Clinical Management of Paroxysmal Nocturnal Haemoglobinuria (PNH)

Dr Richard Kelly

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Reality of Being Diagnosed with PNH

- Scary
- Isolating
- Unusual
- Lucky
- Relief
- Painful
- Different
- Ongoing
Patients Main Concerns

• Transfusion
• Dark Urine
• Blood Tests
• Infection
• Hospital stays
• Warfarin
• Unable to fulfil role in daily life including interpersonal relationships and working
Patient Experience 1

“I was diagnosed with PNH in 2000 after feeling unwell. I had always been fit and healthy. Over the next 4yrs my health gradually deteriorated. My blood count slowly dropped & I had severe bouts of haemolysis where I would have to stay indoors until it stopped. I was always dizzy, I gave up sport and I couldn’t participate in family activities like days out or long walks. I lost my job and became dependent on blood transfusions, which I had every three months.”
“I was having 4 units of blood every month. This was for a couple of years. I was taken into hospital about every 3 weeks and was treated systematically for swelling of the abdomen & eye, thirst and being unable to swallow, I was given high dose steroids and put on a drip knowing I would return in a couple of weeks. My consultant didn’t know how else to treat me. I had no home life as I was too ill to help around the house or look after my children. I was off work for a whole year and could not see myself ever returning to work or even my marriage lasting and it was taking its toll.”
NCG-funded Paroxysmal Nocturnal Haemoglobinuria Service

PNH Designated Centres:

Lead: Professor Peter Hillmen
Leeds Teaching Hospitals NHS Trust
Level 3, Bexley Wing
St James’s University Hospital
Beckett Street
Leeds LS9 7TF
Tel: 0113-206-8625
Email: pnh@leedsth.nhs.uk

Lead: Dr Dupe Elebute
King’s College Hospital NHS Foundation Trust
Department of Haematology
Hambleden Wing
Denmark Hill
London SE5 9RS
Tel: 0203-299-3520
Email: kch-tr.pnh@nhs.net
Intravascular Haemolysis

CD59 & CD55

Impaired quality of life
- Chronic fatigue
- General discomfort
- Pain
- Shortness of breath
- Renal failure
- Pulmonary Hypertension

Thrombosis

Anaemia
- Transfusions
- Fatigue
- Dyspnoea

Smooth muscle dystonia
- Abdominal cramps
- Difficulty swallowing
- Erectile dysfunction

Mortality in Untreated Patients

Age- and sex-matched controls

Patients with PNH

(Hillmen et al., NEJM, 1995;333:1253-8.)
Initial Assessment of a Patient with PNH

Essential components to resolve:

• Establish the size of the PNH clone
• Establish the degree of haemolysis
• Establish the degree of bone marrow failure
• Assess the occurrence of previous complications
• Assess the severity of the symptoms and the impact on the patient’s quality of life
• Estimate the potential risk for complications
**Historical Management of PNH**

- **Transfusions**
  - Risk of iron overload
  - Transient treatment of anemia

- **Anticoagulants**
  - Risk of haemorrhage
  - Non-optimal in many patients*

- **Red cell supplements**
  - ESAs may expand clones and increase haemolysis
  - Folic acid, iron, erythropoiesis-stimulating agents

- **Steroids/androgen hormones**
  - No controlled clinical trials


Historical Management of PNH (cont)

- **Allogeneic bone marrow transplant**
  
  Up to 44% mortality at 2 yrs with HLA-matched sibling donor\(^{(1,2)}\)

  Acute GVHD in 34%; chronic GVHD in 33%\(^{(1,2)}\)

  GVHD-free survival in 14% of patients\(^{(3)}\)

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Eculizumab Treatment

Improves QoL, Reduces or abolishes need for transfusion, Stabilises Hb, Alleviates symptoms, Reduces risk of thrombosis, Stabilises or improves renal function, Improves pul HT

Classical pathway

C3 → C3b → C5

Alternative pathway

C3 → C5b, 6, 7, 8, 9

Blocked by eculizumab

Opsonisation

C5a

C5b, 6, 7, 8, 9

Membrane attack complex
Primary Prophylaxis with Warfarin in PNH
(patients with >50% PNH neutrophils)

# Thrombotic Rates in Patients in PNH Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Pilot</th>
<th>TRIUMPH</th>
<th>SHEPHERD</th>
<th>Extension (all studies combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>11</td>
<td>43</td>
<td>97</td>
<td>195</td>
</tr>
<tr>
<td>Pre-Treatment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Thrombotic Events (n)</td>
<td>5</td>
<td>16</td>
<td>91</td>
<td>124</td>
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<tr>
<td>Patient Years (n)</td>
<td>161.7</td>
<td>309.0</td>
<td>718.3</td>
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<tr>
<td>Thrombotic Event Rate (n per 100 patient years)</td>
<td>3.09</td>
<td>5.18</td>
<td>12.67</td>
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<tr>
<td>Eculizumab Treatment</td>
<td></td>
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<td></td>
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<tr>
<td>Thrombotic Events (n)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Patient Years (n)</td>
<td>34.19</td>
<td>21.8</td>
<td>96.88</td>
<td>281.03</td>
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<tr>
<td>Thrombotic Event Rate (n per 100 patient years)</td>
<td>0.00</td>
<td>0.00</td>
<td>2.06</td>
<td>1.07 (P&lt;0.001)</td>
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</tbody>
</table>

1Comparison of eculizumab treatment versus pre-treatment; signed rank test.
Renal Damage in PNH

- Chronic haemolysis and repetitive free hemoglobin exposure lead to chronic kidney disease (CKD)\textsuperscript{1-3}

- 64% of patients with PNH have chronic kidney disease\textsuperscript{3}

- Historically underappreciated in PNH\textsuperscript{3}

Time to Major Clinical Kidney Event Prior to Eculizumab Treatment

Figure 1. The Kaplan-Meier probability of patients progressing to an MCK event. Event-free; 85% (95% CI; 77.9% - 89.6%) at five years, 73% (95% CI: 63% - 80%) at 10 years, 56% (95% CI 42% - 67%) at 20 years and 25% (95% CI: 10% - 44%) at 30 years.

Effect of Eculizumab Versus Placebo on Renal Outcomes in PNH Patients


**Proportion of patients (%)**

- **Eculizumab**
  - No Change: 65.9%
  - Improvement: 29.3%
  - Worsening: 4.9%
  - *p* = 0.006

- **Placebo**
  - No Change: 69.0%
  - Improvement: 16.7%
  - Worsening: 14.3%
**Prevention**

- Patient and local physician education
- Patient safety cards
- Prophylactic penicillin V 500mg bd
- Vaccinate with tetravalent conjugate vaccine (Menveo)
- Revaccinate depending on serological levels

**Treatment**

- Patient and local physician education
- Prompt treatment with antibiotics that cover *Neisseria* and penetrate the blood/brain barrier
- Involve PNH team as well as local physicians
“Since I started the trial my health has gradually improved. HB regularly above 11g/dl (before often below 8g/dl). I don’t get the dark bouts of urine, my health is more stable and I have experienced no noticeable side effects. It has transformed my life and the way I feel about the future.”
“Since starting this drug my life has changed so much. I have returned to work full time although I do get tired. I can go walking and swimming and look after my children. I have not had any transfusions or colds since starting the drug.”
Specialised Service for PNH Patients

- Not just about eculizumab!
- Monitor for end organ damage
- Educate patients and carers/families
- Educate other healthcare professionals
- Advise on specific therapies needed and on disease complications
- Provide a support structure for patients/families
- Setup of a patient group
- Co-ordination of the global registry
Acknowledgements

PNH Patients

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