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?
Paroxysmal Nocturnal Hemoglobinuria: Long term outcomes

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


PNH – What do patients die from?

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PNH & Thrombosis

- How do you know if you have a blood clot?
  - Symptoms can be quite variable – intense pain, swelling, shortness of breath, headaches.
  - Diagnosis is based on laboratory tests and imaging studies.
    - Ultrasound
    - MRI/MR(V or A).
  - Blood clots can be life threatening. They require immediate medical attention.

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

South Korean National Registry
Lee JS et al. Hematologica. 2010. 95 (s2): Abstract #505.

Incidence of symptoms or complications of PNH Correlation with clone size

International PNH Registry data – 524 patients

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
  - Other risk factors include prolonged immobility, oral contraceptives, inherited thrombophilia.

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.
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 certainly hope so.

Data from recent meetings is encouraging.

Please enroll in the International PNH registry.
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

References:

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\(^2,9\)
- 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\(^9\)

References:
**Time to Major Clinical Kidney Event Prior to Eculizumab Treatment**

Kaplan-Meier probability of patients progressing to an MCK event.


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**Renal pathology in PNH**

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


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**Chronic Kidney Disease Staging Identifies Both Function and Damage**

**Chronic Kidney Disease (CKD) Stages 1-5**

<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>&gt; 90</td>
<td>Evidence of proteinuria</td>
<td>Kidney damage with normal GFR</td>
<td>Diagnosis and treat 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 urinary output decreases</td>
</tr>
</tbody>
</table>

*Includes actions from preceding stages.

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


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
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)
- 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

- 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

Hemolysis-associated pulmonary hypertension

- An important complication in hereditary hemolytic anemias such as thalassemia, stomatocytosis, and spherocytosis
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- 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:
  - 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/mL:
  - Suggestive of PHT

Change in BNP during eculizumab treatment

Eculizumab vs placebo (P<0.001)

Baseline Placebo Treatment group: TRIUMPH
Week 26 Eculizumab (n=72)

PHT with NT-proBNP ≥160 pg/mL:


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

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 surgery

Cardiopulmonary bypass in a patient with classic paroxysmal nocturnal hemoglobinuria during treatment with eculizumab

Surgery, and particularly open heart surgery, has a high risk of complications in patients with PNH. First, eculizumab...
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

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 Gramont 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

Original Articles

Paroxysmal nocturnal hemoglobinuria and pregnancy before the eculizumab era: the French experience

27 pregnancies in 22 PNH patients from 10 different medical centers.

Conclusions
Pregnancy during paroxysmal nocturnal hemoglobinuria is associated with increased maternal and fetal mortality rates (8% and 4%, respectively, in this series). Maternal mortality is related to postpartum thrombosis. Prophylactic anticoagulation is recommended during pregnancy and for six weeks postpartum.

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**

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**Clinical Impact of Extravascular Haemolysis**

Consequences: Increased LDH, Anaemia, Hemoglobinuria, Nitrous Oxide, Squelching Fatigue


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**Does Eculizumab improve survival?**

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PNH Survival – Pre-eclizumab

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

Mortality Rates in PNH: Data from French Patients

O/N: 10-year Survival Rate (SE)

90/454: 0.75 (0.03)
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

Thrombotic Events

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<th>Eculizumab Treatment</th>
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<tr>
<td>Patients (n)</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>Thrombotic events (n)</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Proportion occurring on anticoagulation (%)</td>
<td>47</td>
<td>0.8 (P&lt;0.001)</td>
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<tr>
<td>Patient years (n)</td>
<td>608</td>
<td>260</td>
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<tr>
<td>Thrombotic event rate (n per 100 patient years)</td>
<td>5.60</td>
<td>0.8</td>
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Eculizumab Has a Major Impact on Survival in PNH

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

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

On Eculizumab, n=79
Pre-eculizumab, n=30

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)

Patient Survival in the Eculizumab Study Population

- Overall survival was 97.5% (95%CI 93.7-99.1) at 3 years and was maintained through 5.5 years of ongoing eculizumab treatment (N=195)
Where are we going?

- Improve current therapy
  - Oral eculizumab
  - Increase treatment intervals
- Find other ways to inhibit complement
- Understand how PNH cells take over the bone marrow so we can reverse this process (Restore normal stem cells)
- Gene therapy
- Stem cell transplants

Thank you.

Any questions?