PNH: Complications and Long-Term Issues

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What happens to PNH patients?
What are the long-term complications of PNH and can they be prevented?
  – Thrombosis (blood clots)
  – Renal failure
  – Pulmonary Hypertension
  – Development of aplastic anemia, myelodysplastic syndrome, or AML

Long term complications of therapy

What are some special situations for PNH patients?
  – Pregnancy
  – Surgery
  – Vaccinations
What is PNH and what is the long term outlook?
What is PNH?

- A rare and unusual acquired hematologic disorder characterized by
  - Intravascular hemolysis (breaking of red cells)
  - Bone marrow failure (low blood counts)
  - Thrombosis (blood clots)
- There is a great deal of heterogeneity in the clinical presentation and course in patients with PNH

Signs & Symptoms of PNH

- Episodic dark urine (hematuria)
- Anemia
- Fatigue
- Abdominal pain
- Esophageal spasms (heartburn)
- Impotence
- Low blood counts (cytopenias)
- Blood clots
Paroxysmal Nocturnal Hemoglobinuria: Long term outcomes

Actuarial Survival From the Time of Diagnosis in 80 Patients With PNH

100
80
60
40
20
0
0 5 10 15 20 25
Years After Diagnosis

Patients Surviving (%)

Age- and sex-matched controls

Patients with PNH

(1) Hillmen P et al. NEJM 1995; 333:1253-8;

Paroxysmal Nocturnal Hemoglobinuria: Long term outcomes

Kaplan-Meier Survival Curve of patients with PNH from Duke University (n=173).
Average survival was 19.4 years.

## PNH – What do patients die from?

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Duke</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>16 (42%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Abd site</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Other site</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Arterial</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>4 (10.5%)</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>Severe Infection</td>
<td>14 (36.5%)</td>
<td>14 (36.8%)</td>
</tr>
<tr>
<td>MDS/AML</td>
<td>3 (8%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3 (8%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>Other malignancy</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (5%)</td>
<td>0</td>
</tr>
</tbody>
</table>


## PNH & Thrombosis
Thrombosis in PNH

- Recognized early as a problem
- Occurs in ~40% of European-descended populations
  - less in East Asian populations
- Is the worst prognostic indicator
- Is the leading cause of death
- Once a thrombosis occurs, no clear evidence that any anticoagulant will prevent further clots

Relationship of PNH Clone Size and Thromboembolic Events

![Bar chart showing the relationship between PNH clone size and thromboembolic events (TE).](image-url)
Incidence of symptoms or complications of PNH
Correlation with clone size

<table>
<thead>
<tr>
<th>Symptom or complication</th>
<th>PNH Clone</th>
<th>Bone Marrow Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10%</td>
<td>10-49%</td>
</tr>
<tr>
<td>TE</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>41%</td>
<td>53%</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>40%</td>
<td>44%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>14%</td>
<td>31%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>50%</td>
<td>72%</td>
</tr>
<tr>
<td>Discolored urine</td>
<td>30%</td>
<td>26%</td>
</tr>
</tbody>
</table>

*Chi-square test for differences across three PNH clone size categories. **Chi-square test for differences across two RMS categories.

International PNH Registry data – 524 patients

Urbano-Ispizua A. et al. EHA meeting 2010. Haematologica 95(s2): Abstract 1022

Thrombosis in PNH

CVA, cerebrovascular accident; DVT, deep vein thrombosis; MI, myocardial infarction
Peculiarities of thrombosis in PNH

• Incidence may be much higher
  – small, undetectable thromboses
  – D-dimer data
• Once established, tends to recur and continue
  – inexorable course of hepatic vein thrombosis
• Incidence lower in East Asian populations
  – includes Mexican population
• Role of surgery and pregnancy in initiating thrombosis

Possible causes of thrombosis in PNH

- Platelet activation by complement
- Role for nitric oxide on platelets and endothelium
- ADP release by hemolyzed RBC’s
- Reduced expression of urokinase plasminogen activator receptor
- Increased circulating microparticles from lysed RBC’s
How to manage thrombosis in PNH

- Role of coumadin prophylaxis to prevent clots remains controversial.
- Patients presenting with an acute clot should undergo treatment with a clot-busting drug – TPA, urokinase.
- Patients should then be on anticoagulant therapy (coumadin, lovenox, etc).
- Duration - Probably for their lifetime.
- Patients with a thrombotic event should start eculizumab.
- Whether one can stop anticoagulation once eculizumab is started has not been well studied.
- A bone marrow transplant can be considered.

Historical Management of PNH Bone Marrow Transplant

BMT is associated with significant morbidity and mortality

- In a recent retrospective study in France examining PNH patients\(^1\)
  - 54% had GVHD
- In another study examining PNH patients (n=23)\(^2\)
  - 50% chronic GVHD
  - 42% acute GVHD
- BMT has a significant impact on quality of life post transplant\(^3,4\)

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Allogeneic BM Transplantation With RIC

- 16 patients treated with RIC
  - 14 patients (87.1%) survive after median of nearly 6 years without evidence of PNH, (transfusion independent and off anti-coagulation)
  - Acute GVHD 50%, chronic GVHD 68.8%

RIC = reduced intensity conditioning.

What is the impact of eculizumab on thrombosis?

- Equalized patient-years
- 92% fewer thrombotic events post eculizumab vs pre eculizumab

Effect of eculizumab on thromboembolic event rate: concomitant antithrombotics

- Pre-eculizumab event rate elevated despite use of antithrombotics
- 91% reduction in event rate with eculizumab


Will Eculizumab affect survival by lowering the incidence of thrombosis?

We don’t know but we certainly hope so.

Data from recent meetings is encouraging.

Please enroll in the International PNH registry.
PNH – Renal Failure

PNH & Renal Failure
Renal Damage in PNH: Background

- Renal failure has been identified as the cause of death in approximately 8 – 18% of PNH patients.\(^1\),\(^2\)
- 68% have a significant reduction in creatinine clearance.\(^3\)
- 64% of patients with PNH have chronic kidney disease.\(^2\)
- Historically underappreciated in PNH


Renal Damage in PNH: Background

- Chronic haemolysis and cell-free plasma haemoglobin lead to several serious clinical sequelae in PNH.\(^1\)–\(^3\)
- Evidence of renal damage is highly prevalent in patients with PNH.\(^5\)–\(^9\)
- May be acute renal failure, which is frequently reversible.\(^4\)
- Associated with haemolysis and/or microvascular thrombosis.\(^2\),\(^4\)
- Renal damage in PNH may be due to repetitive exposure of tissue to cell-free haemoglobin.\(^9\)

Evidence of renal sequelae by MRI in PNH

- MRI studies show virtually all PNH patients with low-intensity signal in renal cortex, including PNH patients with:
  - low levels of hemolysis
  - aplastic anemia
  - MDS
  - no hemoglobinuria
  - smaller PNH clones

- MRI findings are typical of intravascular hemolysis and are not typically found with extravascular hemolysis

Suizukawa K et al. Intern Med 1993; 32: 686-690

Autopsy and functional findings in PNH

- 8–18% of mortality in PNH

- Autopsy or biopsy findings with:
  - heavy hemosiderin accumulation in the proximal tubules
  - hemoglobin tubular casts
  - signs of chronic interstitial nephritis and fibrosis

- Functional tubular defects are commonly found with:
  - impaired ability to concentrate urine
    - medullary microinfarction or inability of tubular epithelium to sustain maximum osmotic gradient
  - renal tubular acidosis
  - decreased reabsorption of phosphate
  - aminoaciduria

Nath K et al. Kidney Int 2001; 59: 106-117
Renal pathology in PNH

Micrograph of a renal biopsy from a PNH patient, indicative of vascular damage

Interstitial scarring on the left
Normal tissue on the right


Time to Major Clinical Kidney Event Prior to Eculizumab Treatment

Kaplan-Meier probability of patients progressing to an MCK event.
Chronic Kidney Disease Staging Identifies Both Function and Damage

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (ml/minute/1.73 m²)</th>
<th>Objective Measure of Kidney Damage</th>
<th>Description</th>
<th>Action*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 90</td>
<td>Evidence of proteinuria</td>
<td>Kidney damage with normal GFR</td>
<td>Diagnose and treat; Treat comorbid conditions; Slow progression; CVD risk reduction</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Evidence of proteinuria</td>
<td>Kidney damage with mild decreased GFR</td>
<td>Estimate progression</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>No additional evidence necessary</td>
<td>Moderately decreased GFR</td>
<td>Evaluate and treat complications</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>No additional evidence necessary</td>
<td>Severely decreased GFR</td>
<td>Prep for kidney replacement therapy; Predialysis</td>
</tr>
<tr>
<td>5</td>
<td>&lt; 15 (or dialysis)</td>
<td>No additional evidence necessary</td>
<td>Kidney Failure</td>
<td>Replacement (if uraemia present); Dialysis</td>
</tr>
</tbody>
</table>

*Includes actions from preceding stages.

How to manage renal complications

- Stay well hydrated
- Control other conditions which may affect the kidneys (hypertension, diabetes)
- Avoid drugs which may cause renal problems (eg. Non-steroidal medications such as ibuprofen)
- Monitor kidney function at least once per year.
- Block hemolysis
64% of Patients Exhibit stage 1-5 CKD

Among the 22 patients with minimal (0-1) transfusion history, 59% exhibited CKD


Renal Function with Eculizumab in Different Baseline Populations – 12 Months

Eculizumab Treatment Led to Rapid and Sustained Improvement in Renal Function

Duration of eculizumab treatment increased likelihood of renal function improvement

*When comparing likelihood of improvement versus deterioration in renal function


Renal Function in PNH: Conclusions

- Changes in renal function are common in PNH (65% of PNH patients; 6.6-fold more common than in the general population)\(^1\)
- Severe CKD is observed in 21% of PNH patients and appears to be under-diagnosed in this patient population
- 21% of patients with CKD prior to eculizumab were no longer classified with CKD during eculizumab treatment
- Administration of eculizumab to patients with more mild baseline kidney disease was associated with the greatest likelihood of improvement and prevention of worsening in kidney function
- Long-term eculizumab treatment resulted in a significant improvement and prevention of worsening in CKD at all initial stages of renal disease
PNH & Pulmonary Hypertension

Hemolysis-associated pulmonary hypertension

- An important complication in hereditary hemolytic anemias such as thalassemia, stomatocytosis, and spherocytosis
- A common morbidity in sickle cell disease
- Linked to intravascular hemolysis, leading to the term ‘hemolysis-associated pulmonary hypertension’ (PHT)
- An independent risk factor for death in sickle cell disease

Brain natriuretic peptide

- Elevated levels of BNP:
  - released from stretched right heart chambers
  - reflect cardiac chamber volume and pressure overload
  - indicate increased PHT and right ventricular dysfunction
- In patients with hemolytic syndrome, NT-proBNP ≥160 pg/mL:¹
  - is a highly positive predictive value for diagnosis of PHT
  - is an independent predictor of mortality
- TRIUMPH study: 47% of PNH patients had baseline levels of NT-proBNP ≥160 pg/mL²
  - Suggestive of PHT

¹Machado RF et al. JAMA 2006; 296: 310-316

Change in BNP during eculizumab treatment

Eculizumab vs placebo (P<0.001)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Week 26</th>
<th>Baseline</th>
<th>Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>39.4</td>
<td>43.8</td>
<td>52.5</td>
<td>26.3</td>
</tr>
<tr>
<td>Eculizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PHT with NT-proBNP ≥160 pg/mL¹

Pulmonary Hypertension - Summary

- PHT is a serious and life-threatening complication of hemolytic disorders
- PHT and PNH symptoms are common in patients with hemolytic PNH
- PHT may be under-diagnosed clinically in patients with PNH
- Hemoglobinemia, NO consumption, and disruption of vasomotor tone contribute to PHT in patients with PNH
- Eculizumab treatment significantly reduces PHT, as measured by BNP, and PHT-related symptoms in patients with PNH
- Eculizumab treatment dramatically reduces hemolysis, hemoglobinemia, and NO consumption in patients with PNH

PNH – development of AA or MDS
Sir John V. Dacie (1911 - 2005)


William Dameshek 1900-1962

Dameshek W. Riddle:What do aplastic anemia, paroxysmal nocturnal hemoglobinuria (PNH), and "hypoplastic" leukemia have in common? Blood 30:251, 1967
PNH – Aplastic anemia and MDS/leukemia

- A fairly sizable proportion of patients with aplastic anemia may later develop PNH (20-40%).
- Patients with PNH may often have bone marrow failure and some will develop aplastic anemia.
- Patients with PNH may develop myelodysplastic syndrome and or acute myelogenous leukemia (<5%).
- Patients with MDS may have a small PNH clone present and these patients may respond better to immunosuppressive therapy with ATG and/or cyclosporine.

Models of pathogenesis

- Normal Marrow
- Aplastic Anemia
- PNH
- MDS

Immune Assault

Stromal cell Dysregulation, Immune Assault

PNH (hypoplasia)

PNH (hemolysis)
Treatment of AA or MDS/AML

- Aplastic anemia when severe enough is treated with either immunosuppressive therapy (ATG, cyclosporine) or with a stem cell transplant.
- Myelodysplastic syndrome has multiple different therapies depending on the severity.
- AML is treated with chemotherapy and/or stem cell transplant.
Complications of PNH Therapy

- **Eculizumab**
  - Neisseria infection
  - Cost and convenience
  - Extravascular hemolysis

- **ATG/Cyclosporine**
  - Hospitalization
  - Anaphylactic reactions
  - Serum sickness
  - Immunosuppression / Infection

- **Bone marrow transplantation**
  - Allogeneic bone marrow transplant
  - Prolonged hospitalization
  - Up to 44% mortality at 2 yrs with HLA-matched sibling donor
  - Acute GVHD in 34%; chronic GVHD in 33%
  - GVHD-free survival in 14% of patients

Serious Adverse Events: Clinical Trial Experience

- Meningococcal infections are the most important adverse events that may be experienced by patients receiving Eculizumab

- In PNH clinical studies, 2 patients experienced meningococcal sepsis
  - Both patients had received a meningococcal vaccine

- In clinical studies among patients without PNH, meningococcal meningitis occurred in 1 unvaccinated patient
Special Situations in PNH

- Vaccinations
  - May activate complement
  - Role for Eculizumab

- Surgery
  - May activate complement
  - May lead to thrombosis
  - Role for Eculizumab

- Pregnancy

PNH and Pregnancy

PNH is a known hypercoagulable state

Pregnancy is a hypercoagulable state
- High estrogen levels
- Compression of abdominal and pelvic veins by the enlarging uterus
**PNH and Pregnancy**

23 women: 19 with PNH, 4 with AA/PNH

38 pregnancies
- 11 miscarriages
- Pregnancy: 6 hemolysis, 6 hemorrhage
- Labor: 5 hemolysis, 3 hemorrhage
- 1 thrombosis, 1 sepsis
- No maternal deaths

Uncomplicated in one-third of pregnancies

De Gramond et al., Lancet 1987;1:868

**Women with PNH Effects on Pregnancy (N=33)**

Thrombosis: 5 women
- 2 with previous clots (Budd-Chiari syndrome, pulmonary embolus)
- 1 during pregnancy (phlebitis)
- 2 post-partum (hepatic, intracranial)

Hemolysis: 24 pregnancies (73%)
- 20 required PRBC transfusions

Thrombocytopenia: 9 cases

Obstetrical complications: 4 women
- Hypertension, pre-eclampsia, eclampsia

Ray et al., Haemostasis 2000;30:103-117
Women with PNH
Effects on Infants

Perinatal outcomes of 33 pregnancies
- 45% of the babies were pre-term
- Average birthweight 2800g
- Three infant deaths
- Two had hemolytic disease of the newborn, not related to PNH
- No infant thrombosis

Ray et al., Haemostasis 2000;30:103-117

PNH and Pregnancy
Summary

Pregnancy is possible for women with PNH, with or without aplastic anemia, but is potentially hazardous for mother and infant.

Pregnancy leads to complications in up to 50% of women: worse cytopenia, transfusion dependency, thrombosis, and the need for anticoagulation or immunosuppressants.

Pregnancy for women with PNH is risky, and should be planned carefully with an experienced hematologist and high-risk OB.

There is emerging data on the use of Eculizumab in pregnancy.
Special situations for patients with PNH

- **Surgery**

- **Pregnancy**

Clinical Impact of Extravascular Haemolysis

- Consequences
  - Increased LDH
  - Anemia
  - Hemoglobinuria
  - Nitrous Oxide Squeletching
  - Fatigue

- Consequences
  - Increased LDH
  - Anemia
  - Fatigue?

Does Eculizumab improve survival?

Mortality Rates in PNH: Data from French Patients

<table>
<thead>
<tr>
<th>O/N*</th>
<th>10-year Survival Rate (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>96/454</td>
<td>0.75 (0.03)</td>
</tr>
</tbody>
</table>

Uncontrolled Complement Activation

Haemolysis

Complications Associated With Elevated Haemolysis (LDH)

End Organ Damage

• TE
  • Renal
  • Gastrointestinal
  • Pulmonary
  • Cardiac
  • Hepatic

Poor Outcomes

Increased Mortality

What is the Impact of Eculizumab on Survival?

Long-term Treatment With Eculizumab in PNH: Sustained Efficacy and Improved Survival

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

### Patient Characteristics

#### Presenting Features

<table>
<thead>
<tr>
<th>Presenting Feature</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>40 (51%)</td>
</tr>
<tr>
<td>Age at diagnosis (median)</td>
<td>37 years (12-79)</td>
</tr>
<tr>
<td>Documented history of AA</td>
<td>24 (30%)*</td>
</tr>
<tr>
<td>Haemoglobinuria</td>
<td>50 (63%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24 (30%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>70 (95%)†</td>
</tr>
</tbody>
</table>

*Kelly RJ et al. Blood. 117:6786-6792, June 2011*

### Patient Characteristics

#### At Start of Eculizumab

<table>
<thead>
<tr>
<th>Feature</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46 years (14-84)</td>
</tr>
<tr>
<td>LDH level (normal range up to 430IU/L)</td>
<td>2872 (587-10300)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>2.2x10⁹/L (0.6-11.9)</td>
</tr>
<tr>
<td>Platelets</td>
<td>149x10⁹/L (11-507)</td>
</tr>
<tr>
<td>Reticulocytes (absolute)</td>
<td>171x10⁹/L (57-415)</td>
</tr>
<tr>
<td>PNH granulocyte clone</td>
<td>96.4% (41.8-100)</td>
</tr>
<tr>
<td>Type II erythrocyte clone</td>
<td>3.8% (0-77.4)</td>
</tr>
<tr>
<td>Type III erythrocyte clone</td>
<td>25.0% (2.4-79.6)</td>
</tr>
</tbody>
</table>

#### Concurrent Treatment at Start of Eculizumab

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation</td>
<td>46 (58%)</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>14 (18%)</td>
</tr>
<tr>
<td>Androgens</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>

*Kelly RJ et al. Blood. 117:6786-6792, June 2011*
**Thrombotic Events**

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>79</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombotic events (n)</td>
<td>34</td>
</tr>
<tr>
<td>Proportion occurring on anticoagulation (%)</td>
<td>47</td>
</tr>
<tr>
<td>Patient years (n)</td>
<td>608</td>
</tr>
<tr>
<td><strong>Thrombotic event rate (n per 100 patient years)</strong></td>
<td>5.60</td>
</tr>
<tr>
<td><strong>Eculizumab Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombotic events (n)</td>
<td>2</td>
</tr>
<tr>
<td>Patient years (n)</td>
<td>260</td>
</tr>
<tr>
<td><strong>Thrombotic event rate (n per 100 patient years)</strong></td>
<td>0.8 (P&lt;0.001)</td>
</tr>
</tbody>
</table>


**Eculizumab Has a Major Impact on Survival in PNH**

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

- 96% (76/79) patient survival
- There was no difference in mortality between patients on eculizumab and the normal population (P=0.46)

Mortality in Patients on Eculizumab

3 Patients Died in the 8 Year Study Period

1. 55 year old man died from metastatic caecal carcinoma which was diagnosed prior to eculizumab treatment

2. 76 year old woman died from pneumonia following a long history of recurrent bronchopneumonia prior to starting eculizumab

3. 79 year old man with a preceding history of ischaemic heart disease died from congestive cardiac failure

Improved Overall Survival in Patients Treated With Eculizumab

Overall survival was 97.6% (95% CI 93.7-99.1) at 3 years and was maintained through 5.5 years of ongoing eculizumab treatment (N=195).


Thank you.