</tr>
</tbody>
</table>

What is the Impact of Long-term Soliris Treatment on Clinical Outcomes and Survival?

**Uncontrolled Complement Activation**

- Hemolysis
- End Organ Damage
- Decreased Mortality?

Complications Associated With Elevated Hemolysis (LDH)

- Pulmonary
- Gastrointestinal
- Renal
- Cardiac
- Hepatic

Increased Mortality

- Increased Mortality

Poor Outcomes

Long-term Treatment With Soliris in Paroxysmal Nocturnal Hemoglobinuria: Sustained Efficacy and Improved Survival

- 79 consecutive patients with PNH
  - Treated with Soliris between May 2002 and July 2010
- Mortality and disease symptoms were evaluated

- 96% (76/79) patient survival
- There was no difference in mortality between patients on eculizumab and the healthy population (P=0.46)
- 2 patients over 70 years of age had worse survival (P=0.0042).
  - No patients under the age of 50 years died


Paroxysmal Nocturnal Hemoglobinuria: A Chronic, Systemic and Life-Threatening Disease

- Age and sex matched controls
- Improved Overall Survival in Patients Treated With Soliris
Improved Overall Survival in Patients Treated With Soliris

Summary of Clinical Efficacy

In clinical trials, Soliris significantly reduced hemolysis\(^1\) the underlying cause of morbidities in PNH

- 86% sustained reduction in hemolysis as measured by LDH
- Fewer thrombotic events were observed with Soliris in clinical trials\(^1,3\)
  - The majority of patients (63%) received concomitant anticoagulant therapy\(^1\)
  - The effect of anticoagulant withdrawal during Soliris treatment has not been studied\(^1\)
- 78% clinically meaningful improvement in fatigue
- 73% reduction in need for transfusions across all patient populations\(^2\)

\(^1\) Soliris (eculizumab) [package insert]. Alexion Pharmaceuticals; 2011. \(^2\) Hillmen P et al. Blood. 2007;110(12):4123-
Sustained Complement Inhibition Leads to Reduced Hemolysis, Thrombosis and Improvements in Survival

- Reduction in LDH (P < 0.0001)
- 100% response rate in pivotal clinical trial programs (as measured by reduction in LDH)
- 4-fold improvement in CKD over placebo (P < 0.04)
- Soliris appears to normalize survival in patients with PNH
- Significant reduction in abdominal pain
- Improvement in dyspnea, dysphagia, fatigue, hemoglobinuria

Global, observational, non-interventional study to collect real world safety, effectiveness and QoL data

- Open to all physicians treating patients with PNH regardless of therapy
- Database for publications to enhance understanding of disease and improve outcomes
- Promote evidence-based medicine

Current enrollment
- Over 1200 patients enrolled
- Participation in 21 countries, including Argentina, Australia, Belgium, Canada, Denmark, Finland, France, Germany, Netherlands, New Zealand, Russia, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

Enrollment information: www.pnhsource.com